TREATMENT RESISTANT DEPRESSION

AMANDA FOCHT, MD
ACTING ASSISTANT PROFESSOR
DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES
UNIVERSITY OF WASHINGTON
MEDICAL DIRECTOR
OUTPATIENT PSYCHIATRY
UNIVERSITY OF WASHINGTON MEDICAL CENTER
OBJECTIVES

1. Understand the definitions of unipolar depression, dysthymia/persistent depressive disorder, treatment resistant depression and treatment refractory depression.
2. Understand the treatment strategies of switch and augmentation.
3. Recognize pharmacologic agents commonly used to in difficult to treat depression.
4. Become familiar with some of the risks and benefits of these agents.
5. Understand when to consider somatic therapies such as ECT and TMS.
6. Recognize the role of psychotherapy in treatment resistant and treatment refractory depression.
DEFINITIONS:

- Unipolar depression
- Dysthymia/persistent depressive d/o
- Treatment resistant depression
- Treatment refractory depression
UNIPOLAR DEPRESSION VS. BIPOLAR DEPRESSION—DSM 5

Unipolar depression

• Major depressive d/o
• By definition bipolar d/o has been ruled out and:
  • At least two weeks of symptoms with 5 or more of the following
  • Depressed mood or loss of pleasure is present
  • Weight change
  • Hypersomnia or insomnia
  • Fatigue, loss of energy
  • Feelings of worthlessness or guilt
  • Difficulty concentrating, indecisiveness
  • Recurrent thoughts of death, suicidal ideation
• Dysthymia/persistent depressive d/o

Bipolar disorder

• Bipolar I disorder
  – History of mania
  – Depressive episode not required to diagnose, but present in vast majority of cases
• Bipolar II disorder
  – At least one hypomanic and depressive episode
  – Depression is usually predominate
  – May be difficult to tease out history of hypomania
DYSTHYMIA/PERSISTENT DEPRESSIVE D/O

• DSM IV: dysthymic d/o and chronic major depressive d/o
• DSM 5: persistent depressive d/o
  – Depressed mood most of the time for at least two years
  – Also includes change in appetite, sleep, low energy or fatigue, low self-esteem, poor concentration and/or hopelessness
  – Major depressive d/o commonly co-occurring
TREATMENT RESISTANT DEPRESSION

- Depressive symptoms that do not respond to trials of two antidepressants
  - STAR*D (Sequenced Treatment Alternatives That Relieve Depression)
    - 4 sequential trials of antidepressants to nearly 4000 patient who presented with unipolar depression
    - Rates of remission for 1st and 2nd trial were comparable: 37% and 31%
    - Rates of remission for 3rd and 4th step in treatment: 14% and 13%

From: Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report

American Journal of Psychiatry
PHQ-9: HOW TO USE SCORES TO ASSESS THERAPEUTIC RESPONSE

• No response: improvement < 25%
• Partial response: improvement 25% to 49%
• Response: decrease greater than or equal to 50%
• Remission: score under 5

DIFFERENTIAL/PREDICTORS OF POOR RESPONSE

- Bipolar disorder
- Substance use disorders
- PTSD
- Personality disorder
- Treatment non-adherence
TREATMENT STRATEGIES

• How to administer an adequate 1st line trial:
  – Start at recommended starting dose, or smaller dose if that is not tolerable
  – Change every 1-2 weeks, or as tolerated
  – If no response at all after 4 weeks, consider going to the next step
  – Goal is recommended dose limit, unless remission is achieved prior to reaching this dose
  – It may take 6 to 12 weeks at target dose to achieve full benefit of trial
  – If reduction in symptoms is less than 25 % after 4-6 weeks, go to next step

• What’s the next step?
  – SWITCH
  – AUGMENT

SWITCH: WHAT TO CHOOSE NEXT

PRESENTED IN ORDER OF STRENGTH OF EVIDENCE:
Serotonin-norepinephrine reuptake inhibitors (SNRIs): venlafaxine, duloxetine
Other antidepressants: bupropion or mirtazapine
Tricyclics: imipramine or nortriptyline
Monoamine oxidase inhibitors (MAOIs): tranylcypromine or phenelzine

INDIVIDUAL AGENTS—SOME CONSIDERATIONS

• DOSE LIMITS
• TOLERABILITY VS. EASE OF TITRATION
• COMORBID ANXIETY
• HALF-LIFE—insert once per week fluoxetine
• DRUG SPECIFIC ADVANTAGES
  – BUPROPION—ADHD
  – DULOXETINE—PAIN
  – VENLAFAXINE—HOT FLASHES
  – MIRTAZAPINE—INSOMNIA
• SPECIFIC SIDE EFFECTS
TRICYCLICS AND MAOI—SOME CONSIDERATIONS

• TRICYCLICS:
  – Cardiotoxicity
  – Potentially lethal in overdose
  – Anticholinergic side effects

• MAOIs:
  – Potentially lethal drug-drug and drug-food interactions
  – Danger in overdose
  – Adverse effects
AUGMENT: WHAT ARE THE CHOICES?

- Second-generation antipsychotics
- Lithium
- Thyroid hormone
- A second antidepressant of a different class

ATYPICAL ANTIPSYCHOTICS—CONSIDERATIONS

• Efficacy of adjunctive antipsychotic treatment compared with placebo:
  – 31 v. 17 percent
  – Discontinuation due to adverse effects: 9 v. 2 percent

• Aripiprazole
• Quetiapine
• Risperidone
• Ziprasidone
ATYPICAL ANTIPSYCHOTIC CONSIDERATIONS

- **Aripiprazole (Abilify)**
  - Minimal risk of diabetes and hypercholesterolemia
  - May cause akathisia
  - Low risk of orthostatic hypotension
  - Little to no risk of anticholinergic side-effects

- **Quetiapine (Seroquel)**
  - Higher risk of both diabetes and hypercholesterolemia
  - Sedating
  - May cause orthostatic hypotension
  - Risk of anticholinergic side effects

- **Risperidone (Risperdal)**
  - Higher risk of diabetes
  - Sedating, but less than quetiapine
  - Risk of clinically significant prolactin elevation
  - Higher risk of extra pyramidal side-effects (EPS) and tardive dyskinesia (TD)
  - Lower risk of anticholinergic side effects than quetiapine

- **Ziprasidone (Geodon)**
  - Less evidence for efficacy compared to above
  - Low likelihood of diabetes and hypercholesterolemia
  - Low risk of EPS/TD, sedation, orthostatic hypotension and anticholinergic side effects

OTHER AUGMENTATION AGENTS

• Lithium
  – Has been used for augmentation since the 1960s
  – Risk of toxicity
  – Need for monitoring
  – Some evidence for decreased risk of suicide

• Thyroid hormone (T3)
  – In use since the 1960’s
  – Low quality evidence in support of use

• Addition of a second antidepressant
  – Bupropion and mirtazapine commonly used
  – Considerations: an MAOI plus SRI or tricyclic may cause serotonin syndrome or hypertensive crisis
  – Other interactions may occur based on metabolism, etc.

OTHER ADJUNCTIVE STRATEGIES

• SOME EVIDENCE:
  – Exercise
  – Omega-3 fatty acids
  – S-adenosyl methionine (SAMe)
  – Stimulants

• DRUGS WITH LITTLE TO NO BENEFIT
  – Buspirone
  – Folate
SOMATIC THERAPIES: ELECTRO-CONVULSIVE THERAPY (ECT)

• Superior efficacy when compared to medication in multiple trials
• Can be used as switch therapy or augmentation
• Significant side effects, burden to obtain, negative perception by patients, high relapse rate

SOMATIC THERAPIES: TRANSCRANIAL MAGNETIC STIMULATION

Repetitive transcranial magnetic stimulation

- Magnetic field generated is similar to that of MRI
- Better tolerated than ECT
- Anesthesia not required
- Induction of seizures not necessary for benefit
- Covered by some insurance, including Medicare

PSYCHOTHERAPY

• CAN BE A SWITCH OR AUGMENTATION STRATEGY

– EVIDENCE BASE:

• HOW IT MAY HELP

– CBT: DEPRESSION AND/OR COMORBIDITIES
– CPT/PE: TREAT UNDERLYING PTSD COMPONENT
– DBT: ADDRESS CONTRIBUTION OF MALADAPTIVE BEHAVIORS ASSOCIATED WITH BPD
– SUPPORTIVE: FLEXIBLE, CAN ADDRESS MANY DIFFERENT SYMPTOMS AT ONCE, NOT TIME LIMITED
– PSYCHODYNAMIC: CONSIDER WHEN SHORT-TERM THERAPIES HAVE NOT HELPED
TREATMENT REFRACTORY DEPRESSION

• Unipolar depression that has not responded to multiple therapeutic trials of treatment interventions
• Research definition:
  • Antidepressants: 3-6 trials of agents in multiple classes
  • Adjunctive medications: 2-4 trials with different agents
• At least one course of ECT
• At least one trial of psychotherapy
USUAL CARE FOR TREATMENT REFRACTORY

• Avoid aggressive, complex medication regimens (polypharmacy)
• Maintain regular visits
• In addition to psychotherapy and pharmacotherapy, psychoeducation about depression, family education and care-coordination with physical health providers is important
A CASE OR TWO

• DL--65 y/o man
  – Multiple drug trials
  – Not interested in somatic therapy
  – Depression getting in the way of medication adherence for physical health conditions

• KB—58 y/o woman
  – Multiple drug trials, cannot tolerate many medications
  – Co-morbid migraine
  – Profound fatigue
  – Concern about cognitive decline