Integrated Psychiatric Services

Depressive Disorder Spectrum of Diseases- Diagnosis and Management

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  • (Pharmacology slides courtesy of Jennifer Nelson, Pharm. D)
Psychiatric Services Integration Project

• Community Oriented Primary Care-Population Health
  • Waseem Ahmed, M.D.
“The Body must be treated as a whole and not just a series of parts.”

Hippocrates 430 BC
“Psychiatric Health Services integrated with Primary Care and Specialty Health Services strives to provide to all individuals served:

- Comprehensive psychiatric care through high quality clinical practices, education, and research to achieve the most optimal health and well-being.
- Coordination with all community organizations that are vested in the best outcomes and well-being of the individual”
• STATEMENT OF VISION

• “The Vision Statement of Integrated Psychiatric Services in Community Oriented Primary Care is to create a true center of excellence and be a leader in patient experience, clinical outcomes, research, and education.”
• **Scope of Integrated Psychiatric Services**

  • The scope of Integrated Psychiatric Services at Population Health is:
  
  • Establish a systematic approach to provide comprehensive integrated psychiatric services to reduce stigma promote wellness, education, and hope for recovery across community.
  
  • Suicide prevention.
  
  • Coordination of care with primary care and community organization.
  
  • Improve access to quality care that is culturally competent.
  
  • Accurately identify and treat co-occurring mental and substance use disorders in primary care.
• Guiding Principals
• Based upon these principals, the approach to psychiatric treatment at Dallas County Jail is recovery oriented and Psychiatric Rehabilitation. The component of Psychiatric Rehabilitation includes:

  1) Recovery
  2) Resilience
  3) Symptom and behavior management
  4) Skill acquisition
Psychiatric Services Integration
Project

• Mental illness creates substantial burden for patients, families, and society as a whole.
• Mental and Physical problems are interwoven. Integrating care ensures treatment in a holistic manner.
• Treatment gap for mental illness is enormous. Service integration can help reduce this gap.
• Providing mental health services in a primary care setting can help improve access.
• Delivering mental health services in a primary care setting reduces stigma and discrimination.
• Treating common mental disorders in a primary care setting is cost effective.
• The majority of people with mental health disorders in a primary care setting have good outcomes.
- Enhances the role of “Primary Care Provider” and “Pediatricians” in providing holistic care including psychiatric care.

- **Target is to:**
  - Improve clinical outcomes
  - Patients satisfaction
  - Healthcare providers’ satisfaction
  - Building healthier communities.
Various model of Collaboration Continuum

<table>
<thead>
<tr>
<th>MINIMAL</th>
<th>BASIC at a distance</th>
<th>BASIC On-site</th>
<th>CLOSE Partly integrated</th>
<th>CLOSE Fully Integrated</th>
</tr>
</thead>
</table>

COLLABORATION CONTINUUM
For COPC suggested Models for Psychiatric Services for all patients:

- Close Partially Integrated
- Close Fully Integrated

<table>
<thead>
<tr>
<th>MINIMAL</th>
<th>BASIC at a distance</th>
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<tr>
<td></td>
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<td>CLOSE Partially integrated</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CLOSE Fully Integrated</td>
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</tr>
</tbody>
</table>

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The National HIV/AIDS Strategy
Goals-2020

• Reduce New Infections
• Increase Access to Care and Improve Health Outcomes for People Living with HIV
• Reduce HIV-Related Health Disparities and Health Inequities
• Achieve a More Coordinated National Response to the HIV Epidemic
Cycle of Acceptance

Denial

Acceptance

Anger

Depression, Anxiety, Stress

Bargaining
• Risk for suicide increases during the initial weeks following a diagnosis of HIV disease
• The suicide rate is three times higher than the general population
• Diagnosis of HIV may exacerbate self-destructive behaviors
• Diagnosis of HIV may cause a psychological crisis and cause psychiatric disorders
• Diagnosis of HIV may exacerbate underlying psychiatric disorders
Psychiatric disorders:
- Impairment in ability to function
- Decrease survival
- Impair quality of life
- Decrease adherence to treatment
- Higher demand for treatment
- Higher treatment costs, etc.
Depression and Anxiety Disorders

- More than 40 million people worldwide are living with HIV viral infection
- 1.2 Million people in the USA are living with HIV infection
- Among HIV infected patients Depression affects 20-30% of patients
- Among HIV patients with MDD only 14–24% receive adequate treatment
- Prevalence of panic disorder among HIV patients ranged from 11% to 16%
- Prevalence of Generalized Anxiety Disorder ranged between 6.5% and 20%
Primary motor cortex (voluntary movement)

Premotor cortex (coordinates voluntary movements)

Central sulcus

Primary somatosensory cortex (somesthetic sensations and proprioception)

Sensory association areas (integration of sensory information)

Visual association areas (higher vision processing)

Primary visual cortex (vision)

Wernicke’s area (language comprehension)

Prefrontal association areas (idea and plan for voluntary movement, thoughts, personality)

Broca’s area (speech formation)

Olfactory cortex (smell)

Limbic association cortex (emotions, learning, and memory)

Primary auditory cortex (hearing)

Auditory association areas
New Medical Paradigm: Shift from Linear to Integrated Medicine

- Neurotransmitters
- Hormones
- Cytokines

- Anxiety
- Depression
- Insomnia

- Pain
- Inflammation
- Autoimmunity

HP–Thyroid
HP–Adrenal
HP–Gonadal

Endocrinology

Immunology

Stress

Cytokines
Hormones
Feelings of pleasure
Feelings of satisfaction
GI Track health
Muscle function and control
Focus
Motivation

DOPA
MINE

Urges
Cravings
Impulsivity
Movement disorders

Poor intestinal function
Developmental delays in children
Attention issues
Lack of motivation
Low mood
Sleep difficulties
Uncontrolled appetite
Headaches
Hot flashes

Mood
Sleep
Appetite
Sexual Arousal

Stress
Platelet aggregation

SEROTONIN
GLUTAMATE

Fatigue
Learning difficulties

Anxiousness
Low mood
Activated immune system

Learning
Memory
Primary excitatory neurotransmitter
Major Depressive Disorder

• A. 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. Note: Do not include symptoms that are clearly attributable to another medical condition.
Major Depressive Disorder

• 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.)

• 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).
• 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.)

• Insomnia or hypersomnia nearly every day.

• Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

• Fatigue or loss of energy nearly every day.
• Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
• Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
• 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.
Major Depressive Disorder

- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. The episode is not attributable to the physiological effects of a substance or to another medical condition.
- Note: Criteria A-C represent a major depressive episode.
Major Depressive Disorder

- D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
- E. There has never been a manic episode or a hypomanic episode.
  Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.
Notes: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode.

Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered.

This decision inevitably requires the exercise of clinical judgment based on the individual’s history and the cultural norms for the expression of distress in the context of loss.
Severity/course specifier

- Mild
- Moderate
- Severe
- With psychotic features**
- In partial remission,
  In full remission, Unspecified
- Single episode
- Recurrent episode*
Major Depressive Disorder

- In children and adolescents, the mood may be irritable rather than sad.
- The individual must also experience at least four additional symptoms drawn from a list that includes changes in appetite or weight, sleep, and psychomotor activity; decreased in energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation or suicide plans or attempts.
Nine Symptoms of Depression

1. Depressed mood
2. Anhedonia or diminished interest or pleasure
3. Weight loss or gain-5%
4. Sleep Disturbance- Hypersomnia or Insomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate
9. Recurrent thoughts of death or suicidal ideas
• Twelve-month prevalence of major depressive disorder in the United States is approximately 7%.
• There are differences by age group such that the prevalence in 18- to 29-year-old individuals is threefold higher than the prevalence in individuals age 60 years or older.
• Females experience 1.5- to 3-fold higher rates than males beginning in early adolescence.
Depressive Disorder

• Major depressive disorder may first appear at any age, but the likelihood of onset increases markedly with puberty.
• In the United States, incidence appears to peak in the 20s, however, first onset in late life is not uncommon.
The course of major depressive disorder is quite variable, such that some individuals rarely, if ever, experience remission (a period of 2 or more months with no symptoms, or only one or two symptoms to no more than a mild degree), while others experience many years with few or no symptoms between discrete episodes.
• Recovery typically begins within 3 months of onset for two in five individuals with major depression and within 1 year for four in five individuals.
• Recency of onset is a strong determinant of the likelihood of near-term recovery, and many individuals who have been depressed only for several months can be expected to recover spontaneously.
• Features associated with lower recovery rates, other than current episode duration, include psychotic features, prominent anxiety, personality disorders, and symptom severity.
• The risk of recurrence becomes progressively lower over time as the duration of remission increases.
• The risk is higher in individuals whose preceding episode was severe, in younger individuals, and in individuals who have already experienced multiple episodes.
• The persistence of even mild depressive symptoms during remission is a powerful predictor of recurrence.
• Many bipolar illnesses begin with one or more depressive episodes, and a substantial proportion of individuals who initially appear to have major depressive disorder will prove, in time, to instead have a bipolar disorder.

• This is more likely in individuals with onset of the illness in adolescence, those with psychotic features, and those with a family history of bipolar illness.
• There appear to be no clear differences by gender in phenomenology, course, or treatment response.
• There are no clear effects of current age on the course or treatment response of major depressive disorder.
• There is higher prevalence in females but there are no clear differences between genders in symptoms, course, treatment response, or functional consequences.
• In women, the risk for suicide attempts is higher, and the risk for suicide completion is lower.
• Impairment may range to complete incapacity such that the depressed individual is unable to attend to basic self care needs or is mute or catatonic.
• Among individuals seen in general medical settings, those with major depressive disorder have more pain and physical illness and greater decreases in physical, social, and role functioning.
• Environmental. Adverse childhood experiences, particularly when there are multiple experiences of diverse types, constitute a set of potent risk factors for major depressive disorder.

• Stressful life events are well recognized as precipitants of major depressive episodes.
Depressive Disorder

- Genetic and physiological. First-degree family members of individuals with major depressive disorder have a risk for major depressive disorder two- to fourfold higher than that of the general population.
- Heritability is approximately 40%, and the personality trait neuroticism accounts for a substantial portion of this genetic liability.
• Temperamental. Neuroticism (negative affectivity) is a well-established risk factor for the onset of major depressive disorder, and high levels appear to render individuals more likely to develop depressive episodes in response to stressful life events.
• However, sustained clinical improvement in depressive symptoms may depend on the appropriate treatment of underlying illnesses.
• Chronic or disabling medical conditions also increase risks for major depressive episodes.
• Such prevalent illnesses as HIV infection, diabetes, morbid obesity, and cardiovascular disease are often complicated by depressive episodes, and these episodes are more likely to become chronic than are depressive episodes in medically healthy individuals.
Persistent Depressive Disorder

- In DSM V this disorder represents a consolidation of chronic major depressive disorder and dysthymic disorder as defined in DSM-IV-TR.

- A. Depressed mood for most of the day, for more days than not, as indicated by either
  - subjective account or observation by others, for at least 2 years.
  - Note: In children and adolescents, mood can be irritable and duration must be at least 1 year.
  - B. Presence, while depressed, of two (or more) of the following:
    - Poor appetite or overeating.
    - Insomnia or hypersomnia.
    - Low energy or fatigue.
    - Low self-esteem.
    - Poor concentration or difficulty making decisions.
    - Feelings of hopelessness.
Persistent Depressive Disorder

- C. During the 2 year period (1 year for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 months at a time.
- Criteria for a major depressive disorder may be continuously present for 2 years.
- There has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder.
- The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
Persistent Depressive Disorder

- The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g. hypothyroidism).
- These symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Persistent Depressive Disorder

- **Specify if:**
  With anxious distress (p. 184)
  With mixed features (pp. 184-185)
  With melancholic features (p. 185)
  With atypical features (pp. 185-186)
  With mood-congruent psychotic features (p. 186)
  With mood-incongruent psychotic features (p. 186)
  With peripartum onset
Persistent Depressive Disorder

- The 12-month prevalence in the United States is approximately 0.5% for persistent depressive disorder and 1.5% for chronic major depressive disorder.
- Persistent depressive disorder often has an early and insidious onset (i.e., in childhood, adolescence, or early adult life) and, by definition, a chronic course.
- Early onset (i.e., before age 21 years) is associated with a higher likelihood of comorbid personality disorders and substance use disorders.
• Premenstrual Dysphoric Disorder is now an official diagnosis in the DSM-5.
• In most menstrual cycles during the past year, five (or more) of the following symptoms occurred during the final week before the onset of menses, started to improve within a few days after the onset of menses, and were minimal or absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):
Premenstrual Dysphoric Disorder

- (1) marked affective liability (e.g., mood swings; feeling suddenly sad or tearful or increased sensitivity to rejection)
- (2) marked irritability or anger or increased interpersonal conflicts
- (3) markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
- (4) marked anxiety, tension, feelings of being “keyed up” or “on edge”
Premenstrual Dysphoric Disorder

- (5) decreased interest in usual activities (e.g., work, school, friends, hobbies)
- (6) subjective sense of difficulty in concentration
- (7) lethargy, easy fatigability, or marked lack of energy
- (8) marked change in appetite, overeating, or specific food cravings
- (9) hypersomnia or insomnia
- (10) a subjective sense of being overwhelmed or out of control
- (11) other physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of “bloating,” weight gain
• A prominent and persistent period of depressed mood or markedly diminished interest or pleasure in all, or almost all, activities that predominates in the clinical picture.

• There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition.
Depressive Disorder Due to another Medical Condition

• The disturbance is not better explained by another mental disorder (e.g., adjustment disorder, with depressed mood, in which the stressor is a serious medical condition).
• The disturbance does not occur exclusively during the course of a delirium.
• The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Management of Depressive Disorders

- Medications
- Psychotherapies
  - Cognitive Behavioral
  - Supportive
  - Family
  - Group
  - Educational
Human immunodeficiency virus (HIV) has a high comorbidity with major depression.

Symptoms of depression may be attributed to ongoing HIV infection.

Depression can decrease quality of life for these patients, decrease adherence with HIV medications, and it has shown to decrease positive outcomes overall.

Timely identification of the symptoms and treatment improves treatment outcome.
• However, only imipramine, fluoxetine, sertraline, and paroxetine have evidence from double-blind trials
• TCAs, including nortriptyline, desipramine, imipramine, amitriptyline, clomipramine, and doxepin, have all been shown to have increased levels in plasma by ritonavir and ritonavir combinations
• TCA blood levels can and should be checked even in patients not on other medications with possible interactions
• SSRIs-Sertraline and Citalopram have been shown to have decreased metabolism in the Ritonavir
• Fluoxetine and fluvoxamine are both decreased by Nevirapine,
• Fluoxetine and fluvoxamine increase the levels of the following HIV medications: Amprenavir, Delarvidine, Efavirenz, Indinavir, Lopinavir/ritonavir, Nelfinavir, Ritonavir, and Saquinavir
• Darunavir, Indinavir, Lopinavir/Ritonavir, Ritonavir may potentially increase the side effects Trazodone such as of nausea, dizziness, hypotension, and syncope
Antidepressant Classes

- Tricyclic Antidepressants (TCAs)
- Monoamine Oxidase Inhibitors (MAOIs)
- Serotonin Selective Reuptake Inhibitors (SSRIs)
- Serotonin Partial/Agonst Reuptake Inhibitors (SPARIs)
- Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
- Others: mirtazapine, bupropion, nefazodone/trazodone
• Need an acute and continuation phase
• Stage 1: SSRI (fluoxetine, citalopram, or sertraline)
• Stage 2: alternate SSRI (any)
• Stage 2a: augment SSRI with lithium, bupropion, or mirtazapine
• Stage 3: bupropion, duloxetine, mirtazapine, venlafaxine

Texas Children’s Medication Algorithm Project (CMAP), updated in 2007
<table>
<thead>
<tr>
<th>Medication</th>
<th>Labeled Indications</th>
<th>Off-Label Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Depression</td>
<td>Bulimia Nervosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia (adults)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Obsessive-compulsive disorder</td>
<td>Panic disorder</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Depression and/or anxiety</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insomnia (Silenor® only)</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>Depression</td>
<td>Bulimia Nervosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cocaine dependence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panic disorder</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Depression</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Depression</td>
<td>Attention deficit hyperactivity disorder (ADHD) (adults, adolescents, children)</td>
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<tr>
<td></td>
<td></td>
<td>Bulimia Nervosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tourette syndrome with comorbid ADHD</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Amoxapine</td>
<td>Depression</td>
<td></td>
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<tr>
<td>Medication</td>
<td>Dose</td>
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</tr>
<tr>
<td>Amitriptyline</td>
<td>Depressive disorders: Adolescents (12 years and older): 10mg TID or 20mg QHS</td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>OCD: Children 10 years and older: Initial: 25mg/day; do not exceed: 3 mg/kg/day or 200mg/day (whichever is smaller)</td>
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<tr>
<td>Doxepin</td>
<td>Not approved for use in pediatric patients</td>
<td></td>
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<tr>
<td>Imipramine</td>
<td>Depression: Adolescents: 30-40 mg/day, do not exceed 100mg/day Children: 1.5 mg/kg/day in 2 to 3 divided doses, do not exceed 5 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Depression: Adolescents: 50 mg/day, do not exceed: 100 mg/day</td>
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</tr>
<tr>
<td>Nortriptyline</td>
<td>Depression: Adolescents and 6-12 years old: 1-3 mg/kg/day divided 3-4 times a day, do not exceed 150mg/day</td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Off-label</td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>Depression: Adolescents: 25-100 mg/day QD or divided doses, do not exceed: 150mg/day ADHD: Children 5 years and older and adolescents: 1.5 mg/kg/day in divided doses Children and adolescents between 7-13 years old: 25mg QHS, do not exceed 3 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Depression: Adolescents: 15 mg/d in 3 divided doses, do not exceed 60 mg/day</td>
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</tr>
<tr>
<td>Amoxapine</td>
<td>Safety and efficacy has not been established</td>
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</tr>
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</table>
Selective Serotonin Reuptake Inhibitors (SSRIs)

**Available agents**
- Fluoxetine (Prozac®)
- Paroxetine (Paxil®)
- Sertraline (Zoloft®)
- Citalopram (Celexa®)
- Escitalopram (Lexapro®)
- Fluvoxamine (Luvox®)

**Pharmacology**
- Selectively inhibit the reuptake of serotonin
  - 5HT neuron has a relative deficiency of NT 5HT, as well as 5HT receptors are upregulated
  - SSRIs block the serotonin reuptake pump or serotonin transporter (SERT), causing serotonin increase at the serotonin neuron
  - 5HT$_{1A}$ autoreceptors desensitize or downregulate
  - Neuronal impulse flow is turned on, and there is release of 5HT in the axon terminal
  - No muscarinic, histaminic, or alpha blockade
<table>
<thead>
<tr>
<th>DRUG</th>
<th>%PB</th>
<th>T1/2 (HR)</th>
<th>ACTIVE METABOLITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>80</td>
<td>35</td>
<td>Desmethylcitalopram</td>
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<tr>
<td>Escitalopram</td>
<td>56</td>
<td>27-32</td>
<td>S-Demethylcitalopram</td>
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<tr>
<td>Fluoxetine</td>
<td>94</td>
<td>24-72</td>
<td>Norfluoxetine</td>
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<tr>
<td>Fluvoxamine</td>
<td>77</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>95</td>
<td>21</td>
<td>None</td>
</tr>
<tr>
<td>Sertraline</td>
<td>99</td>
<td>26</td>
<td>Desmethylsertraline</td>
</tr>
</tbody>
</table>
• **Dosing**
  - Fluoxetine: tab, cap, ER, soln
  - Paroxetine HCl: tab, ER, soln
  - Paroxetine Mesylate: tablets
  - Sertraline: tab, soln
  - Fluvoxamine: tab, ER
  - Citalopram: ODT, tab, soln
  - Escitalopram: tab, soln

• **Children/Adolescent specific side effects**
  - Nausea, loss of appetite or diarrhea
  - Irritability
  - Trouble sleeping (activation) or drowsiness
  - Headache
  - Changes in appetite
  - Tendency to bruise
  - Later-onset frontal lobe symptoms
    • Disinhibition, apathy and indifference
Serotonin Partial Agonist/Reuptake Inhibitors (SPARIs)

Vilazodone (Viibryd®)
- Currently not on PMH formulary
- Safety and effectiveness has not been established in children/adolescents
- SERT inhibition
- 5-HT1A receptor partial agonist
  - 50% of SERTs and 5HT_{1A} receptors are occupied
  - Enhanced dopamine release

Vortioxetine (Brintellix®)
- Currently not on PMH formulary
- Safety and effectiveness has not been established in children/adolescents
- 5HT_{1A} receptor agonist
- 5HT_{3} receptor antagonist
<table>
<thead>
<tr>
<th>ISOENZYME</th>
<th>INHIBITOR (MOD-HIGH)</th>
<th>DRUGS METABOLIZED</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP450 1A2</td>
<td>Fluvoxamine</td>
<td>Theophylline, R-Warfarin, TCAs (demethylation), clozapine, tizanidine, pimozide,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ramelteon</td>
</tr>
</tbody>
</table>
| CYP450 2C9/19 | Fluoxetine  
Fluvoxamine  
Sertraline  
Vilazodone  | Phenytoin, S-Warfarin, TCAs (demethylation), tolbutamide, diazepam, methadone   |
| CYP450 2D6 | Fluoxetine  
Paroxetine  
Vilazodone  | Codeine, 1C antiarrhythmics, TCAs (hydroxylation), antipsychotics, beta-blockers |
| CYP450 3A4 | Fluvoxamine  
Fluoxetine  
Sertraline  
Vilazodone  | BZD (triazolo-), CBZ, TCAs (demethylation), pimozide, ramelteon, methadone       |

Lexi-Comp Online TM, Hudson, Ohio: Lexi-Comp, Inc.; April 2016
• NSAIDS – SSRIs may enhance the antiplatelet effect of NSAIDs (rating: MAJOR) – to minimize risk of bleeding, addition of a gastroprotective agent (such as a PPI) should be added
• Clopidogrel – SSRIs may decrease the serum concentration of the active metabolite(s) of Clopidogrel – increase monitoring for signs/symptoms of bleeding
• Herbal products (Alfalfa, Anise, Bilberry) – SSRIs may enhance the adverse/toxic effect of antiplatelet agents. Bleeding may occur
Warnings/Precautions

Monitoring Parameters

• **Warnings/Precautions**
  – Activation of mania/hypomania
  – QTc prolongation (specifically citalopram, fluoxetine and escitalopram)
  – Abnormal bleeding
  – Hyponatremia risk

• **Monitoring Parameters**
  – Pregnancy test (as clinically indicated)
  – Emergence of suicidal ideation or behavior
  – Weight and growth
  – Serum sodium, if symptoms of hyponatremia occur (headaches, confusion, etc)
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

- Venlafaxine (Effexor®)
- Duloxetine (Cymbalta®)
- Desvenlafaxine (Pristiq®)
- Levomilnacipran (Fetzima®)
• **Venlafaxine (Effexor®)**
  – Not approved for use in pediatric patients
  – Potent inhibitor of 5-HT and NE reuptake and a weak inhibitor of DA reuptake
  – Unlike TCAs, it has virtually no affinity for cholinergic, histaminergic, and alpha-1 adrenergic receptors

• **Duloxetine (Cymbalta®)**
  – Currently not on PMH formulary
  – Approved for generalized anxiety disorder
  – Potent inhibitor of neuronal serotonin and norepinephrine reuptake and weak inhibitor of dopamine reuptake.
  – No significant activity for muscarinic, cholinergic, histaminergic or alpha-adrenergic receptors.
  – 7-17 years old: 30mg QD; do not exceed 120mg/day
SNRIs

- **Desvenlafaxine (Pristiq®)**
  - Currently not on PMH formulary
  - Not approved for use in pediatric patients
  - Potent and selective serotonin and norepinephrine reuptake inhibitor.

- **Levomilnacipran (Fetzima®)**
  - Currently not on PMH formulary
  - Not approved for use in pediatric patients
  - Inhibition of reuptake of serotonin and norepinephrine (lacks affinity for any other receptors)
• **Warnings/Precautions**
  – Abnormal bleeding
  – Severe skin reactions
  – Activation of mania/hypomania
  – Hepatotoxicity (TCAs)
  – Elevated blood pressure and pulse
  – Seizures (TCAs)
  – Hyponatremia

• **Monitoring Parameters**
  – Pregnancy test (as clinically indicated)
  – Emergence of suicidal ideation or behavior
  – Blood pressure
  – Hepatic function tests (as clinically indicated)
  – CBC and EKG (TCAs)
  – Weight and growth
• Mirtazapine (Remeron®)
• Bupropion (Wellbutrin®, Forfivo XL®, Aplenzin®)
• Nefazodone (Serzone®)
• Trazodone (Desyrel®, Oleptro®)
- **Mirtazapine (Remeron®)**
  - Classified as an alpha-2 Adrenergic Antagonist
  - Blocks presynaptic alpha-2 receptors, both alpha-2 autoreceptors and alpha-2 heteroreceptors with resultant increases in both NE and 5-HT neurotransmission, respectively: Potent 5-HT-2 and 5-HT-3 receptor blockade
    - Alpha-2 antagonism keeps NE from being able to turn off its own release, as well as acts on heteroreceptors to keep serotonin from turning off
    - NE neurons innervate the cell bodies and stimulate serotonin release
    - Result in increase in 5HT and NE independent of blockade of monoamine transporters
  - Blocks muscarinic cholinergic, histamine-1, and alpha-1 adrenergic receptors
  - *Off-label:* Insomnia: 12-18 years old: 30-45mg QHS
  - Monitoring: weight and height, serum cholesterol levels, CBC

- **Bupropion (Wellbutrin®)**
  - Aplenzin®: Bupropion Hydromide
  - Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®, Zyban®, Forfivo XL®, Buproban: Bupropion HCl
  - Additional boxed warning: smoking cessation treatment: serious neuropsychiatric events have occurred in patients taking bupropion for smoking cessation
  - Norepinephrine/Dopamine reuptake inhibitor (NDRI)
  - Inhibits the reuptake of both dopamine and norepinephrine
    - Metabolized to several active metabolites (active drug and precursor for other active drugs)
    - Most potent: + enantiomer of the 6-hydroxy metabolite of bupropion: radafaxine
  - Lacks blockade of cholinergic, histaminergic, and alpha-1 adrenergic receptors
  - *Off-label:* ADHD
    - IR/ER/SR: up to 3mg/kg/day or 150mg/day; do not exceed 6mg/kg/day or 300mg/day, single dose should not exceed 150mg; given as BID for children and up to TID for adolescents
**Trazodone (Desyrel®, Oleptro®)**
- Classified as Serotonin Antagonist/Reuptake Inhibitors (SARI)
  - Serotonin 2A/2C antagonist and serotonin reuptake inhibitor
- These agents block 5HT2A and 2C, as well as serotonin reuptake
  - Nefazodone: 5HT2A > 2C, SERT
- Trazodone also blocks histaminergic and alpha-adrenergic receptors
- **Off-label**:
  - Aggressive behavior: 50mg QHS; do not exceed 200mg/day, divided into 3 daily doses
  - Depression: 6 years or older: 1.5 to 2mg/kg/day divided 2-3 times a day; do not exceed 6mg/kg/day
  - Insomnia: 6-17 years of age: 50-150mg QHS

**Nefazodone (Serzone®)**
- Not on PMH formulary
- Nefazodone also has weak NE reuptake inhibition and weak alpha-adrenergic blocking properties
- Additional boxed warning: hepatotoxicity: reported rate in the US is 1 case of liver failure resulting in death or transplant per 250,000 to 300,000
- Safety and efficacy in the pediatric population has not been established
• Thank you.
• Comments
• Questions

• References are available if requested.