When Depression Doesn’t Get Better: Management of Treatment Resistant Depression

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Objectives

- Define treatment resistant depression
- Describe factors that contribute to treatment resistance
- Discuss pharmacological treatments for TRD
- Identify nonpharmacological, complementary and alternative treatments for TRD
Depression
Past Year Prevalence of Major Depressive Episode Among U.S. Adults (2016)

Data Courtesy of SAMHSA

<table>
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<tr>
<th>Sex</th>
<th>Age</th>
<th>Race/Ethnicity</th>
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<tbody>
<tr>
<td>Overall</td>
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<td>NH/OPI*</td>
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<td>8.5</td>
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<td>White</td>
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<td>NH/OPI*</td>
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</table>

*All other groups are non-Hispanic or Latino | **NH/OPI = Native Hawaiian / Other Pacific Islander |
| ***AI/AN = American Indian / Alaskan Native
SYMPTOMS

Not sleeping or sleeping too much

Restlessness or slowness observable by others

Can't make decisions and can't concentrate

Feeling down all day

Blaming yourself too much and feeling worthless

Fatigue or loss of energy nearly every day

Significant change in weight or appetite

Thinking about death frequently

No longer interested in favorite activities
Definition of TRD

MDD without remission after 2 courses of antidepressant tx of:
- Adequate dose
- Adequate duration
Mary
Psychosocial Hx

- Alcoholic fam/abuse/divorce (10y)
- Depression/anxiety—mother, sister
- Depression high school—no Tx
- Married/PG at 19; 3 children in 5 years.
- Divorced at 35; prim custody; problems w/child
- Working part-time and on SSI—financial/health issues
- Son living with her and is unemployed/addiction
- Little social support
- Assists mother with developing dementia
- Past psychotherapy; PHP after having SI after divorce
Problem List

- Recurrent depression
- Anxiety/panic attacks
- Insomnia
- Hypertension
- Hypothyroidism
- Fibromyalgia
- Fatigue
- Sleep apnea
- GERD
- Postmenopausal
- Migraine HA
- Chronic back pain
- Obesity—37 BMI
- Prediabetes
- Restless Leg Syndrome
Medication list

- Trintellix (vortioxetine)
- Rexulti (Brexpiprazol)
- Zolpidem (Ambien)
- Clonazepam
- Amitriptyline
- Gabapentin
- Lisinipril
- Requip

- Levothyroxine
- Flexeril
- Metformin
- Omeprazole
- Imitrex
- Calcium/Vit D3
- Fish Oil

- CPAP
Major Contributors

TRD
Inadequate Screening

❖ For adolescents/young adults
❖ High risk patients
Achieving Remission

STAR*D Study demonstrates that current treatments have limited effectiveness

- Likelihood of achieving remission is limited and declines with each successive treatment attempt.
- First-Line Treatment Effect: 27.5% (n=2876)
- One Prior Treatment Failure: 21.2% (n=727)
- Two Prior Treatment Failures: 16.2% (n=221)
- Three Prior Treatment Failures: 6.9% (n=58)

References:
STAR-D† Algorithm for Depression

**Level 1**
- Citalopram

**Switch**
- Sertraline
- Bupropion
- Venlafaxine
- CBT

**Augment**
- Bupropion
- Buspirone
- CBT

**Level 2A**
- Venlafaxine
- Bupropion

**Level 3**
- Mirtazapine
- Nortriptyline

**Switch**
- Lithium
- Thyroid Hormone

**Level 4**
- Tranylcypromine OR Venlafaxine/mirtazapine combo

†Sequenced treatment alternatives to relieve depression. Target enrollment N=4000.
Physiologic Barriers to Remission

- Genetic factors—polymorphisms
- Pharmacogenomic patterns-metabolism of medication
- Impact of stress hormones
- NT circuitry alteration
Relapse

• When not treated to remission
  – Worsening course
  – More frequent
  – More chronic
  – Less linked with stressors

  – Kindling/Sensitization occurs
Adherence

• After 6 months of treatment adherence drops—50% remain faithful

• Multiple factors
  – Side affects
  – Cost
  – Stigma
  – Misinformation
Other Contributors

- Psychiatric comorbidity
- Medical comorbidity
- Substance abuse
- Sleep/circadian rhythms
Population Contributors

➢ Adolescence
➢ College age
➢ Pregnancy
➢ Late life
Management Strategies

**Pharm Algorithms:**
- STAR*D
- Texas Medication Algorithm Project for MDD (2008)
- Harvard Psychopharm Algorithm Project, 2018

**Psychotherapies:**
- CBT
- IPT
- CBASP
  – Cogn Behavioral Analysis System of Psychotherapy
Psychotherapy

• Comparable efficacy/ more preventative
• Effective in combination
  – Improved adherence
  – Mechanisms are synergistic
• Accessibility to well trained clinicians is critical
Pharmacological Approaches

Harvard Psychopharmacological Algorithm for Depression Project, 2018
Non-psychotic Unipolar Depression?

Yes

Is this an inpatient with severe melancholic depression?

Yes

Urgent need for ECT?

Yes

Try ECT

No

Tried one of these: sertraline, escitalopram or bupropion?

Yes

Try one: sertraline, escitalopram or bupropion

No

Try ECT
Pharmacogenomic Testing

DNA TESTING
Exercise
Nutrition/Gut Microbiota
Device Related Neuromodulation

*Electrical/magnetic currents to alter or modulate neurocircuitry*

- Non-convulsive, non-implantable stimulation
- Convulsive therapies
- Implantable stimulation
Non-convulsive Stimulation

- Repetitive Transcranial Magnetic Stimulation rTMS (FDA 2008)

- Transcranial Direct Stimulation tDCS
Convulsive Therapies
Electroconvulsive Therapy
Magnetic Seizure Therapy
Implantable Stimulation

- Vegas Nerve Stimulation (VNS) \textit{FDA 1998}
- Deep Brain Stimulation (DBS)
- Epidural Cortical Stimulation (ECS)
Research/Novel Therapeutic Targets

- Opioid neuropeptide system
- Histone deacetylase (HDAC)
- Melatonergic system
- Acetylcholine system
- Glutaminergic system
- Bioenergetics
- Intracellular signaling system
- Inflammatory system
- Indolamine Hallucinogens
Opiode System

- Narcotics (heroin, morphine, etc)
  - Addiction
  - Escalating doses

- Buprenorphine + Samidorphan (ALKS 5461)
  - Antidepressant effects
  - Non-addictive opiate modulator
Glutaminergic System

➢ Ketamine ("Sp. K")
  – Anesthetic-IV
  – antidepressant
• Targets NMDA receptor
• 70% response in 2 weeks/24 hr.
• Challenge
  – Short duration
  – Cost
  – Access/delivery
Indoleamine Hallucinogens

- Psilocybin (Magic Mushrooms)
- Lysergic acid diethylamide (LSD)
- 3,4-Methylenedioxymethamphetamine, (ecstasy/MDMA)
PET Scan Imaging
Treatment Principles

- Eval, labs, medication history
- Combine with psychotherapy
- Exercise/optimize nutrition
- Restart effective Rx—optimize
- SSRI
- Trial another type of ADP (SNRI, TCA, MAOI)
- Augment with SGA
• Combine two ADP from different classes
• Augment with
  – Lithium
  – Thyroid hormone
  – Psychostimulants
  – Omega-3s, Vit D, methylfolate
• Complete pharmacogenomic testing
• Consider Neuromodulation
• Consider ketamine, DBS, experimental tx
References

- Webb, C.A., Madhukar H. et al. Personalized prediction of antidepressant v. placebo response: evidence from the EMBARC study. Psychological Medicine, 2018; 1 DOI: 10.1017/S0033291718001708
Webpages

- https://www.managedcaremag.com/archives/2014/7/should-mental-health-patients-get-pharmacogenomic-testing
doi: 10.1097/01.pra.0000430504.16952.3e
- https://www.psychcongress.com/article/l-methylfolate-promising-therapy-treatment-resistant-depression