Treatment Strategies for Depression

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Disclosure
I am a minor stockholder in Pfizer
– maker of Zoloft/sertraline

Objectives
• Discuss the differential diagnosis of “depression”
• Consider cultural aspects in depression
• Optimally utilize psychosocial & pharmacologic treatments for depression, including
  – Efficacy
  – Tolerability/quality of life
  – Side effect profile
  – Effective prescribing – MD as “drug delivery system”

Diagnosing “Depression” - 1

Major Depressive Disorder (MDD)
MDD—Diagnostic Criteria

Five or more of the following symptoms are present most of the day, nearly every day, during a period of at least 2 consecutive weeks

- 1. Depressed mood
- 2. Loss of interest or pleasure in all, or almost all, usual activities (i.e., anhedonia)
- 3. Significant weight loss or weight gain
- 4. Insomnia or hypersomnia
- 5. Psychomotor agitation or retardation
- 6. Fatigue or loss of energy
- 7. Feelings of worthlessness or excessive/inappropriate guilt
- 8. Diminished ability to think or concentrate or indecisiveness
- 9. Recurrent thoughts of death or suicide

MDD is #1!!

- According to the WHO, MDD is #1 cause of disability in the world.

- Depression & disability have a reciprocal relationship, each increasing the risk for the other

Depression Is Bad for Your Health

Over the life span, depression is as unhealthy as smoking a pack of cigarettes a day!

According to the WHO, MDD is #1 cause of disability in the world.

- Depression & disability have a reciprocal relationship, each increasing the risk for the other

MDD is

- Under-diagnosed
  Large numbers do not present for treatment
  Large percentage of dx are missed

- Usually under-treated
  – Psychotherapy is particularly underutilized
Major Depressive Disorder

Culture Diversity

• Prevalence in women twice that of men
• No simple linkage between specific cultures & likelihood of specific sx
• In many cultures, somatic sx are the presenting complaint
• Race & ethnicity do not influence AD response

Depression—Somatic Presentation

• Overall, 69% of depressed patients (range 45%-95%; \(P=0.002\)) present with somatic complaints that can complicate diagnosis, such as
  – Headaches
  – Weakness
  – Constipation
  • -- Back pain
  • -- Joint pain
  • -- Abdominal pain

Simon 1999; Depression in Primary Care 1 (AHCPR), 1993.

Diagnosing “Depression” - 1

• Major Depressive Disorder (MDD)
• Blah’s - the ups and downs of everyday life
• Persistent Depressive Disorder (Dysthymia)
• Disruptive Mood Dysregulation Disorder
• Premenstrual Dysphoric Disorder
• Other Specified Depressive Disorder

Diagnosing “Depression” - 2

• Bipolar I
  – Major Depressive Episodes & Manic Episodes
• Bipolar II Disorder
  – Major Depressive Episodes & Hypomanic Episodes
• Cyclothymic Disorder
## Diagnosing “Depression” - 3

- Substance/Medication-Induced Disorders
- Mood Disorders Due to Another Medical Condition

Whenever the clinical presentation looks psychiatric, be certain to **FIRST** consider these!

### Substance-Induced Disorders

- **Illegal** – stimulant withdrawal
- **Legal**
  - Non-Rx – etoh
  - Rx - Beta blockers, sedative/hypnotics, steroids, cimetidine, anti-Parkinson drugs, methyldopa, clonidine, resperine, progesterone, propoxphene, interferon

### Depression Due to Another Medical Condition

- Viral infections
- Endocrinopathies (thyroid, parathyroid)
- B-12 deficiency
- Cancer - lymphoma, pancreatic
- Stroke - esp head of the caudate
- Dementia
- Etc

### Diagnosing “Depression” - 3

- Substance/Medication-Induced Disorders
- Mood Disorders Due to Another Medical Condition
- Unspecified Mood Disorders
- Personality Disorders
- Adjustment Disorders
- Bereavement
Grief & Depression

- **Similarities**
  - Sadness, tearfulness, loss of appetite, sleep disturbance, & diminished interest in the world

- **Differences**
  - Mood disturbance - waves vs. pervasive
  - Shame & guilt - circumscribed vs. pervasive
  - Time-limited perspective vs. hopelessness
  - Degree of functional impairment
  - Suicidality

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Grief & Depression

- One third of those manifesting a depressive syndrome within a few months of loss will continue to be depressed 1 year later

- Prevalence of MDD continues to increase during 2nd year of bereavement.

- These depressions carry risk of suicide, medical morbidity, and psychosocial disability

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Grief & Depression

- Even in bereavement, depressive symptoms may herald disabling & life threatening illness

- Idea that medication or psychotherapy will impede the grief process is old & unsupported

- Effective treatment of depression facilitates grieving

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Grief & Depression

**DEPRESSIVE SYMPTONS ALWAYS REQUIRE CAREFULL ASSESSMENT!!!!!!**

Screen for & **diagnose** Major Depressive Disorder when it exists

**Treat**

Medication - Standard antidepressants & dosages

Psychotherapy
Depression Evaluation

- Assess medical & neurological status
  - Including contributing substances/medications
- Assess psychological issues & concerns
  - Including psychiatric dx
- Assess functional impairment
- Assess psychosocial stressors & supports

Treat Medical & Psychiatric!!

Since medical illness & psychological illnesses interact & each worsen the other, it is vital to interrupt this negative spiral by effectively treating **BOTH** medical & psychiatric issues to get good pt outcomes.

Effective treatment enhances quality of life & lowers health care costs.

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Depression Treatment Goals

- Remission of Depression
- Reduction in risk of relapse/recurrence
- Improvement of cognitive & functional status
- Development of skills & supports for coping with handicaps & psychosocial adversity

Not only do I want pts to recover from depression, I want their lives to be BETTER than before they became depressed.

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Many Psychiatric Treatments

Many different modalities are available & important in treating psychiatric illness.
### Suicide

**Preventing suicide**

*Ask about it!!!*

- 8th Leading cause of death in USA
- Significant percentage of persons who kill themselves have seen primary care MD in weeks prior to their suicide
  - More than 1/3 in week preceding death

**Psychiatric Treatments for Major Depressive Disorder**

- Hospitalization
- ECT (Electroconvulsive Therapy)
- Psychotherapy
  - Supportive, Cognitive-Behavioral, Interpersonal, (Brief) Psychodynamic Therapy, Family
- Exercise
- Phototherapy (Light Therapy)
  - Seasonal Affective Disorder, ?other depression
- Pharmacotherapy

*Combining treatments usually indicated*

**Ask about it!!!**

- Have you had thoughts…
  - That life is not worth living?
  - Of ending your life?
- For a pt with difficulty directly engaging, asking about meaning of suicide &/or life after death may open a discussion
- Asking demonstrates concern & caring
Psychotherapy
The evidence for & importance of psychotherapy in the treatment of psychiatric illness can not be overstated.

**Good psychotherapy is a first-line treatment!**
Psychotherapy may be more effective than meds.
Good psychotherapy can reduce need for meds, or avoid the need for meds altogether.
Good psychotherapy has longer-lasting effects than meds.

What Kind of Psychotherapy?
More important than the “type” of psychotherapy is the _quality_ of the psychotherapy.

Good psychotherapy is not always easy to find.
There is often an element of “fit” twixt therapist & patient

Good psychotherapy is not always easy or quick.
Some problems are entrenched & difficult.

Antidepressant (AD) Usefulness
While AD are potentially useful in many D/o, the level of response can vary widely, even within the same DSM diagnostic category!

Let’s briefly consider.

Bio-Psycho-Social Treatment
Humans are bio-psycho-social (& spiritual) beings

_AD’s are a biological treatment that do little for the other elements of human illness & distress!_
Why aren’t AD more effective?

If we only treat the biological, we don’t address other parts of the person.

Not addressing the psychological, social (& spiritual) components of the depression promotes inadequate treatment response & treatment failure.

Bio-psycho-social treatment is optimal, & often essential!

Do Alcohol & Marijuana undermine AD effectiveness?

While data is spotty, I have seen clinically that using alcohol &/or drugs can reduce the effectiveness of AD.

Do Antidepressants Cause Suicide?

- In 2004, FDA requires a warning about potential increased suicidality with antidepressants
- Warning based on studies that found
  - Increased verbalization of suicidal thinking with meds
  - And no suicides

NB: Similar concerns about suicide were raised and disproven when fluoxetine (Prozac) first became available.
Antidepressants & Suicide

- Since the mandated suicidality warning
  - Decreased anti-depressant use in adolescents
  - Increased suicides in adolescents

While decreased antidepressant use has not been shown to cause the increased suicides, many believe this to be the case.

Antidepressants & Suicide

- Some experience agitation as an initial side effect medication
  - Agitation = increased dysphoria/suffering/pain
  - ?cause of increased “suicidality”

  - Such agitation usually decreases & resolves early
  - Agitation avoided/minimized by reducing the dose, or using a lower starting dose for a few days

Antidepressants & Suicide

Suicidality & suicide are part of depressive illness

Patients struggling with a potentially lethal illness deserve careful monitoring

whether or not an AD is prescribed

Which Antidepressant to Use?

Are all antidepressants equally efficacious?

Clinically in 2016
For Depressive Disorders

Yes!

Choice of AD not based on efficacy!
Other factors guide AD choice.
Selective Serotonin Re-uptake Inhibitors (SSRIs)

- escitalopram - Lexapro
- citalopram - Celexa
- sertraline - Zoloft
- fluoxetine - Prozac
- fluvoxamine - Luvox
- paroxetine - Paxil
- vortioxetine - Brintellix

SSRIs are generally safe & effective Rx. SSRIs have the very significant & clinically useful benefit of treating anxiety, which is often present in Depressive Disorders.

SSRIs are a good first choice for many Anxiety Disorders

SSRI common side effects
- Nausea, constipation, diarrhea, headache
  - Dose dependent; generally resolve in a few days
- Agitation/shakiness/“akathisia”
  - Dose dependent; generally resolve in a few days
- Dysphoria, including emotional numbness
- Sexual
  - Difficulties with erection/vaginal lubrication
  - Impairment of orgasm (both sexes)
  - Changes in libido/sexual desire
- ?wgt gain – perhaps 1 in 5 pts gain wgt
- Inappropriate secretion of ADH -> hyponatremia

Citalopram & sertraline
- least possibility of drug-drug interactions
- Least side effects, mild withdrawal syndrome

Paroxetine
- Increased chance of (bad) withdrawal syndrome
- Use correlated birth defects & breast cancer

Fluoxetine
- Longer ½ life may be a benefit for poor adherence
- Longer ½ life is why Prozac weekly was marketed

Fluvoxamine - sedating
**Depression: Pharmacology - 2**

- **SNRI’s**
  - Serotonin Norepinephrine Re-uptake Inhibitors
    - venlafaxine (Effexor)
    - duloxetine (Cymbalta)
    - desvenlafaxine (Pristiq)
    - levomilnacipran (Fetzima)

- **Side effect profile similar to SSRI with**
  - Increased chance of nausea
  - Possible increase in diastolic BP

**Depression: Pharmacology - 3**

- **SSRI + Dopamine**
  - lurasidone (Latuda)

- **Used in Bipolar Depression**
  - Maintenance therapy
  - Adjunct therapy with lithium or valproate

- **Same SSRI side effect profile**

- **Dopaminergic action confers additional risk**
  - Metabolic syndrome
  - Neuroleptic malignant syndrome
  - Tardive dyskinesia

**Depression: Pharmacology - 4**

- **bupropion** (Wellbutrin)
  - (not buspirone!)
  - NOT AN ANXIOLYTIC
  - Decreased desire to smoke
    - Consider using in pt who smokes
  - Same medicine as Zyban
    - Beware overdosing a pt with a double dose of same med!!

- **Side effect profile**
  - More activating: a positive &/or negative
    - Including increased anxiety & sleep disturbance
  - Only antidepressant generally free of sexual se

**Depression: Pharmacology - 5**

- **mirtazapine** (Remeron)
  - Sedating
    - Has seen wide use as a hypnotic
  - Increased appetite leading to wgt gain

- **trazodone** (Desyrel)
  - Very sedating
    - Limits use as antidepressant
  - Most widely prescribed hypnotic in USA
Depression: Pharmacology - 6

• nefazadone (Serzone)
  – Addresses depression, anxiety, & insomnia
  – Rarely used
    • Severe liver damage occurs once in every 250,000 to 300,000 patient-years of use
• tricyclics (eg, Elavil), tetracyclics (eg, Asendin)
  – Effective antidepressants & anxiolytics
  – Dirty drugs with many troublesome se
    • Inc low Lethal Dose 50
      – People have successfully killed themselves by taking 1 week of pills
  – Use for non-psychiatric indications

Bipolar: Pharmacology

• Mood stabilizers for bipolar illness
  – lithium, valproic acid, carbamazepine
  – lurasidone, lamotrigine – bipolar depression
    • Use of other AD carry (small) risk of switch to mania
  – atypical antipsychotics

  • Bipolar treatment can be complicated
    – Some studies suggest value of single provider for medication & therapy

Depression: Pharmacology - 7

• monoamine oxidase inhibitors (MAOI)
  – Tranylcypromine (Parnate); Phenelzine (Nardil)
  – selegine patch (Emsam)
• Effective AD and anxiolytic
  – Motivated pts can safely use
• Proven more effective in Atypical Depression
  – Hyperphagia, hypersomnia, leaden paralysis, rejection sensitivity

Which Antidepressant to Use?

Recommendations for initial therapy
given equal efficacy:

• Patient’s thoughts & feelings about medication
• Side effects, price, prior hx, family hx, drug-drug interactions
**Initial Therapy Recommendations**

- SSRI – Safe, well tolerated, target anxiety
  - Sertraline, citalopram*
  - *caution with doses over 40 mg - QT prolongation
  - Fluoxetine – long ½ life can help when adherence is poor
- Bupropion – Can increase energy, less desire for cigarettes, preserves sexual functioning, help for ADHD
  - Not buspirone
- Mirtazapine – cachectic pt with insomnia

**How to Utilize Antidepressants**

- Spend a few minutes discussing the potential AND realistic benefits of the drug
- Never promise more than the drug can deliver – “I can’t guarantee anything, &…”
  - I think this medicine is worth a try
  - I am (very) hopeful that…
- Inform the patient of the time to expected response

**How to Utilize Antidepressants**

- Spend a few minutes discussing the most common side effects
  - A prepared pt is prepared
  - You look like you know what you are doing
  - Gives the patient - & you - a chance to deal with ambivalence, reluctance, & stigma
  - Adherence to med is greatly improved

**Prescribing Antidepressants**

You as the drug “delivery system” are crucial
<table>
<thead>
<tr>
<th>Krupnik et. al., 1996</th>
<th>Acquiescence</th>
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<tbody>
<tr>
<td>Dr-Pt alliance is key outcome factor</td>
<td>Initial placebo response</td>
</tr>
<tr>
<td>Alliance is directly correlated with treatment response</td>
<td>Subsequent nocebo response</td>
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<tr>
<td>Alliance is stronger determinant of outcome than drug condition.</td>
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<tr>
<td>Alliance is NOT the same as compliance</td>
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<th>McKay, et. al., 2006</th>
<th>Bingel, et. al., 2014</th>
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<tr>
<td>Physician effects accounted for greater outcome variability than medication condition</td>
<td>Negative expectations promote nocebo response</td>
</tr>
<tr>
<td>Top 1/3 of Psychiatrists got better outcome with placebo than bottom third got with active drug</td>
<td></td>
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Discussing Side Effects

“If you go on the web, you can find all kinds of horrible & scary things. I can’t promise you that such terrible things won’t happen to you. I can to tell you what I (& my colleagues) find in actual clinical experience. We don’t see these horrible things.”

Discussing Side Effects

“Since everyone is an individual, the only way to know what – if any – side effects you will have is by trying the medication.
And if something bad would happen, what do you think we would do?
Stop medicine & fix the problem!!!”

Discussing Side Effects

“So you will be prepared, I want to tell you about the most common se that we actually see in pts taking this medication.”
List the most common side effects.

Discussing Side Effects

“What questions do you have?
Should we prescribe this medicine for you?”

“If you experience something else that you think might be a se of the medicine, I want you to call promptly so we can investigate.
How to Utilize Antidepressants

- Inform the pt that the correct dose for them is unknown & that you will work together to find & maintain an optimal dose

- Start at the lowest end of the dosage range as detailed by manufacturer (PDR)
  - In elderly, consider starting even lower – ¼, ½ of low PDR

- For those particularly fearful, anxious, or sensitive, start at a lower dose for 3-4 days
  - “So your body will get used to the medicine.”

REMEMBER

You

*as the drug “delivery system”*

are vital

How to Utilize Antidepressants

Time spent “up front” on these issues enhances adherence & successful treatment

Antidepressants Follow-up

**Encourage pt to call prn**

- **1 week** - check patient and treatment
  - This can be via phone call, though office more effective

- **Follow about q 2 weeks till stable**
  - In office until you “know” the patient
  - Assess clinical picture
  - Level of medication response
Antidepressants Follow-up

• Once stable, may slowly increase time between visits upwards from 2 weeks

• Patients who have been very stable for a long time can be seen q 3-4 months

• An office visit can be treatment in and of itself

Adjusting Antidepressants

When response is inadequate, consider

• Dose increase
• Switch medication
• Augment

Improvement at any given dose likely to continue for 4-6 weeks

Pharmacologic strategies for Rx resistant MDD - 1

**Dose increase**

• All Antidepressants have a dosage range
• Adequate dose for Adequate Duration
  – Adequate trial is defined 4-6 weeks
• Some people require doses above PDR limits
  – Ultra-rapid metabolizers
  – Document rationale
• Check compliance/adherence

Pharmacologic strategies for Rx resistant MDD - 2

**Switching Medications**

• Same class
  – E.g. SSRI -> SSRI

• Different class
  – SSRI -> bupropion, SNRI or mirtazapine, MOAI, TCA, Nefazadone
Pharmacologic strategies for Rx resistant MDD - 3

**Augmentation**

- Add bupropion
- Add buspirone
- Add lithium or T3 (triiodothyronine)
- Add atypical antipsychotic
- (Add psychotherapy)

**How Long to Treat with Antidepressant?**

**PHASE 1: Acute Phase of Treatment**
- Remission
- Recovery

**PHASE 2: Continuation Phase of Treatment**
- Maintenance
- Remission
- Recovery

**PHASE 3: Maintenance Phase of Treatment**
- Normalcy

**IMPORTANT NOTE!**

In MDD, Remission & Recovery are NOT necessarily the same.

Because the pt appears well, remission can look like recovery, but the MDD continues “underneath” until the depressive episode runs its course (6-9 months).

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*Agency for Health Care Policy and Research currently known as the Agency for Healthcare Research and Quality (AHRQ), an agency within the US Department of Health and Human Services.

Kupfer 1991, Depression in Primary Care: 2 (AHCPR) 1993.*
How Long to Treat with Antidepressant?

In MDD, treatment must be continued for a minimum of 6 to 9 months after remission to avoid relapse.

How to D/C Antidepressants?

Wean over several months.

Depression Summary

- The label “depression” describes multiple illnesses with many etiologies.
- Depression is common & deleterious.
- Depression is under recognized.
- Even when recognized, depression is undertreated.
- Bio-psycho-social treatments provide the best chance for successful treatment of depression.
- Psychotherapy is a first-line treatment option.

Summary

- AD are a generally safe & effective treatment.
- Choice of AD is guided by
  - Pt psychology (thoughts, feelings, preferences)
  - Prior response (pt & family)
  - Side effect profile
  - Cost
  - Drug – drug interactions.
Questions????