Refractory Depression

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Objectives

• Define Depression and Treatment Resistant Depression (TRD)
• Extent of the problem
• Depression and comorbid medical illnesses
• Treatments in Refractory Depression
• Discuss novel treatments like Ketamine in Depression and Suicide

Disclosures

Grants/Research Support – Otsuka, Novartis, Allergan, Janssen, Biogen & Relmada
Consultant – Janssen

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<th>Source</th>
<th>Research Funding</th>
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Extent of the problem

- According to WHO:
  Depression is the leading cause of disability worldwide, and is the major contributor to the overall global health burden of disease

- Centers for Disease Control and Prevention reported in 2018—Suicide rates rose in nearly every US State from 1999-2016. Rates spiked by >30% in half of the country

- Nearly 45,000 people committed suicide in 2016 making it one of the 3 leading causes of death on rise in US along with Alzheimer Disease and Drug OD and rates have not significantly decreased in recent years

Depression in Physical Illness

MAJOR DEPRESSIVE EPISODE

- At least one of the following—Depressed mood or anhedonia—during the same 2 week period
- At least 5 (or more) of the following—
  - Depressed mood
  - Decreased interest or pleasure
  - Insomnia or hypersomnia
  - Significant weight loss or gain (>5% change in body weight in a month) or changes in appetite
  - Psychomotor retardation
  - Fatigue or loss of energy
  - Decreased concentration or thinking, indecisiveness
  - Negative thinking—worthlessness, inappropriate or excessive guilt
  - Recurring thoughts of death or suicide

- Not organically caused
- Not uncomplicated bereavement or grief
- A change from previous functioning—clinically significant distress or impairment in social, occupational functioning

NATURAL COURSE OF UNTREATED DEPRESSION

- 1 year
  - Normal Mood
  - Depression
  - 40% Recovery
  - 40% Stay Depressed
  - 20% Dysthymia or Partial Recovery
Depressive Disorders: Treatment Goals

- Reduce/Remove Signs, Symptoms
- Restore Role/Function
- Minimize Relapse/Recurrence Risk

Adapted from WPA/PTD Educational Program on Depressive Disorders

Recurrence of Depressive Disorders

- 30% of Patients Become Chronically Depressed
- 20% of Patients Exhibit a Recurrent Course

Merikangas et al, WPA/PTD Educational Program on Depressive Disorders

Treatment Resistant Depression (TRD)

- Typically refers to inadequate response to 2 or more treatment trials of adequate doses and duration
- TRD is relatively common in clinical practice ranging from 30-50%
- Accurate and systematic assessment of TRD is a challenge to researchers and clinicians
- Use of Clinician-rated like MGH ATRQ (Antidepressant treatment response questionnaire) or self rated instruments can be helpful

M Fava, Society of Biological Psychiatry 2003

And Problem is not getting better....

- Treatment resistant depression (TRD) is around 30-50% in patients who have received pharmacotherapy
- TRD costs employers in US up to $48 billion/yr
- Health care resource use and costs were double ($17,261) for employees with TRD compared with non-TRD depression ($9,790) and quadruple without depression ($4,782)
- Health care costs for employees with TRD increased with each treatment failure
- Employees with TRD were absent approx. 35.8 days per person per year, almost 6 times more than without depression

Greenberg Psych News 2018
How Depression Is Treated

- Drug therapy has been the standard of care
- But drug therapy...
  - doesn’t work for many people
  - may produce unwanted side effects in other parts of the body

TRD: A Large Patient Population - Treatment Challenges

- 16.2 Million US ADULTS WITH MDD
- RESPONSE ~50% after 6 wk
- 1/3rd are non-responders
- RELAPSE RATE 40% AFTER 1 YEAR

Clinical Status And Treatment Phases Of Depression

- Depression
- Remission
- Recovery
- Relapse
- Recurrence

Antidepressants

- SSRIs - selective serotonin reuptake inhibitors (eg fluoxetine)
- SNRIs - selective serotonin and norepinephrine reuptake inhibitors (eg venlafaxine)
- TCAs - tricyclic antidepressants (eg amitriptyline)
- MAOIs - monoamine oxidase inhibitors (rarely used today)
- Others or Atypical (eg Trazodone)
- NOVEL Antidepressants - NMDA Receptor Modulators (eg Ketamine)
PSYCHOTHERAPY FOR DEPRESSION

- High number of studies, meta-analysis, reviews exist
- Types of psychotherapy in treatment of depression
  - Cognitive behavioral therapy
  - Existential therapy
  - Psychodynamic therapy
  - Expressive-supportive therapy
  - Mindfulness and relaxation therapy
  - Educational therapy

Clinical Approach to TRD

Ensure Adequate Diagnosis
- Organic etiology of depressive symptoms
- Co-morbid psychiatric illness like substance abuse d/o, anxiety disorders, personality disorders

Accurately assess treatment response
- Obtain collateral information from family, past records
- Use standard Assessment scale for depression and past treatment
- Differentiate between partial response vs non response
- R/o Tachyphylaxis

Determine adequate trial of Treatment
- Compliance, Intolerance or other reasons
- Adequate trial dosage and duration

Consider test of Pharmacogenomics

NNDC TRD task force
Highlights

- Treatment Resistant depression causes huge societal and personal burden worldwide
- Clinical depression is a serious psychiatric complication in medical illness
- Evidence that antidepressants are effective in reducing depression/depressive s/s is shown in clinical trials but there is no evidence for the superiority of one treatment modality over another
- Combined approaches to the treatment of depression may be more effective
- There are still inconsistencies across providers in terms of patient selection, duration, optimal dosing and frequency of the treatments in patients with co-morbid medical conditions
- There is growing interest in developing newer drugs with similar mechanisms with fewer side effects and rapid acting.

Assessment of Therapeutic Adequacy

- Antidepressant Treatment History Form (ATHF-SF)

Electroconvulsive Therapy

Most frequent indications

Depressive Disorders
- Major Depressive Disorder
- Bipolar I/II Disorder, current episode depressed
- Schizoaffective Disorder, Depressed Type
- Schizoaffective Disorder, Bipolar Type, current episode depressed

Manic Disorders
- Bipolar I Disorder
- Schizoaffective Disorder, Bipolar Type, current episode manic

Catatonic Disorders
- Catatonia associated with another mental disorder
- Catatonia associated with another medical condition

Schizophrenia
- Cases of incomplete response to clozapine
Benefits and Risks

**Benefits:**
- Effective in treatment resistant depression
- Average time to improvement with depressive disorders: ~7 treatments (6-12 treatments range)
- Provided Mondays, Wednesdays, Fridays

**Risks:**
- Headache
- Nausea
- Myalgias
- Working memory disruption
- Emerging in treatment, persisting for 2-12 weeks post treatment (average)
- Serious morbidity and mortality (ischemia, cardiac or cerebral, arrhythmia, arrest)
- 2.2 per 100,000 incidence

Electroconvulsive Therapy

**Efficacy and Speed of Response**


**Maintenance of Response**

TMS for Major Depressive Disorder: Outcomes

Comparison of response and remission rates based on PHQ-9 and CGI-S scores for the same patients or PHQ-9 scores only.

Response and remission rates for female and male patients in a random sample of 216 individuals with MDD during the 1-month follow-up period. PHQ-9 indicates the Patient Health Questionnaire-9.

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<th>Response/Remission</th>
<th>PHQ-9</th>
<th>CGI-S</th>
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<tr>
<td>Response</td>
<td>64%</td>
<td>76%</td>
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<tr>
<td>Remission</td>
<td>48%</td>
<td>60%</td>
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TMS in Major Depressive Disorder

Figure 2: Summary of VIS-68 Total Score Changes During 12-Week Treatment with rTMS as Adjunctive Treatment to Antidepressant Medication (N=287). Response rate of 75% or greater.


6/2/2021
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

- Compared different doses of esketamine (28, 56, 84 mg) in patients with TRD started on a new oral antidepressant (one of several)
  - Least square mean change in MADRS primary outcome
  - Allows for comparisons between unequal groups
- MADRS change at 24 hrs statistically significant (~5 placebo to ~8 Spravato)
- At day 28, continued statistically significant difference favoring Spravato (~16 placebo to ~20 Spravato)
Vagus Nerve Stimulation

- FDA-approved in 2005
- Indications:
  1. Major depressive disorder
  2. Adjunctive treatment
  3. Age > 18
  4. Two or more adequate trials

Vagus Nerve Stimulation

Comparison of controlled trials utilizing ketamine and esketamine

- Ketamine
- Esketamine

Favors experimental
Favors control

标准化均值差异: -6 -4 -2 0 2 4 6
5 year outcomes with VNS

- Compared to Treatment as Usual (TAU), VNS showed cumulative response rates of almost 70% at 60 months (40% TAU)
  - Remission rates >40% (VNS) v 25% (TAU)
- Patient with response had approximately 50% probability of sustaining response at 60 months, versus 30% with TAU
- Patients with ECT non-response history were ~10% less likely to achieve response with VNS
- Comorbid anxiety disorders and presence of Bipolar Disorder did not appear to meaningfully impair response with VNS