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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

TREATMENT RESISTANT DEPRESSION

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project ECHO

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

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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 an 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-occuring

TREATMENT RESISTANT DEPRESSION

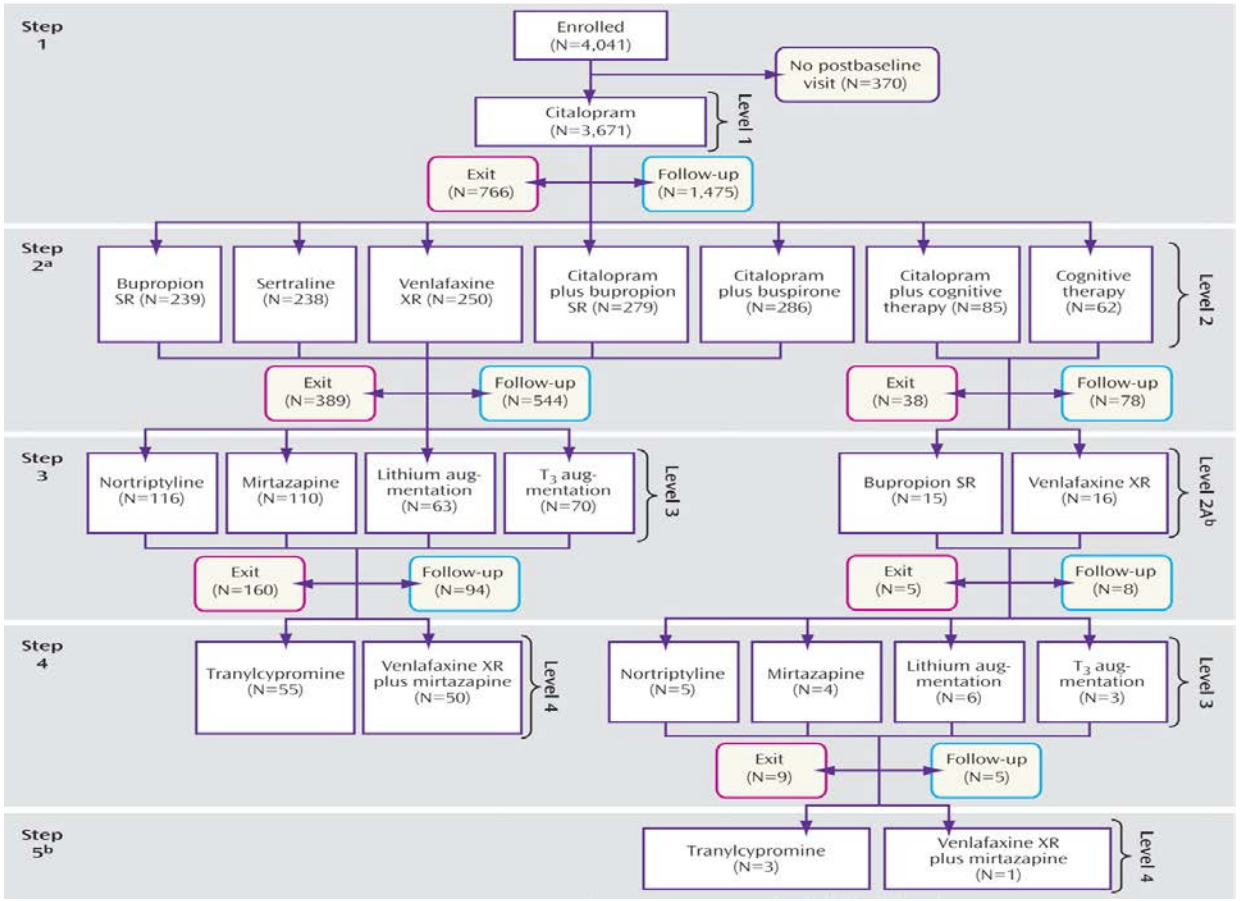
- Depressive symptoms that do not respond to trials of two antidepressants
  - STAR*D (Sequenced Treatment Alternatives That Relieve Depression)
    - 4 sequential trials of antidepressants to nearly 4000 patient who presented with unipolar depression
    - Rates of remission for 1st and 2nd trial were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

Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M Am J Psychiatry. 2006;163(11):1905.

THE AMERICAN JOURNAL OF PSYCHIATRY

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

Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. Spitzer RL, Kroenke K, Williams JB JAMA. 1999;282(18):1737.

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

Practice Guideline for the Treatment of Patients with Major Depressive Disorder, third edition. American Psychiatric Association. Am J Psychiatry. 2010;167 (supplement)(10):1.

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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

Partial response and nonresponse to antidepressant therapy: current approaches and treatment options. Hirschfeld RM, Montgomery SA, Aguglia E, Amore M, Delgado PL, Gastpar M, Hawley C, Kasper S, Linden M, Massana J, Mendlewicz J, Möller HJ, Nemeroff CB, Saiz J, Such P, Torta R, Versiani M

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

Managing partial response or nonresponse: switching, augmentation, and combination strategies for major depressive disorder. Papakostas GI. J Clin Psychiatry. 2009;70 Suppl 6:16-25.

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 akathesia
  - 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

Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Nelson JC, Papakostas GI. Am J Psychiatry. 2009;166(9):980.

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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.

A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. Nierenberg AA, Fava M, Trivedi MH, Wisniewski SR, Thase ME, McGrath PJ, Alpert JE, Warden D, Luther JF, Niederehe G, Lebowitz B, Shores-Wilson K, Rush AJ

Am J Psychiatry. 2006;163(9):1519.

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

Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. UK ECT Review Group. Lancet. 2003;361(9360):799.

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

Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder. Schutter DJ.Psychol Med. 2010;40(11):1789.

PSYCHOTHERAPY

- CAN BE A SWITCH OR AUGMENTATION STRATEGY
  - EVIDENCE BASE:
    - HOW IT MAY HELP
      - CBT: DEPRESSION AND/OR COMORBITIES
      - 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

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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