Treating Geriatric Depression

Benjamin S. Alderfer, M.D.
Medical Director
Geriatric Psychiatry Unit
Porter Adventist Hospital

Overview

1. Why treating depression matters
2. Utilizing depression screens
3. Diagnosing depression accurately
4. How to make medication choices
Depression

• In a given year, 18.8 million American adults (9.5% of adults) will have a depressive illness
• 6.7% of U.S. adults experienced a major depressive episode in the past 12 months
• Lifetime MDD in women (11.7%) > men (5.6%)
• 20% ≥ 55 years have some mental health issue
  – Depression most prevalent for elderly

http://www.cdc.gov/workplacehealthpromotion/implementation/topics/depression.html

The Cost of Depression

• 80% of depressed report functional impairment
  – 27% report serious difficulties at work & home
• Nationally < 25% of persons experiencing an episode of depression during a 12-month period received appropriate treatment
• Only 29% of depressed pts reported contacting a mental health professional in the past year
  – Of the severely depression, only 39% contacted

http://www.cdc.gov/mentalhealth/basics/burden.htm
The (Financial) Cost of Depression

• Major depression is currently the first (or second) leading cause of disability in the U.S.
• In 2004, unipolar depression was 3rd cause of disease burden in world (WHO)
  – In “eighth place in low-income countries, but at first place in middle- and high-income countries”
• By 2020 it is projected to be #1 worldwide
• Annual U.S. $ cost of depression is ~$144 billion (treatment & lost productivity)

Mental Health Quality Enhancement Research Initiative (MH-QUERI), Strategic Plan. MHQUERI Center. 11/06, p. 6.

Geriatric Depression Prevalence

• Few large population-based studies
  – Many studies exclude those with comorbid medical or psychiatric disorders or those living in facilities
• 10-20% of adults older than 65
  – lower among community-dwelling older adults
  – higher among those in nursing homes
• Women > men (10.4% vs. 6.5%)
• Geriatric depression is undertreated & associated with functional disability, comorbid medical issues, and social isolation
Sequelae of Depression

• Depression in later life directly relates to broader health (psychiatric and physical well-being)
• Advanced age can mask vulnerability to a cascade of psychiatric & physical problems
  – A single psychiatric or physical problem can trigger
• Reveals the interrelatedness of:
  – Psychiatric issues
  – Decline in functioning (↑ disability)
  – Medical comorbidity
  – Quality of life

Depression as a Correlate of Adverse Health Behaviors

• Depression as disease AND associated with behaviors linked to other chronic diseases
• Difficult to access cause vs. effect, but association clear:
  – Smoking
  – Alcohol consumption
  – Physical inactivity
  – Sleep disturbance

http://www.cdc.gov/mentalhealth/basics/mental-illness/depression.htm
Depression is Costly and Debilitating

• Depression can adversely affect the course and outcome of common chronic conditions:
  – Arthritis
  – Asthma
  – Cardiovascular disease
  – Cancer
  – Diabetes
  – Obesity

http://www.cdc.gov/features/dsdepression

Sequelae of Depression

• Depression has a similar, and perhaps stronger, impact on disability than chronic illness
  – The reverse is also true, that chronic illness and disability predict the onset and persistence of depression
• Shorter-term outcomes of depression can be social & physical disabilities
• Longer term consequence can be death
Depression in Primary Care
• At least 10% of all primary care office visits are depression-related
• PCPs provide nearly half the outpatient care for depressed patients
• PCPs log approximately as many outpatient visits for depression as psychiatrists do
• Medical comorbidity is especially common in primary care settings
• When to refer to a psychiatrist is not clear

Treating Depression in Primary Care
• Depression can be treated successfully by PCPs under “real-world” conditions (STAR*D)
• The particular drug or drugs used are not as important as following a rational plan:
  1. Give antidepressant medications in adequate doses and for adequate duration
  2. Monitoring the patient’s symptoms and side effects and adjust the regimen accordingly
  3. Switch or augment appropriately
Use Depression Screens

- Geriatric Depression Scale (GDS) self-rated
  - high sensitivity (82-97%) & specificity (75-94%)
- Hamilton Rating Scale for Depression (HAM-D) is interviewer-administered
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Cornell Scale for Depression in Dementia (CSDD)

Geriatric Depression Scale (GDS)

1. Are you basically satisfied with your life? Yes/No (No)
2. Have you dropped many of your activities and interests? Yes/No (Yes)
3. Do you feel your life is empty? Yes/No (Yes)
4. Do you often get bored? Yes/No (Yes)
5. Are you in good spirits most of the time? Yes/No (No)
6. Are you afraid something bad is going to happen to you? Yes/No (Yes)
7. Do you feel happy most of the time? Yes/No (No)
8. Do you often feel helpless? Yes/No (Yes)
9. Do you prefer to stay at home, rather than going out and doing new things? Yes/No (Yes)
10. Do you feel you have more problems with your memory than most? Yes/No (Yes)
11. Do you think it is wonderful to be alive now? Yes/No (No)
12. Do you feel pretty worthless the way you are? Yes/No (Yes)
13. Do you feel full of energy? Yes/No (No)
14. Do you feel that your situation is hopeless? Yes/No (Yes)
15. Do you think most people are better off (in their lives) than you are? Yes/No (Yes)

Questions 1, 2, 6 and 7 make up the 4-item version.
Questions 1, 4, 8, 9 and 12 make up the 5-item version.
The answers shown in parentheses indicate possible depression.
Possible cut-offs: ≥5 for the 15-item version; ≥2 for the 4-item and 5-item versions.
Brief Depression Screening

For an even briefer screen, ask your patients these 2 questions:

1. Over the past month, have you felt down, depressed, or hopeless?
2. Over the past month, have you felt little interest or pleasure in doing things?

→ Patients who answer Yes may need more in-depth screening and clinical assessment


Criteria for Major Depression

≥ 5 for ≥ 2 weeks (#1 or #2 must be present):

1. depressed mood
2. anhedonia – loss of interest or pleasure
3. change in appetite
4. sleep disturbance
5. psychomotor retardation or agitation
6. decreased energy
7. feeling of worthlessness or inappropriate guilt
8. diminished ability to think or concentrate
9. recurrent thoughts of death or suicidal ideation

*causing marked distress/impairment in social/occupational functioning
*not caused by medical problem or substance
Depression in the Elderly: Different

- Reduced complaint of sadness
  - hypochondriasis and somatic concerns instead
- Poor subjective memory
- Late-onset neurotic symptoms (marked anxiety, obsessive-compulsive or hysterical symptoms)
- Apathy and poor motivation
- “Medical” or psychiatric (or both)?
  - Anorexia
  - Weight loss
  - Reduced energy

Suicide in the Elderly

- Suicide is twice as frequent as in the general population
  - fewer attempts but increased lethality
- Severity of depression is strongly correlated with suicidal ideation
“Minor Depression”

• Subsyndromal depression (similar to dysthymia)
• In older adults, minor depression is associated with significant functional disability
  – Progresses to major depression (MDD) in 25% of cases over 2 years
  – Old-old may have longer prodromal periods (3 years) prior to onset of MDD
• Should be treated when functionally impairing

Differentiating MDD from …?

• Two important clinical states to differentiate from depression
• Important because there are significant treatment implications
  1. Apathy
  2. Major depression with psychotic features
Apathy

• Apathy is defined as a state of decreased goal-directed cognition, behavior, & emotion, resulting from diminished motivation or volition
• It exists on a spectrum between mild decreased motivation (least severe) and akinetic mutism (most severe)
• Much more common in elderly

What is Motivation?

• Refers to the intrinsic drive of a system to produce goal-directed:
  1. Cognition
     • Using basic & complex cognitive processes
  2. Emotion
     • Generating emotional responses and using social intelligence
  3. Behavior
     • Putting cognition and emotion into action
Decreased Motivation

- Dopaminergic and glutamatergic function are important in the normal system
- Serotonergic augmentation (i.e. treatment with SSRIs) will predictably worsen diminished motivation or the apathy syndrome
  - distinguishing apathy from depression is critical to selecting the proper treatment
## Emotional Disorders

<table>
<thead>
<tr>
<th>MOOD</th>
<th>Production Excess</th>
<th>Production Deficit</th>
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<tbody>
<tr>
<td>Positive → Mania</td>
<td></td>
<td>Negative → Apathy</td>
</tr>
<tr>
<td>Negative → Depression</td>
<td></td>
<td>Positive → Placidity</td>
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<table>
<thead>
<tr>
<th>AFFECT</th>
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<tbody>
<tr>
<td>Negative</td>
<td>Essential Crying</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>Pathologic Crying</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Witzelsücht</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pathologic Laughter</td>
<td></td>
</tr>
</tbody>
</table>

### Disorders of Mood

- The disorders to which these sustained disturbances of emotion (mood episodes) contribute are by definition mood disorders, not affective disorders
  - No DSM IV diagnoses for affective disorders

- Mood episode-related changes in cognition, behavior, and/or physical (neurovegetative) functions are required features of these disorders

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Depression: Cardinal Features

- Remember, depression is primarily a disorder of **depressed mood** (i.e. increased sadness)
- Does your patient have increased sadness?
- Does your patient have less ability to enjoy things?
- If your patient meets diagnostic criteria for depression (checklist style), is there another diagnosis that better explains the signs and symptoms?

Depression: Key Diagnostic Questions

- If the patient endorses “depression,” what does he or she mean by this term?
- Instead, is the patient **persistently and excessively** sad, downhearted, or blue?
  - Emphasize persistent over transient sadness
  - Emphasize psychological over neurovegetative symptoms
  - Emphasize depressed mood over apathy
Apathy Scales

1. Marin’s Apathy Scale (1991)
2. Starkstein et al. (1992)
3. Neuropsychiatric Inventory (1994)
4. Dementia Apathy Interview and Rating (DAIR)
5. The Apathy Inventory (2002)

Treatment of Apathy

1. Remove potentially offending agents
   • Medications that ↑5HT or ↓DA
2. Stimulants (Ritalin, Adderall, Vyvanse)
3. Dopaminergic medications (ropinirole, pramipexole, bromocriptine)
4. Cholinesterase inhibitors
5. Bupropion
Psychotic Depression

• Severe form of depression in which depression drives psychotic symptoms
• ~15% of depressions develop into psychotic depressions
• In young person, often thought of as a harbinger of a bipolar spectrum disorder
• A more typical story is depression in a ≥ 50 y/o with agitation, delusional guilt, weight loss, hypochondriacal preoccupations, & EMA

Psychotic Depression: Treatment

• The treatment algorithm is quite different in psychotic depression
• Traditional teaching is responds:
  – poorly to antidepressants alone,
  – slightly better to antipsychotics alone, and
  – very well to combo treatment
• Both TMAP & APA treatment guidelines for depression recommend AD + AP 1st line (or ECT 1st if psychosis dangerous b/c of faster response time) (Literature is murky)
How to choose a first-line agent

• Make a neurochemically-informed choice
• What are the patient’s primary depressive symptoms?
• Do those symptoms fit most or best into a dysregulation of 5HT, NE, or DA?
• Does your patient have secondary or associated psychiatric or medical symptoms that suggest you consider one class or mechanism of action AD?
  – sleep disruption, pain, anxiety, etc.

General Guidelines for Antidepressant Use

• Selection is based on symptoms, past history of a response, side effect profile and coexisting medical conditions and/or psychiatric conditions/symptoms
• There is often a delay of 2-6 weeks after initiation/therapeutic dose achieved before full response
• If NO improvement is seen after a trial of adequate length (4-12 weeks) and adequate dose, switch to a different medication
• If partial response, augment with another agent
Antidepressants in the Elderly

• SSRIs are generally recommended 1st line (especially ESC) based mainly on tolerability
• Augmentation strategies not adequately studied
  – But frequently needed, so must extrapolate
• Take longer to respond and are more likely to experience side effects
• “Start low, go slow”
• Once treated, the elderly, as a group, are prone to relapse sooner than younger adults

Norepinephrine, Dopamine, and Neuropsychiatric Function

• Both systems facilitate information processing by increasing the signal-to-noise ratio with the systems to which they project
  – When present in adequate amounts, information processing may be directed towards cognitively, emotionally, or behaviorally relevant targets
  – When present in excess, receptor desensitization may occur, thereby increasing the relative amount of “noise” within information-processing circuits
  – When present in relatively deficient amounts, the signal-to-noise ratio is low making information processing relatively difficult
Serotonin and Neuropsychiatric Function

- Modulatory neurotransmitter, generally acting to inhibit CNS excitability
- Participates in pacemaking the system as a whole
- Modulates neurotransmission and information processing in multiple systems

Neurotransmitter functions

- Serotonin (5HT)
  - Mood, anxiety, appetite, sleep, temperature regulation
  - Nausea, platelet functioning
- Norepinephrine (NE)
  - Attention, anxiety, mood
  - Sympathetic nervous system
- Dopamine (DA)
  - Motivation, pleasure/reward, attention, arousal/wakefulness
  - Motor functioning
Major Depressive Disorder Symptoms

1. Depressed mood most of the day $\downarrow 5HT, \downarrow NE$
2. $\downarrow$ interest/pleasure in all/most activities $\downarrow DA$
3. Significant weight loss or gain $5HT$
4. Insomnia $5HT$ or sleeping too much $\downarrow DA$
5. Agitation $\downarrow 5HT$ or psychomotor retardation $\downarrow DA$
6. Fatigue or loss of energy $\downarrow DA$
7. Feelings of worthlessness or excessive guilt $\downarrow 5HT$
8. $\downarrow$ concentration or $\uparrow$ indecisiveness $\downarrow NE, \downarrow DA$
9. Recurrent thoughts of death $\downarrow 5HT, \downarrow NE$
STAR*D

- The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study evaluated feasible treatment strategies to improve clinical outcomes for real-world patients with treatment-resistant depression
- The study found no clear-cut “winner,” but it does provide guidance on how to start therapy and how to proceed if initial treatment fails

Results of STAR*D

- Remission (i.e. complete relief from a depressive episode) NOT just response (merely substantial improvement) should be the goal of treatment
  - It is associated with a better prognosis and better function
- If the first treatment fails:
  - switch treatment or
  - augment the current treatment
Results of STAR*D

• For most patients, remission will require repeated trials of sufficiently sustained, vigorously dosed antidepressant medication

• Physicians should give maximal but tolerable doses for at least 8 weeks before deciding that an intervention has failed

• After two well-delivered medication trials, the likelihood of remission substantially decreases, and these patients likely require more complicated regimens (refer to psychiatry)

Results of STAR*D

• With persistent and vigorous treatment, most patients will enter remission, if he/she stays in treatment:
  – ~33% after one step
  – 50% after two steps
  – 60% after three steps
  – 70% after four steps

• Geriatric depression treated in primary care clinics shows similar response at one step

Figure 1. Treatment strategies and options in Levels 1 to 4. BUP-SK = Bupropion sustained-release; BUS = buspirone; CIT = clonipramine; CT = cognitive therapy; IT = imipramine; MIE = milnacipran; NTP = nortriptyline; SEM = sertraline; T1 = tricyclic antidepressant; TCP = tranylcypromine; VEN-XR = venlafaxine extended release.

Algorithm for the Treatment of Major Depressive Disorder

Stage 0
Patient Assessment & Discussion of Treatment Options

Stage 1
Response

Stage 2
Alternate AD monotherapy from different class from above

Stage 3
SERO + BUP + MRT, SSRI + TCA

Stage 4
If not clinically Stage 3, use TCA + SSRIs, BUP

Nonresponse
Partial Response

Stage 5A
Continuation

Stage 5B
Optimization

Stage 6A
Continuation

Stage 6B
Continuation

Discuss CBT as option
Stage 5
ECT or VNS
Response
Nonresponse or Partial Response
Stage 6
Triple AD Rx
Response
Nonresponse or Partial Response
Stage 7
Alternate 2 or 3 drug combo not used previously\(^6\)
Consider ECT or VNS if not used.
Nonresponse or Partial Response
Stage 8
Alternate 2 or 3 drug combo not used previously
Response
Continuation\(^7\)
Go to Maintenance phase when indicated

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1 EBPT = Evidence based psychotherapy. EBPT is an option before starting pharmacotherapy or in combination with pharmacotherapy at any stage in the algorithm.
2 TCAs = Li or MAOIs should be considered over combination Rx, unless tolerability, prior response, or patient preference otherwise.
3 Use MRT as an augmenting agent if a SSRI/SSNRi + BUP is used in stage 3; use BUP as an augmenting agent if a SSRI/SSNRi + MRT is used in stage 3.
4 If VNS chosen, it augments pharmacotherapy.
5 Use agents with different MOA; use agents with response in the past (even minimal); choose among SSRIs, SNRIs, BUP, MRT, TCAs, MAOIs, ARPIs, LDA, Li.
6 Use agents with a different MOA; use agents with response in the past. If not previously used, consider ECT or VNS here.
7 Continuation phase treatment should include treatment 6-9 months after remission of symptoms with antidepressant(s) that achieved symptom remission.

**Abbreviations**

<table>
<thead>
<tr>
<th>AD</th>
<th>antidepressant</th>
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<tbody>
<tr>
<td>AAP</td>
<td>atypical antipsychotic</td>
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<tr>
<td>BUP</td>
<td>bupropion SR/XL</td>
</tr>
<tr>
<td>BUS</td>
<td>buspirone</td>
</tr>
<tr>
<td>EBPT</td>
<td>evidence based psychotherapy</td>
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<tr>
<td>ECT</td>
<td>electroconvulsive therapy</td>
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<tr>
<td>Li</td>
<td>lithium</td>
</tr>
<tr>
<td>LTO</td>
<td>lamotrigine</td>
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<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
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<tr>
<td>MOA</td>
<td>mechanism of action</td>
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<tr>
<td>MRT</td>
<td>minocycline</td>
</tr>
<tr>
<td>CLZ</td>
<td>clonazepam</td>
</tr>
<tr>
<td>RIS</td>
<td>risperidone</td>
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<tr>
<td>SNRI</td>
<td>serotonin-norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TCA</td>
<td>tricyclic antidepressant</td>
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</table>
Antidepressant Classes

1. Selective Serotonin Reuptake Inhibitors (SSRI) [FLX, PRX, SRT, CTL, ESC, FLV]
2. Serotonin/Norepinephrine Reuptake Inhibitors (SNRI) ([des]-VNL, MRT, DLX)
3. Novel antidepressants (BPR, BSP)
4. Tricyclics (TCAs) [AMT, NRT]
5. Monoamine Oxidase Inhibitors (MAOIs) [phenelzine, tranylcypromine, selegiline]
Other Meds Used to Treat Depression

1. Mood stabilizers (Lithium, LMT)
2. Stimulants (Ritalin, Adderall, Vyvanse)
3. Dopamine agonists (ropinirole, pramipexole)
4. Antipsychotics (RIS, OLZ, QTP, ARP)
5. Thyroid medication (only T3 studied)

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SSRIs

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Block presynaptic serotonin reuptake
- Treat both anxiety and depressive sxns
- Most common side effects include GI upset, sexual dysfunction (30%+!), anxiety, restlessness, nervousness, insomnia, fatigue or sedation, dizziness
- Very little risk of cardiotoxicity in overdose
- Can develop a discontinuation syndrome with agitation, nausea, disequilibrium and dysphoria
**fluoxetine (Prozac) FLX**

- Most activating of SSRIs
- Long $\frac{1}{2}$ life (norfluoxetine $\frac{1}{2}$ life ~9 days)
- Many med-med interactions (2D6 inhibition)
- Start 10 mgs QAM x 1 week, ↑ to 20 mgs (max 80 mgs TDD)

- Be very careful in person with ANY hint of bipolar spectrum disorder

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**paroxetine (CR) (Paxil) PRX**

- Most sedating of SSRIs
- Tons of side effects (dry mouth, constipation, weight gain)
- Very short $\frac{1}{2}$ life & discontinuation syndrome
- Many med-med interactions via 2D6 inhibition (worse than FLX)
- (Don’t start) but if do, 10 mg QHS x 1 week, then ↑ to 20 mg QHS (max 50 mgs TDD)
**sertraline (Zoloft) SRT**

- Generally activating (has some DA agonism)
  - Less sedating when compared to paroxetine
- Only slight 2D6 inhibition
- Short half life, little build-up of metabolites
- Max absorption requires a full stomach
- More GI adverse drug reactions
- Start 25 mgs QAM x 1 week, ↑ to 50 mgs QAM (max 200 mgs)

**citalopram (Celexa) CTL**

- Somewhat sedating
- Few medication interactions
- Associated with increased QTc prolongation in doses over 40 mgs
- Start 10 mgs po QHS x 1 wk, then ↑ to 20 mgs (max 40 mgs TDD, 20 mgs in elderly)
escitalopram (Lexapro) ESC

- Fewest medication interactions & side effects
- Tends to be neutral from sedation/activation perspective
- Start 5 mgs po QHS x 1 week, then ↑ to 10 mgs (max 20 mgs TDD)

fluvoxamine (Luvox) FLV

- Shortest $\frac{1}{2}$ life of SSRIs
- Has some analgesic properties
- Common side effects include GI distress, headaches, sedation, weakness
- Strong inhibitor of CYP1A2 and CYP2C19
- Start 50 mgs QAM, ↑ by 50 mgs/week (max 300 mgs TDD)
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Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

- Inhibit both serotonin and noradrenergic reuptake like the TCAS but without the antihistamine, antiadrenergic or anticholinergic side effects
- Used for depression, anxiety and possibly neuropathic pain
venlafaxine IR, XR (Effexor) VNL

• Some evidence it works faster than other ADs
• Almost exclusively an SSRI up to 112.5 mg, then becomes progressively more noradrenergic at 150 mgs and higher
• Tends to be activating (especially ≥ 150 mgs)
• Start 37.5 mgs QAM x 3 days, ↑ to 75 mgs QAM x 1 week, then 150 mgs QAM (max 375 mgs TDD)

desvenlafaxine (Pristiq) des-VNL

• Minimal drug interactions
• Short ½ life and fast renal clearance avoids build-up (good for geriatric populations)
• GI distress in 20% +
• Dose-related increase in total cholesterol, LDL and triglycerides
• Dose related increase in BLOOD PRESSURE
• Start 50 mgs QAM, can ↑ to 100 mgs QAM (max 100 mgs TDD)
**duloxetine (Cymbalta) DLX**

- Mostly an NRI
- Approved for DPN, GAD, fibromyalgia, chronic musculoskeletal pain, & MDD
- Generally activating
- Fewer GI SEs than many
- Expensive
- Start at 30 mgs QAM x 1 week, ↑ to 60 mgs QAM (max 120 mgs TDD)

**mirtazapine (Remeron) MRT**

- Unique mechanism
- Great for sleep, ↑ appetite, & ↑ energy the next day (eventually & at higher doses)
- Anticholinergic SEs: weight gain, urinary retention, dry mouth
- Start 15 mgs QHS x 1 week, then ↑ to 30 mgs QHS (max 45 mgs TDD)
  - Tends to be more sedating at lower doses & more activating at higher doses
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bupropion SR, XL (Wellbutrin) BPR

- Mechanism of action likely reuptake inhibition of dopamine and norepinephrine
- ↓ weight gain, sexual side effects
- Low induction of mania
- May increase seizure risk
  - avoid in patients with TBI, bulimia and anorexia
- Can ↑ anxiety, agitation and insomnia
- Start 150 mgs QAM, ↑ to 150 BID (9A,3P) if SR, or 300 QAM if XL (max 400-450 mgs TDD)
buspirone (Buspar) BSP

- Good augmentation strategy
- Mechanism of action is 5HT1A agonist
  - independent of endogenous release of serotonin
- Little or no sedation
- Unlikely to reduce anxiety in patients used to taking benzodiazepines
- Start 5 mgs BID or TID, can ↑ by 15 mgs/week (max 60 mgs TDD)

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TCAs

- Very effective but potentially unacceptable side effect profile i.e. antihistaminic, anticholinergic, antiadrenergic
- Can be lethal in overdose (even a one week supply can be lethal!)
- Can cause QTc lengthening even at therapeutic serum level

Tertiary TCAs

- Have tertiary amine side chains
- Side chains cross react with other receptors → SEs:
  - antihistaminic (sedation and weight gain)
  - anticholinergic (dry mouth, dry eyes, constipation, memory deficits and potentially delirium)
  - antiadrenergic (orthostatic hypotension, sedation, sexual dysfunction)
- Act predominantly on serotonin receptors
- Examples: imipramine, amitriptyline, doxepin, clomipramine
- Have active metabolites including desipramine and nortriptyline
Secondary TCAs

- Are often metabolites of tertiary amines
- Primarily block norepinephrine
- Side effects are the same as tertiary TCAs but generally are less severe
- Examples: desipramine, nortriptyline

Dosing TCAs

- Amitriptyline (Elavil)
  - Start 25-50 mgs QHS, ↑ by 25-50 mgs/week to target of 150 mgs QHS (max 300 mgs TDD)
    - Amitriptyline + nortriptyline blood level 120-250
- Nortriptyline (Pamelor)
  - Start 25-50 mgs QHS, ↑ by 25 mgs/week to target of 75 mgs QHS (max 150 mgs TDD)
    - Nortriptyline blood level 50-150
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3. Novel antidepressants (BPR, BSP)
4. Tricyclics (TCAs) [AMT, NRT]
5. Monoamine Oxidase Inhibitors (MAOIs) [phenelzine, tranylcypromine, selegiline]

Monoamine Oxidase Inhibitors (MAOIs)

• Bind irreversibly to monoamine oxidase thereby preventing inactivation of biogenic amines such as norepinephrine, dopamine and serotonin leading to increased synaptic levels.
• Are very effective for depression
• Side effects include orthostatic hypotension, weight gain, dry mouth, sedation, sexual dysfunction and sleep disturbance
• Hypertensive crisis can develop when MAOIs are taken with tyramine-rich foods or sympathomimetics
MAOIs (continued)

- Serotonin syndrome can develop if take MAOI with meds that increase serotonin or have sympathomimetic actions
- Serotonin syndrome sx's include abdominal pain, diarrhea, sweats, tachycardia, HTN, myoclonus, irritability, delirium
- Can lead to hyperpyrexia, cardiovascular shock and death
- MUST wait 2 weeks before switching from an SSRI to an MAOI (except FLX ≥ 5 weeks)

SSRIs vs. TCAs vs. SNRIs (and others)

- A meta-analysis of 102 studies found no overall difference in efficacy between TCAs and SSRIs
- TCAs appeared more efficacious in inpatients
  - amitriptyline was more effective than SSRI comparators
- SSRIs comparable efficacy to other non-TCAs
  - venlafaxine shows superior efficacy in some studies
  - mirtazapine showed better efficacy in elderly
- SSRIs as a class had a significantly lower rate of dropouts for side effects

MAOIs vs. TCAs

• MAOIs have comparable efficacy to TCAs for most patients with MDD
• MAOIs may be particularly effective in treating subgroups of patients with major depressive disorder with atypical features:
  – reactive moods
  – reversed neurovegetative symptoms
  – and sensitivity to rejection
• MAOIs effective for some patients with TRD
• ECT superior to SSRIs, TCAs, and MAOIs


Other Meds Used to Treat Depression

1. Mood stabilizers (Lithium, LMT)
2. Stimulants (Ritalin, Adderall, Vyvanse)
3. Dopamine agonists (ropinirole, pramipexole)
4. Antipsychotics (RIS, OLZ, QTP, ARP)
5. Thyroid medication (only T3 studied)
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Lithium

- Shown to ↓ suicide risk, independent of etiology
- Before start, check BMP, TSH, EKG, CBC, preg
  - 1st trimester exposure associated with Ebstein’s anomaly
- Start 300 mgs daily, can ↑ by 150 mgs/week (dose based on level)
- Steady state achieved after 5 days
  - Check level 12 hours after last dose
  - Once stable check level q 3 months
  - TSH & creatinine q 6 months
- Target blood level 0.6-1.2
Lithium Side Effects

• Most common are GI distress including reduced appetite, nausea/vomiting, diarrhea
• Thyroid abnormalities
• Insignificant leukocytosis
• Polyuria/polydypsia (ADH antagonism)
• Hair loss, acne
• Intention tremor

• ER forms minimize many side effects

Lithium Toxicity

• Mild (1.5-2.0)
  – vomiting, diarrhea, ataxia, dizziness, slurred speech, nystagmus
• Moderate (2.0-2.5)
  – nausea, vomiting, anorexia, blurred vision, clonic limb movements, convulsions, delirium, syncope
• Severe (>2.5)
  – generalized convulsions, oliguria, renal failure
**lamotrigine (Lamictal) LMT**

- Indications similar to other anticonvulsants
  - But clearly effective for depression
- Before start: baseline LFTs
- Start with 25 mgs daily x 2 weeks, then ↑ to 50 mgs x 2 weeks, then ↑ to 100 mgs daily (max 200 mgs TDD)
  - faster titration has a higher incidence of serious rash
- If the patient stops for 5 days or more have to start at 25 mg again!

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Stimulants

• Methylphenidate better studied than Adderall
  – Start either at 5 mgs BID (7A,12P) x 3-7 days, ↑ to 10 mgs BID x 1 week, ↑ to 15 mgs BID x 1 week, ↑ to 20 mgs BID (max 40-60 TDD)
• Vyvanse
  – Shire is seeking MDD indication
  – More expensive but truly lasts 12 hours
  – Start 20 mgs QAM, can ↑ by 10-20 mgs/week (max 70 mgs TDD)

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Dopamine Agonists

- ropinirole (Requip)
  - Start 0.25 mgs QHS, can ↑ by 0.25 mgs/week (max 2 mgs TDD)
- pramipexole (Mirapex)
  - Start 0.125 mgs TID, can ↑ by 0.375 mgs/week (max 1.5 mgs TDD)

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risperidone (Risperdal) RIS

- Functions more like a typical antipsychotic at doses greater than 6 mg
- Increased extrapyramidal side effects (dose dependent)
- Most likely atypical to induce hyperprolactinemia
- Less weight gain and sedation than other atypicals
- Start at 0.25-0.5 mgs QHS, can ↑ by 0.5 mg q 3-7 days (max 3 mgs TDD)

olanzapine (Zyprexa) OLZ

- Weight gain (can be as much as 30-50 pounds, even with short term use)
- May cause hypertriglyceridemia, hypercholesterolemia, hyperglycemia (even without weight gain)
- May cause hyperprolactinemia (<< risperidone)
- May cause transaminitis (2% of all patients)
- Start at 2.5-5 mgs QHS, can ↑ by 5 mgs q 3-7 days (max 20 mgs TDD)
quetiapine (Seroquel) QTP

- Available in IR & XR forms
- Very sedating and often associated with weight gain (< olanzapine)
- May cause hypertriglyceridemia, hypercholesterolemia, hyperglycemia (even without weight gain) (< olanzapine)
- Most likely to cause orthostatic hypotension
- Start at 50-100 mgs QHS, can ↑ by 100 mg q 3-7 days up to 400 mgs TDD

aripiprazole (Abilify) ARP

- Unique mechanism of action
  – Presynaptic antagonist/postsynaptic agonist
- Not associated with weight gain
- Activating < 15 mgs (give in AM)
  – Can cause intolerability due to akathisia
- More sedating at higher dose (give at HS)
- Start 2 or 2.5 mgs QAM for 3-7 days, can ↑ to 5 mgs QAM x 1 week, can ↑ to 10 QAM x 1 week (or even 15 mgs, but then switch to HS)
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liothyronine (Cytomel) T3

- Independent of thyroid status
- Start 25 mcg QAM (empty stomach), can ↑ to 50 mcg QAM after a week