The Medication Management of Major Depression

American Association of Pharmacy Technicians

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Learning objectives

- List presentation, symptoms and diagnostic criteria
- Recommend an optimal therapeutic regimen
- Monitor the effectiveness of the selected therapy

Key Concepts

- Extensive treatment guidelines are available to assist in the treatment of major depressive disorder (MDD), including medication management. Clinicians treating individuals with MDD should be familiar with these guidelines
- When evaluating a patient for the presence of depression, it is essential to rule out medical causes of depression and drug induced depression
- The goals of treatment for depression are the resolution of current symptoms (i.e. remission) and the prevention of further episodes of depression (i.e. relapse or recurrence)

Key Concepts

- When counseling patients with depression who are receiving antidepressant medications, the patient should be informed that adverse effects might occur immediately while resolution of symptoms may take 2 to 4 weeks or longer.
- Adherence to the treatment plan is essential for a successful outcome, and tools to help increase medication adherence should be discussed with each patient
- Antidepressants are generally considered equally efficacious in groups of patients with major depressive disorder. Therefore other factors, such as age, side effect profile and past history of response, are used to guide the selection of antidepressants

Key Concepts

- When determining if a patient has been nonresponsive to a particular pharmacotherapeutic intervention, it must be determined whether the patient has received an adequate dose for an adequate duration and whether the patient has been medication adherent
- Pharmacogenetic tests (e.g. the FDA approved test to evaluate 2D6 and 2C19 polymorphisms) are now commercially available. However there are no standard or well accepted recommendations for the use of pharmacogenetic testing as it relates to antidepressant treatment of MDD

Key Concepts

- When evaluating response to an antidepressant, in addition to target signs and symptoms, the clinician must consider quality of life issues, such as role, social and occupational function.
- In addition, the tolerability of the agent should be assessed because the occurrence of side effects may lead to medication nonadherence, especially given the chronicity of the disease and the need for long term medication management.

Depressive Disorders

Major Depressive Disorder (MDD)

- Diagnosed when 1 or more episodes of depression without mania or hypomania
- Guidelines for treatment are available at www.psych.org (3rd edition) and British Association of Psychopharmacology (BAP)

Epidemiology

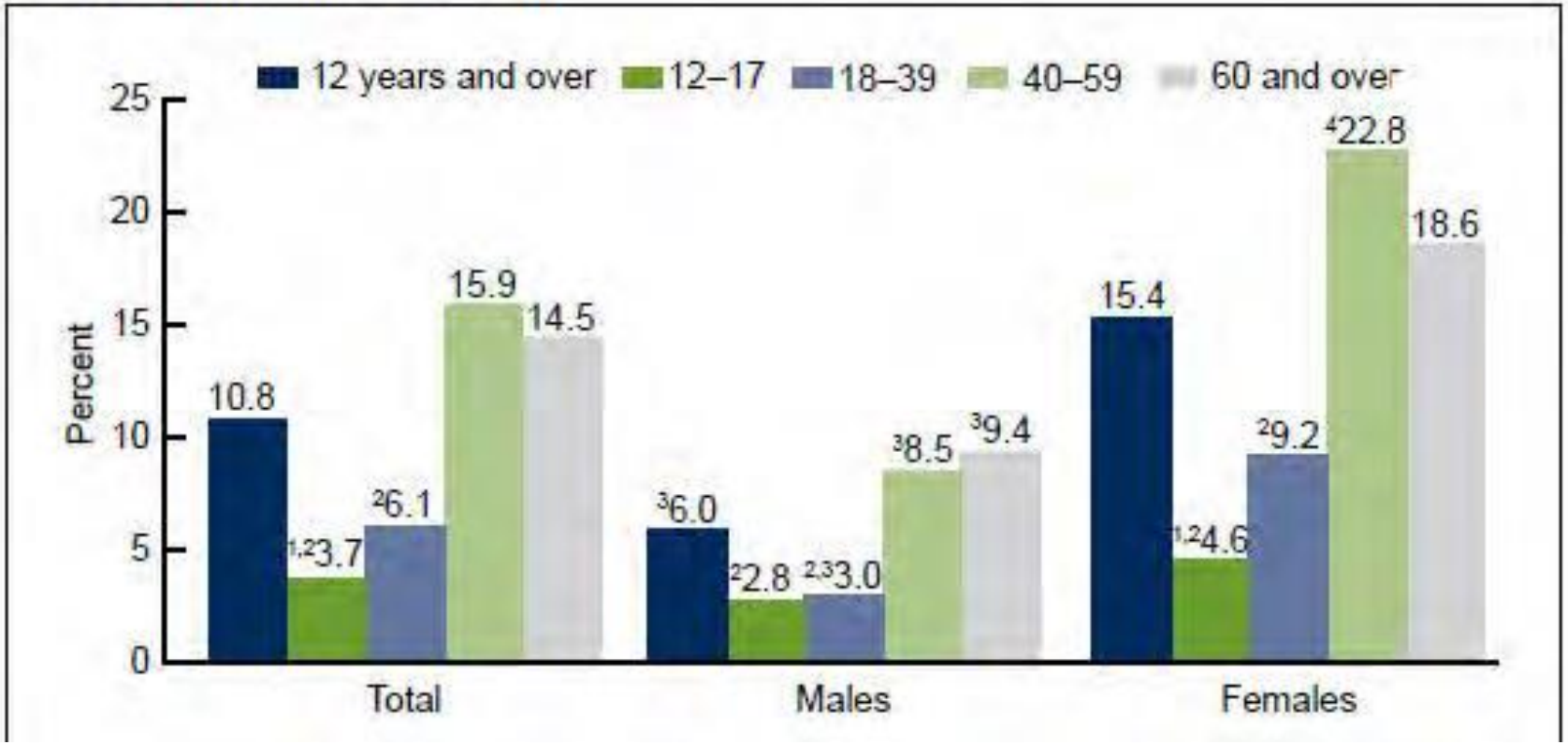
Major Depressive Disorder (MDD)

- 12 month prevalence nearly 7%; lifetime prevalence up to 16%
- Women higher risk teens until mid 50s (lifetime prevalence roughly 2.5 X greater than men)
- Most common age range in any given year 18-29 bimodal peak elderly
- For those aged 65 to 80 lifetime prevalence ~20% women, 10% men
- Family history
  - Medical conditions may cause depression (hypothyroidism)
  - Untreated pain may worsen depression
- Untreated depression can put people at risk for suicide

Epidemiology

About one in 10 Americans aged 12 and over takes anti-depressant medication.

Figure 1. Percentage of persons aged 12 and over who take antidepressant medication, by age and sex: United States, 2005–2008



Etiology

Major Depressive Disorder (MDD)

- Etiology is unknown and complicated
- Consistent consensus: altered neurotransmitters
  - Cause of this alteration is controversial
  - Imaging has detected anatomical changes
  - Changes to receptors may account for delay of AD

Biologic Markers

- Neuroendocrine abnormality
- Hypersecretion of cortisol-chronic stress model depletion of brain derived neurotropic factor (BDNF), decreased neurogenesis (AD action to increase neural cell proliferation)
- Substance P released during stress as well

MDD Presentation

- Initial symptoms develop over days to weeks
- Symptoms of anxiety often appear first
- If left untreated, can last 4 months or more
- The symptoms vary person to person (rating scales; MADRS, BDI)
- Depression may end completely, partially, or not at all (35% partial, 15% never remit)
- Repeat episodes are common
  - 60% have 2nd episode
  - 70% have 3rd episode
  - 90% have 4th episode
- Medical disorders must be ruled out
  - TSH, CBC and electrolytes

How Effective are Common Medications? A Perspective Based on Meta-Analyses of Major Drugs

Rx Class (Outcome)	Effect Size	95% Confidence Interval
PPI (Remission of GERD)	1.39	1.18 – 1.60
Oxycodone/APAP (↓50%)	1.04	0.74 – 1.34
Levodopa (Parkinson's)	0.93	0.65 – 1.20
Metformin (NIDDM)	0.87	0.61 – 1.13
Antipsychotic (Schizophrenia)	0.51	0.43 – 0.59
Antidepressants (MDD)	0.38	0.34 – 0.41
ACE Inhibitors (↓CV events)	0.16	0.12 – 0.21
Statins (↓CV events)	0.15	0.13 – 0.17
Aspirin (↓CV events)	0.12	0.06 – 0.18

Leucht et al. *BMC Medicine.* 2015;13:253-258.

Presentation

- **Emotional Symptoms**
  - continued diminished capacity to experience pleasure in activities that brought pleasure before the episode
  - life stressors may trigger depression in some but not others
  - anxiety symptoms present in ~90% of OP
  - psychotic features may be present, but this may require hospitalization and stabilization with APS

Presentation

- **Physical Symptoms**
  - psychomotor retardation-slowed physical movements or speech
  - psychomotor agitation-pacing, purposeless restless movements
  - more common in elderly: chronic fatigue, pain
  - sleep disorders—like insomnia, early awakenings and daytime sleepiness
  - changes in appetite

Watch for residual symptoms!

Depression Contributions

Common Medication Induced Causes	
Cardiovascular:	• Beta-blocker • Clonidine • Methyldopa • Reserpine
Antiepileptic drugs	• Topiramate • Levetiracetam • Vigabatrin
Hormonal	• Oral contraceptives • Steroids • Tamoxifen
Other: Immunologic agents (interferons), smoking cessation medications (varenicline), acne treatment (isotretinoin)	

Depression Contributions

Common Medical Causes
Hypothyroidism
Anemia
HIV/AIDS/STDs
Autoimmune disease
Cardiovascular disease
NEUROLOGIC DISORDERS Epilepsy Huntington's Disease Parkinson's Disease Alzheimer's disease Post-stroke

Major Depressive Disorder (MDD)-DSM5 Diagnostic Criteria

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure (not to include symptoms that are clearly attributable to another medical condition).

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).

3. Significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Depressive Disorders

Depressive Disorders

DSM 5 contains new depressive disorders including

- premenstrual dysphoric disorder (PMDD) provides specific criteria that sets this disorder apart from PMS*

- Bereavement is now included in diagnostic criteria if lasts more than 2 months
  - Bereavement-related major depression is most likely to occur in individuals with past personal and family histories of major depressive episodes.
  - It is genetically influenced and is associated with similar personality characteristics, patterns of comorbidity, and risks of chronicity and/or recurrence as non–bereavement-related major depressive episodes.
  - The depressive symptoms associated with bereavement-related depression respond to the same psychosocial and medication treatments as non–bereavement-related depression.

Presentation

Suicide Risk evaluation and management (inc risk):

- Male
- Single/living alone
- Describing feelings of hopelessness/suicide plans
- Substance abuse
- Unusual behavior-missed work, giving things away
- During initial stages of medication therapy (risk can increase with those recovering from MDD as they experience increased energy to act on plans.)

Black Box Warning

- In 2004, FDA required Black Box Warning on antidepressants
  - stating risk in short term studies in children and teens with depression

- In May 2007, the FDA expanded the Black Box Warning regarding suicidality
  - Now includes warnings about the increased risk of suicidality (thoughts and behavior) in young adults 18-24 years of age *especially at the early stage of treatment.*

What to do?

Black Box Warning

What to do?

- Counsel patients/families to monitor closely at beginning of treatment
- Possible ADRs could include agitation
- Deal with the subject of suicide directly
- Get help immediately

Phases of MDD

Acute Phase
- Duration: 6-12 weeks
- Goal: remission (absence of symptoms)

Continuation Phase
- Duration: 4 to 9 months after remission is achieved
- Goal: to **prevent relapse** or residual symptoms

Maintenance phase
- Duration: lasts 12-36 months
- Goal: to **prevent recurrence** (a new episode of depression)

*risk of recurrence increases as number of episodes increase

*lifelong therapy recommended for highest risk pts

Treatment expectations

Symptom Resolution Timeline	MDD Symptoms
Week 1	• Decreased anxiety • Improved sleep • Improved appetite
Weeks 1-3	• Increased activity, sex drive, self care and memory • Thinking and movements become more normal • Sleeping and eating become more normal
Weeks 2-4	• Relief of depressed mood • Thoughts of suicide begin to subside

Treatment expectations

Pharmacotherapy initiated	Partial or no response	Full response
Weeks 1-4	• Assess adherence • Increase dose if clinically indicated • For severe symptoms, consider ECT	Maintain treatment if no issues with tolerability
Weeks 4-8	• Increase the dose OR • Change to alternative antidepressant OR • Change psychotherapy OR • Consider ECT	Move to continuation phase

Treatment

Non-Pharmacologic Therapy

- Psychotherapy whenever possible
- Not for exclusive use in severe cases
- Combination with medicine is best practice
- For mild cases, combination does not produce advantage
- Cognitive behavioral therapy (CBT)
- Transcranial Magnetic Stimulation (TMS)

Treatment

Non-Pharmacologic Therapy

- Electroconvulsive Therapy (ECT)
- Safe and effective treatment for severe mental illness including MDD
- Good option in severe cases when a rapid response is required
- Risk includes cardiovascular changes and apnea
- Avoid: recent MI, intracerebral bleeding, unstable vascular conditions, increased cranial pressure

Treatment

Pharmacologic Treatment

Need to Know:

- Class of drug
- Dosing ranges
- Drug interactions
- Monitoring parameters
- Adverse effects
- Therapeutic controversies

Treatment mechanisms are based on the following neurotransmitters:

- Serotonin
- Norepinephrine
- Dopamine

Treatment

Pharmacologic Treatment

- Extensive treatment guidelines are available, however there are no universally agreed upon for treatment resistant depression
- Practice guideline for the treatment of MDD 2nd edition available online at www.psych.org
- All antidepressants are considered equally efficacious for treatment of MDD when given at comparable doses
  - other factors that should guide the selection of treatment options (history of personal and family response, other medical and psychiatric conditions….)
- Failure to respond to one AD within a class does not predict another failure to respond to another within class or entirely different class. Up to 60% patients respond to AD compared to 40% respond to placebo

Selective Serotonin Reuptake Inhibitors (SSRIs)

Patient education:

- See timeline for symptom resolution all ADS. 1st episode tx for 6-12 months at minimum.
- 2-4 weeks at minimum to see the start of symptom resolution, high degree of personal variability
- Watch for a response that is extreme and < 2 weeks
- When discontinuing SSRI, taper if possible-except for Prozac due to long T1/2
- There may be initial anxiety, so use lower doses and titrate more slowly if this is anticipated.
- No consensus for approach to tapering to discontinue; longer vs shorter should be individualized and monitored

Selective Serotonin Reuptake Inhibitors (SSRIs)

Patient education:

- Insomnia or sedation
  - take in morning or switch to another with less insomnia
- Sexual dysfunction
  - may need to switch to another agent such as bupropion
- Serotonin syndrome counsel on symptoms
  - Mental status changes
  - Autonomic instability
  - Neuromuscular abnormality
  - GI symptoms

Selective Serotonin Reuptake Inhibitors (SSRIs)

Patient education on how to avoid Serotonin syndrome

- Avoid concomitant use of serotonergic drugs
- Others:
  - Triptan migraine agents
  - Pain medications: fentanyl and tramadol
  - Nausea products: zofran and reglan
  - Buspirone
  - Linezolid
  - ritonavir
- Drugs that impair the metabolism of serotonin

Selective Serotonin Reuptake Inhibitors (SSRIs)

Other drug interactions…

- QTC prolongation with concomitant medications
- Increased risk of bleeding for patients on NSAIDS, anti-platelets and anticoagulants

Other issues…

- SSRI/SNRI hyponatremia (SIADH)

Depression Treatment SSRI

SSRI agents		Indications for use	Dosing
Citalopram	Celexa	**Depression**	Initial: 20mg Usual range: 10-40mg MDD 20mg for ≥60 y/o
Escitalopram	Lexapro	**Depression** (GAD)	Initial:10mg Usual range: 10-20mg
Fluoxetine	Prozac; Sarafem; Selfemra Symbyax *(w/ olanzapine)*	**Depression** (bulimia nervosa, OCD, panic disorder, PMDD)	Initial:20mg Usual range: 20-60mg
Fluvoxamine	Luvox	OCD	Initial: 50mg Usual range:50-300mg
Paroxetine	Paxil; Pexeva	**Depression** (GAD, OCD, panic disorder, PTSD, PMDD, social phobia)	Initial: 20mg Usual range:20-50mg
Sertraline	Zoloft	**Depression** (OCD, panic disorder, PTSD, PMDD, social phobia)	Initial:50mg Usual range: 50-200mg

Selective Serotonin Reuptake Inhibitors (SSRIs)
FDA approved uses

	Celexa	Lexapro	Prozac	Luvox	Paxil	Zoloft
MDD	X	X	X		X	X
GAD		X			X	
OCD			X	X	X	X
Panic			X		X	X
PTSD					X	X
PMDD			X		X	X
SAD					X	X
Bulimia nervosa			X			

SNRI agents		Indications for use	Dosing
Desvenlafaxine succinate salt	Pristiq	**Depression**	Initial: 50mg usual range: 50mg
Desvenlafaxine extended-release tablets	Khedezla	**Depression**	Initial: 50mg Usual range: 50-400mg
Duloxetine	Cymbalta	**Depression** diabetic neuropathy, fibromyalgia, GAD, musculoskeletal pain, osteoarthritis	Initial: 30mg Usual range: 30-90mg
Levomilnacipran	Fetzima	**Depression**	Initial: 20mg x 2, then 40 x 2 Usual range:40 to 120mg
Venlafaxine	Effexor	**Depression** GAD, panic disorder, social phobia	Initial: 75mg usual: 75-225mg

Serotonin-Norepinephrine reuptake Inhibitors (SNRIs)-

	Desvenlafaxine	Duloxetine	Venlafaxine	Levomilnacipran
MDD	X	X	X	X
GAD		X	X	
Fibromyalgia		X		
Musculoskeletal pain		X		
Neuropathic pain		X		
Panic disorder			X	
Social phobia			X	

Tricyclic Antidepressants (TCA)

Indications

- MDD
- Insomnia
- Nocturnal enuresis

- **Uses off-label**: fibromyalgia, neuropathic pain, GAD, SAD, OCD, PTSD, nocturnal enuresis, headache and migraine PPX.

- Other agents: trimipramine (Surmontil) protriptyline (Vivactil), and maprotiline (Ludiomil)

Tricyclic Antidepressants (TCA)

MOA: Not fully understood.

Believed to influence NT: 5HT and NE

- NT involved in regulation of mood, appetite, sleep, attentiveness and other brain functions
- Side effects: anticholinergic and cardiovascular effects
  - CV ventricular tachycardia and heart block** lethal in overdose
- Tertiary amines more ADR than the secondary
- Give at bedtime to decrease impact of sedative properties
- Cognitive impairment, urinary retention possible

Tricyclic Antidepressants (TCA)

Can also cause …

- Weight gain
- Sexual dysfunction
- Need to consider…
- Drug interaction potential 2D6
- Monitoring serum concentration?
  - Generally for verification of adherence or toxicity/overdose
- High variability and does not correlate reliably with efficacy
- Patients should have baseline EKG (esp > 40 years old)
- Withdrawal upon abrupt discontinuation

TCA		Indications for use	dosing
Amitriptyline	Elavil	**Depression**	Initial 25mg Usual range 100-200mg (up to 300mg**)
Desipramine	Norpramin	**Depression**	Initial 25mg Usual range 100-200mg (up to 300mg**)
Doxepin*	Sinequan	**Depression**	Initial 25mg Usual range 100-200mg (up to 300mg**) *Children >6=weight based+*
Imipramine	Tofranil	**Depression** **Enuresis**	Initial 25mg Usual range 100-200mg (up to 300mg**) *Children >6=weight based+*
Nortriptyline	Pamelor	**Depression**	Initial 25mg usual range 50-150mg *Children >6=weight based+*

**another form now available Silenor for sleep (3-6mg)*

***higher doses recommended for inpatient/hospitalization*

- Amitriptyline → Nortriptyline (Active Metabolite)
- Imipramine → Desipramine (Active Metabolite)

Monoamine Oxidase Inhibitors (MAOI)

- MAO-A
  - Inhibition of MAO-A is responsible for antidepressant effects
  - Metabolizes 5HT, NE, DA
- MAO-B
  - Metabolizes DA, Phenethylamine
  - Selective MAO-B inhibitors have the ability to inhibit MAO-A also at higher doses (>6mg/24h for the patch)

Monoamine Oxidase Inhibitors (MAOI)

- Many drug interactions! After d/c of interacting medication, must wait 4 to 5 half-lives of drug or active metabolite
- Fluoxetine and Vortioxetine have the longest T1/2 of the SSRIs so need to wait >2 weeks before start of an MAOI
  - Fluoxetine: 5 weeks
  - Vortioxetine: 3 weeks
- Dietary restrictions of Tyramine Containing foods
  - Aged products, smoked and pickled products, yeast extracts
  - Risk life threatening hypertensive crisis
- Monitor blood pressure
- Other side effects: **postural** hypotension, diarrhea, anticholinergic drying effects, sexual dysfunction

MOA inhibitors		Indication for use	dosing
Phenelzine	Nardil	**Depression**	Initial:15mg (dosed TID) Early Phase:30-90mg Maintenance: 15mg QDay or QoDay ≥16 years of age
Selegiline transdermal patch	Emsam	**Depression**	Initial: 6mg usual range: 6-12mg
Tranylcypromine	Parnate	**Depression**	Initial: 10mg Usual range: 20-40mg (up to 60mg**) Divided doses ≥16 years of age

Selegiline (MAO-B, doses > 9mg both A and B):

- -Tablet
- -ODT
- -*Transdermal (EMSAM): Only the patch has an indication for depression

All approved for MDD, but used for many off-label indications including anxiety

Dietary Restrictions for patients taking monoamine oxidase inhibitors

Aged cheeses (B)	Monosodium glutamate
Sour cream(C)	Liver (chicken or beef, more than 2 days old)
Yogurt (C)	Fermented foods
Cottage cheese (C)	Canned figs
American cheese (C)	Raisins
Mild Swiss cheese(C)	Pods of broad beans (fava beans)
Wined (especially Chianti and sherry) (D)	Yeast extract and other yeast products
Beer	Meat extract (marmite)
Herring (pickled, salted, dry)	Soy sauce
Sardines	Chocolate(E)
Snails	Coffee (E)
Anchovies	Ripe avocado
Canned, aged, or processed meats	Sauerkraut
	Licorice

(A)According to the FDA-approved Prescribing Information for the transdermal selegiline patch, patients receiving the 6 mg/24-hour dose are not required to
modify their diet. However, patients receiving the 9 or 12 mg/24 hours are still required to follow the dietary restrictions similar to the other MAOIs.

(B)Clearly warrants absolute prohibition (e.g., English Stilton, blue, Camembert, cheddar).

(C)Up to 2 oz (59 mL) daily is acceptable.
(D)3 oz (89 mL) white wine or a single cocktail is acceptable.
(E)Up to 2 oz (59 mL) daily is acceptable; larger amounts of decaffeinated coffee are acceptable.

NDRI — Norepinephrine & Dopamine Reuptake Inhibitors

GENERIC	US BRAND	FDA APPROVED USE	Daily dosing
Bupropion	Wellbutrin	**Depression,** seasonal affective disorder, smoking cessation	Initial: 150mg divided bid Usual: 150-300mg (MDD 450mg)

Mixed 5-HT — Mixed Serotonergic Effects

GENERIC	US BRAND	FDA APPROVED USE	Daily dosing
Nefazodone	Serzone	**Depression**	Initial: 150mg divided bid Usual: 150-300mg (MDD 450mg)
Trazodone	Desyrel/ Oleptro	**Depression**	Initial: 150mg divided bid Usual: 150-300mg (MDD 450mg)
Vilazodone	Viibryd	**Depression**	Initial: 10 mg Usual range: 10-40 mg
Vortioxetine	TRINTELLIX	**Depression**	Initial: 10 mg Usual range: 20 mg

5HT & alpha — Mixed Serotonergic and alpha antagonist effects

GENERIC	US BRAND	FDA APPROVED USE	Daily dosing
Mirtazapine	Remeron	**Depression**	Initial: 15 mg Usual range: 15-45 mg

Treatment

- Therapeutic controversies
  - Adherence is more likely with the most uncomplicated drug regimens
  - Fewest dosing times per day=optimal
  - Monotherapy whenever possible
  - Augmentation?
  - Refractory cases?

Treatment

- **Recommending an optimal therapeutic regimen**
  - Must consider patient preference
  - Multiple uses of single agents, when possible
    - Some medications can treat both psychiatric and medical illness
  - Should be sure to avoid certain medications in patients with special conditions
    - Seizure disorders (bupropion)
    - Substance abuse (benzodiazepines)
    - Cardiac complications (TCAs)
    - GI bleeding and anticoagulation (SSRIs)

Therapeutic Response

Once a regimen is selected, how do we monitor for effectiveness?

Several factors can help evaluate therapeutic outcomes

- Serum concentrations
- Side effects
- Remission of target symptoms
- Rating scales
  - provide objective results of subjective descriptions
  - formal tool

Special Populations

- Elderly
- Children
- Pregnancy
- Black box warnings

Special Populations

Elderly

- Beers List
  - Should be used as a guide for the identification of medications which may have risks which outweigh the benefits for the elderly
  - The criteria is not applicable in all circumstances
  - Designation for close monitoring with careful use may be the clinically appropriate plan for the patient.

Special Populations

Elderly

- Major health concern due to suboptimal tx or missed diagnosis (dementia, physical symptoms)
- Anhedonia (lack of ability to experience pleasure)
- altered PK/PD-leading to increased ADR or suboptimal tx by overly conservative clinicians
- SSRI usually best choice as initial treatment
- Second choices often bupropion and venlafaxine
- Evidence of mirtazapine benefits on anxiety, sleep, and appetite stimulation (watch cholesterol)
- Avoid TCA

Special Populations

Children

- Uncomplicated, mild depression may do well with psychoeducation and psychotherapy alone
- **Fluoxetine** is the only medication approved for tx of *children 8 years and older* as well as for adolescent depression
  - Fluoxetine 10 to 20 mg daily
  - sertraline studied, but not approved at this time
- **Escitalopram** is FDA approved for *children over 12 years old*
- Other studies looked at TCA, venlafaxine, mirtazapine…no better than placebo

Special Populations

Children

- The FDA in 2004 required antidepressant manufacturers to revise labeling to include BBW about the risk of suicide in children and adolescents being treated with their antidepressants.

- Then in May 2007, the FDA extended the BBW to include young adults up to the age of 25.

Medication	Indication	Age	Initial Dose	Maximum Dose	Other Information	Generic Availability
clomipramine[1]	OCD	10 to 17 years old	25 mg once a day	3 mg per kg or 200 mg per day, whichever is lower	Dose may be increased gradually over the first 2 weeks to 3 mg per kg or 100 mg per day, whichever is lower. Further dose increases should occur gradually over several weeks. During initial titration, give in divided doses with meals. After initial titration, dose may be given once a day at bedtime.	Yes
escitalopram[2]	MDD	12 to 17 years old	10 mg once a day	20 mg once a day	Dose may be increased to 20 mg once a day after 3 weeks.	Yes
fluoxetine[3]	MDD	8 to 18 years old	10 mg or 20 mg once a day	20 mg once a day	Lower weight children should be started on 10 mg once a day.	Yes
fluoxetine	OCD	7 to 17 years old	10 mg once a day	60 mg per day	After 2 weeks, the dose may be increased to 20 mg once a day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. Doses above 20 mg per day may be given once a day or in 2 divided doses.	Yes
fluvoxamine*[4]	OCD	8 to 11 years old	25 mg once a day	200 mg per day	Dose may be increased by 25 mg every 4 to 7 days. Doses over 50 mg per day should be given in 2 divided doses.	Yes
fluvoxamine*	OCD	12 to 17 years old	25 mg once a day	300 mg per day	Dose may be increased by 25 mg every 4 to 7 days. Doses over 50 mg per day should be given in 2 divided doses.	Yes
imipramine[5]	childhood enuresis	6 to 11 years old	25 mg once a day, 1 hour before bedtime	2.5 mg per kg up to 50 mg once a day	Dose may be increased after 1 week. Evidence suggests that in early-night bedwetters, the medication is more effective given earlier and in divided amounts.	Yes
imipramine	childhood enuresis	12 years old and older	25 mg once a day, 1 hour before bedtime	2.5 mg per kg up to 75 mg once a day	Dose may be increased after 1 week. Evidence suggests that in early-night bedwetters, the medication is more effective given earlier and in divided amounts.	Yes
sertraline[6]	OCD	6 to 12 years old	25 mg once a day	200 mg once a day	Dose changes should not occur at intervals of less than 1 week.	Yes
sertraline	OCD	13 to 17 years old	50 mg once a day	200 mg once a day	Dose changes should not occur at intervals of less than 1 week.	Yes

This fact sheet was prepared by the Education Medicaid Integrity Contractor (MIC) for the CMS Medicaid Integrity Program (MIP). For more information on the MIP, please visit http://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/pharmacy-ed-materials.html on the CMS website or scan the Quick Response (QR) code on the right with your mobile device.

Special Populations

Pregnancy

Key principles to consider:

- Pregnancy does not protect against depression and untreated, can result in relapses
- Maternal depression can adversely affect the development of the child
- Risk versus benefit must be weighed
- SSRIs are the most commonly used and best tolerated medication during pregnancy, but these too carry a small but significant risk (AVOID PAROXETINE)

Treatment Resistant Depression

Refractory patients:

- Non response to 2 separate trial of different antidepressants (AD)
  - with adequate dose and duration in current episode
  - Need to ensure trials were optimized
- Switch to alternative AD medication class
- Strategies to switch: can cross titrate or discontinue and start
  - risk of withdrawal but can accomplish more quickly
- Combinations that have been used
  - SSRI or SNRI + bupropion (or mirtazapine)
  - SSRI plus TCA
- Sequenced Treatment Alternatives to Relieve Depression (STAR*D)
  - 1 of 4 patients achieved remission with a switch to different AD
  - 1 of 3 patients who previously did not remit, improved with augmentation

Treatment Resistant Depression

Refractory patients:

- No support for 2 agents within the same class
- Augmentation is an option, but consider the risks:
  - Lithium
  - Pindolol
  - Stimulants
  - Dopamine agonists
  - Folic acid (helps synthesis of monamines)
  - Thyroid supplementation
  - Atypical Antipsychotic**

Treatment Resistant Depression

Atypical Antipsychotics

- Abilify, Seroquel XR & brexpiprazole approved in combo with AD
- Abilify 2 to 5mg once daily, usual range 2-15mg/d
- Symbyax (olanzapine 6mg/fluoxetine 25mg up to 18-75mg)
- Brexpiprazole target to 2mg (0.1mg to start) up to max 3mg
- Seroquel XR 50mg start up to 150mg (can range up to 300mg)
- AAP augmentation doses for TRD less than schizophrenia
- Change in depression scores were reduced 1 to 3 points better than placebo
- Long term risks? How long continue? …..

QUESTIONS?