TREATMENT RESISTANT DEPRESSION

Anne Emmerich, MD
MGH Department of Psychiatry
Disclosure

• Anne Emmerich MD reports no personal or family financial conflict of interest related to the content of this session.
Session Goals

- Define treatment resistant depression.
- Review therapeutic options for patients whose depression is not responding to treatment.
- Describe role of psychiatric and neuropsychiatric co-morbidity in treatment failure.
CONTEXT
Depression

- Depressed mood most of the day, nearly every day.
- SIGECAPS – sleep, interest, guilty ruminations, energy, concentration, appetite, psychomotor, suicidal thoughts
- 5 or more sxs, 2 weeks or more, causing significant distress or impairment in functioning.
Persistent Depressive Disorder

- New term in DSM V
- Covers both chronic major depression and the old dx of dysthymia (depressed mood with only one or two sxs but more than 2 years)
- Pts/providers often think it is just personality; treatment often not adequate to prevent “double depression” episodes
U.S. Preventive Service Task Force, 2016

• “The USPSTF recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up.”

• “The USPSTF found convincing evidence that screening improves the accurate identification of adult patients with depression in primary care settings, including pregnant and postpartum women.”

(Siu, 2016)
Screening Tool - PHQ-2

• “Over past 2 weeks, how often have you felt down, depressed or hopeless?”

• “Over past 2 weeks, how often have you felt little pleasure or interest in doing things?”

• If pt answers “several days”, ask about suicidal thoughts and screen further with PHQ-9.
Treatment Resistant Depression

- No consensus definition
- Research study definition: 1 failed trial at 6 weeks.
- Insurance definition: 2-4 failed trials of meds before ECT/TMS.
- ICSI: “failure to achieve remission with an adequate trial of therapy and 3 different classes of antidepressants at adequate duration and dosage”
- Patient/Clinician definition: “I/my patient is not getting better”
WHAT ARE THE BASICS?
Anti-depressants

- Primary Care doctors write 2/3 of all antidepressant scripts.
- All antidepressants have side effects.
- Use the side effect profile of drug to patient’s advantage.
How to start

Start low, titrate, to diminish side effects and improve compliance.

Contact in 2 weeks (sooner for more severe depression) “I don’t expect you to be feeling better in 2 weeks but I do want to know how you are tolerating the medication”.
Set expectations

4-6 weeks for onset of action.

Response is not linear. “There will be a phase of good days and bad days before you feel truly well. This does not mean the medicine is not working or that you will not get better”.

Re-evaluate at 10-12 weeks.

DON’T LOSE FOCUS. Goal is to get to full dose and achieve remission.
Black Box Warning

• “Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of ..... or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.” (FDA)
Psychotherapy

• For more severe depression, evidence says meds plus therapy is better than either alone.
TREATMENT RESISTANT DEPRESSION

What questions should we ask?
4 questions

- Is there really a treatment failure?
- Is the lack of progress really due to depression?
- Has the patient had trials of medication from different categories?
- Nothing is working. What do I do now?
QUESTION #1
IS THERE REALLY A TREATMENT FAILURE?
CASE #1

• 48 yo male, school teacher, out of work 2 months using “vacation time” due to depression, now on FMLA x 1 month. Trigger was divorce and death of father within year prior to onset of symptoms. Sleeping poorly, eating mainly junk food, no interest in anything, finding it hard to be present for his children, not keeping up with household chores. One prior bout of depression in college following a break-up, resolved with 3 months of supportive therapy.

• No suicidal thoughts. No access to firearms. No psychosis. No alcohol or drugs.
Case #1 continued

- **Treatment to date:**
  - Sertraline 50 mg x 3 weeks, stopped due to severe nausea.
  - Remeron 30 mg x 3 weeks, stopped due to 12 lb weight gain and edema
  - Cymbalta 20 mg x 4 weeks – patient afraid to increase dose due having side effects with the two prior meds
  - 2 sessions with social worker in medical office in early weeks out of work. Pt has called multiple therapists but none are taking new pts.
Data shows:

- 40% of patients who begin an antidepressant discontinue it within a month
- Only 25% of patients receive even minimal follow-up, 75% below that
- Of patients who begin psychotherapy only half attend 4 or more sessions

Simon et al, JAMA, 292(8), 25 August 2004
Case #1 continued

Pt is running out of FMLA time. What to do next?

Treatment needs a “jump start”.

Refer patient to partial hospital program (9 am to 3 pm for 2-4 weeks).

Provides support for medication changes, therapy groups, team to work on “aftercare planning”.
Case #1 summary

- Many factors contribute to situation in which patient has not actually received treatment.
  - Side effects
  - Patient compliance (which can be impacted by depression),
  - Financial barriers
- Ancillary question is “what is the appropriate level of services” (treatment setting)
  - Outpatient
  - Home based
  - Partial hospital program
  - Day program
  - Inpatient
QUESTION #2

IS THE LACK OF PROGRESS REALLY DUE TO DEPRESSION?
Case #2

• 50 yo man, new to your practice.
• 2 years prior fell and injured his back working on a large construction site. Was told by doctor he could no longer work. Loss of role as provider for family, marriage suffered, felt ashamed.
• Two serious suicide attempts and psych hospitalizations.
• On initial evaluation in your office appears depressed, blunted, cries a bit. A quiet man, doesn’t say a lot. He is taking sertraline 50 mg per day.
• Currently not suicidal. No substances.
Case #2 continued

- Over the next 10 months you see the patient monthly.
- You increase his sertraline to 200 mg per day.
- You add bupropion 150 mg per day.
- You add aripiprazole 10 mg per day.

- Despite these, 10 months after first coming to your office the patient seems no different than the day you met him. He is a quiet man, answers questions briefly, doesn’t initiate conversation.
Case #2 continued

- You have been assuming the patient is a quiet man by nature.
- You have also thought maybe the fact English is not his first language is a factor.
Case #2 continued

• One day you ask more about the work related accident.

• You learn that patient hit his head but has never had neuropsychiatric testing. You send him for testing which reveals significant damage consistent with a head injury and consistent with his low verbal content, isolation, lack of initiating activities.

• You ask permission to have a family meeting. You tell patient and his family that testing shows head injury may be the primary problem. You refer him to a head injury clinic.
Case #2 continued

- Pt and family go for consultation but refuse further head injury services.

- 5 years later patient is living with siblings for several months at a time each and family shares making sure that someone is available to provide day structure for patient and bring him to appointments.

- He remains on antidepressant and daughter calls MD whenever she is concerned he is becoming more morose or is having any suicidal thoughts.
Case #2 summary:

• If treatment doesn’t seem to be working, don’t forget to re-examine the diagnosis.

• Is there a co-morbid condition that interferes with recovery or mimics the symptoms of depression?

• Inform patient/family of co-morbidities and appropriate treatment options for these.
Common comorbidities

- Substances
- Anxiety Disorders
- PTSD
- Personality Disorders
- Neuropsychiatric conditions
- Medical
Cognitive Behavioral Therapy (CBT)

Cognitive restructuring: changing thought patterns

Behavioral activation: overcome obstacles to participation in meaningful activities

Useful for patients with comorbid depression and anxiety disorders
Dialectical Behavioral Therapy (DBT)

“Emotional Skills Training”.

Developed by Marsha Linehan PhD, initially for tx of pts with borderline personality disorder.

Structured group setting, workbook, homework.

Useful in depression especially when there is chronic suicidal thinking, Axis II.
Comorbid Treatment

- **SSRI's**: PTSD, PMDD, OCD, bulimia, GAD, Panic D/O, Social Anxiety D/O, pain
- **Bupropion**: ADD/ADHD, smoking cessation, sexual dysfunction
- **SNRI**: PTSD, PMDD, OCD, GAD, Social Anxiety, pain
- **TCA**: diarrhea, urinary incontinence, sleep, diabetic neuropathy, ADD
QUESTION #3

HAS THE PATIENT HAD TRIALS OF MEDICATIONS FROM MULTIPLE CATEGORIES?
Case #3

• Your long term patient Mrs Smith, age 58, comes in with chief complaint of return of her depression since her son left for college 5 months ago. She has 3 children, the youngest is a junior in high school.

• She has struggled with depression for years, since the premature death of her parents in a car accident around the time she had her first child.

• She has had many trials of antidepressants, all prescribed by you. She has taken fluoxetine, sertraline, citalopram, fluvoxamine, bupropion. She is currently taking escitalopram (lexapro) 20 mg per day and lorazepam 1 mg at bedtime. She has seen a therapist for years but your sense is that the therapist does not challenge her much.
What do you do next?

- Mrs Smith appears to have had no trial of an SNRI medication.
  - You decide venlafaxine is too risky given her underlying hypertension and start her on duloxetine (cymbalta). You start at 20 mg and titrate to 80 mg per day and plan to re-evaluate 8 weeks later.
  - On return, she rates herself as 50% improved. She is having some mild nausea from the duloxetine which she feels is tolerable but she does not want to increase the dose.
  - She wonders about the medication she has seen on TV which her friend is taking.
Next Steps

• Good response at 6 weeks
  • First episode - continue 6-9 months, then attempt taper
  • Recurrent episodes – continue med long term

• Partial response at 6 weeks
  • increase dose as tolerated; combination therapy or augmentation

• No response or minimal response at 6 weeks
  • switch within category or change category (ie SSRI to SNRI)
Combination Therapy

• Two anti-depressants: from different categories to reduce risk of side effects and serotonin syndrome
  • SSRI/SNRI with Wellbutrin
  • SSRI with Trazodone
  • Venlafaxine/Duloxetine with Mirtazapine
Augmentation Therapy

• Adding a second agent that is not an antidepressant.

• STAR-D “do something”
Augmentation Strategies

- **Lithium** – old standard, works within two weeks, check TSH and creatinine, studies show reduction in risk of suicide.
- **Atypical neuroleptics** – risk of metabolic syndrome, watch weight, check glucose and lipid profile.
- **Aripiprazole** – quick onset of action, risk of TD.
- **Bupropion** – stimulating effect can help in patients who are feeling blunted by antidepressant that is otherwise working well.
- **Stimulants** – sometimes the only effective strategy for patients for whom typical antidepressants are not working.
- **Buspirone** – titrate to 30-60 mg per day, watch for GI sxs
Case #3 continued

• You offer Mrs Smith a trial of aripiprazole 2 mg and titrate over several weeks to 10 mg per day.

• She has a good response and 4 weeks later reports she is feeling 100% like herself again.

• At your quarterly to twice yearly visits, you check for any evidence of movement disorder and metabolic syndrome.
Case #3 summary

- There are a number of medication options for patients suffering from depression.
- If trials of SSRIs and SNRIs are not helping patient achieve 100% remission of symptoms, it is appropriate to offer augmentation therapies.
QUESTION #4

NOTHING I AM DOING IS WORKING.
WHAT DO I DO NOW?
Psychosomatic Therapies

• ECT (electroconvulsive therapy): 8-15 sessions, maintenance monthly therapy needed for some pts. Transient memory loss and H/As most common side effects.

• TMS (Transcranial Magnetic Stimulation): FDA approved, no anesthesia, approx 1 hour per day for 30 days.
Ketamine

• Increasing evidence for reduction of suicidality in patients with severe treatment refractory depression
• Requires specialized provider site that offers off-label highly monitored treatment or a clinical trial
Case #4

• 63 yo female with long h/o recurrent depression with psychosis. 6 lifetime episodes, always able to taper the anti-psychotic medication in between for at least a couple of years.

• Used to work in a store, stopped working in early 50s due to her illness.

• Lives with sister. Functional in her family. Loving aunt, babysits for her great nieces and nephews.

• Now presents with recurrence of depression, no obvious psychosis but anxious about being told she needs cataract surgery.
Case #4 continued

- Medication changes are made but do not help.
- Progressively declines over a number of months.
- Perseverates on her vision and her fear of having the surgery.
- Isolating, avoiding fun family gatherings, not babysitting.
- Appetite severely impaired, sister is spoon feeding her.
- Not suicidal. Refuses psychiatric hospitalization, doesn’t feel it will help.
Case #4

- Primary care doctor and psychiatrist confer. PCP recommends medical admission to patient.
- Once on medical floor, ECT team is consulted and persuade patient and her family that ECT is the treatment of choice.
- 6 months later she is fully recovered and has successful cataract surgery.
- 7 years later she remains well.
Case #4 summary

- ECT, TMS, and Ketamine therapies offer hope for patients who are failing to show response to antidepressant medications.
- The support of the primary care physician can make a difference.
Conclusions

Treatment of depression can be complicated by a number of factors including:

- Medication intolerance
- Medication ineffectiveness
- Psychiatric co-morbidities
- Lack of patient engagement

Clinicians have access to a number of tools including:

- Multiple level of service options
- Multiple forms of psychotherapy
- Multiple augmentation strategies
- Psychosomatic therapies and ketamine
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