Psychopharmacological Management of Depressive and Anxiety Disorders

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Psychiatric Services Integration Project
“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.”
• 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
• 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 and outcomes
  – cost effective
  – reduces stigma and discrimination.
• 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.
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>
<th>BASIC On-site</th>
<th>CLOSE Partially integrated</th>
<th>CLOSE Fully Integrated</th>
</tr>
</thead>
</table>
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

Figure 9
The diagram illustrates the balance of mood, cognitive function, andneurochemical processes involving Norepinephrine, Serotonin, and Dopamine.

- **Norepinephrine**:
  - Alertness
  - Concentration
  - Energy
  - Anxiety
  - Impulse
  - Irritability

- **Serotonin**:
  - Obsessions
  - Compulsions
  - Memory
  - Appetite
  - Sex
  - Aggression

- **Dopamine**:
  - Pleasure
  - Reward
  - Motivation
  - Drive

The intersection of these processes is labeled "Balance," emphasizing the importance of maintaining equilibrium in these neurochemical systems for optimal mental health.
New Medical Paradigm:
Shift from Linear to Integrated Medicine

- Neurology
  - Anxiety
  - Depression
  - Insomnia

- Endocrinology
  - HP-Thyroid
  - HP-Adrenal
  - HP-Gonadal
  - Cytokines
  - Hormones

- Immunology
  - Pain
  - Inflammation
  - Autoimmunity

- Stress
  - Neurotransmitters
  - Cytokines
Depression

- Frustration
- Sadness
- Worthlessness
- Irritability
- Loss of interest in normal activities
- Thoughts of suicide or death
- Tiredness
- Disturbance in sleep or appetite

Anxiety

- Trembling
- Increased breathing rate
- Feeling nervous or powerless
- Having a sense of impending danger or panic
- Restlessness
  - Trouble thinking, concentrating, or making decisions
- Excessive worrying
  - Unexplained physical complaints, such as headaches or stomach aches
- Agitation
  - Disturbance in sleep or appetite
- High Heart rate
- Sweating
Depressive Disorders

- Major Depressive Disorder
- Persistent Depressive Disorder > 2 years
- Premenstrual Dysphoric Disorder
- Depressive Disorder Due to Medical Condition or Substance Abuse
- Depressive disorder due to other specifier - postpartum
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.
Depressive Symptoms

- Depressed mood
- Loss of pleasure
- Insomnia or hypersomnia
- Weight loss or weight gain
- Fatigue or loss of energy
- Psychomotor agitation or retardation
- Feelings of worthlessness or Guilt
- Diminished ability to think or poor concentration
- Suicidal Ideas

Feelings of worthlessness or Guilt

Diminished ability to think or poor concentration

Suicidal Ideas
Anxiety Disorders

- Generalized Anxiety Disorder
- Adjustment Disorder with Anxiety

Post Traumatic Stress Disorder

- Panic Disorder
- Obsessive-Compulsive Disorder
- Social Phobia

Anxiety Disorder Due to Medical Condition or Substance Abuse

Anxiety disorder due to other specifier-
Anxiety Disorders

- **Fear**
  
  “Fear is emotional response to real or perceived imminent threat”

- **Anxiety**
  
  “Anxiety is anticipation of real or perceived future threat.”
Anxiety Disorders

- *Panic attacks* feature prominently within the anxiety disorders as a particular type of fear response.

- The anxiety disorders differ from one another in the types of objects or situations that induce fear, anxiety, or avoidance behavior, and the associated cognitive ideation.
Symptoms of Panic Attack

- An abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four or more of the following symptoms occur.
- 1. Palpitations, pounding heart, or accelerated heart rate
- 2. Sweating
- 3. Trembling or shaking
- 4. Sensations of shortness of breath or smothering
- 5. Feeling of choking
- 6. Chest pain or discomfort
- 7. Nausea or abdominal distress
- 8. Feeling dizzy, unsteady, lightheaded, or faint
- 9. Chills or heat sensations
- 10. Paresthesias (numbness or tingling sensations)
- 11. Derealization (feelings of unreality) or depersonalization (being detached from oneself)
- 12. Fear of losing control or going crazy
- 13. Fear of dying
Social Anxiety Disorder

- In social anxiety disorder (social phobia), the individual is fearful or anxious about or avoidant of social interactions and situations that involve the possibility of being scrutinized.

- Marked fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others.

- Examples include social interactions (e.g., having a conversation, meeting unfamiliar people), being observed (e.g., eating or drinking), and performing in front of others (e.g., giving a speech).

- The social situations almost always provoke fear or anxiety.
Generalized Anxiety Symptoms

- Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months

- The anxiety and worry are associated with three (or more) of the following six symptoms
Generalized Anxiety Disorder

- Difficulty concentrating or mind going blank.
- Irritability.
- Muscle tension.
- Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
- The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The disturbance is not attributable to the physiological effects of a substance or another medical condition
- The disturbance is not better explained by another mental disorder
• If an individual's primary fear or anxiety is of an object or situation as a result of obsessions (e.g., fear of blood due to obsessive thoughts about contamination from blood-borne pathogens [i.e., HIV]; fear of driving due to obsessive images of harming others), and if other diagnostic criteria for obsessive-compulsive disorder are met, then obsessive-compulsive disorder should be diagnosed.
Psychopharmacology of Depression and Anxiety Disorders
Antidepressant/Antianxiety Classes

- Tricyclic Antidepressants (TCAs)
- Monoamine Oxidase Inhibitors (MAOIs)
- Serotonin Selective Reuptake Inhibitors (SSRIs)
- Serotonin Partial/Agonist Reuptake Inhibitors (SPARIs)
- Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
- Others: mirtazapine, bupropion, nefazodone/trazodone
<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>Bulimia Nervosa</td>
</tr>
<tr>
<td></td>
<td>Insomnia (Silenor® only)</td>
<td>Cocaine dependence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panic disorder</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Depression</td>
<td>Bulimia Nervosa</td>
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<tr>
<td></td>
<td></td>
<td>Cocaine dependence</td>
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<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>
</tr>
<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>
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Selective Serotonin Reuptake Inhibitors (SSRIs)

• **Available agents**
  – Fluoxetine (Prozac®)
  – Paroxetine (Paxil®)
  – Sertraline (Zoloft®)
  – Citalopram (Celexa®)
  – Escitalpram (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
    – 5HT1A 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>SNRIs</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Venlafaxine</td>
<td>75 mg</td>
</tr>
<tr>
<td>Effexor</td>
<td>150 mg</td>
</tr>
<tr>
<td></td>
<td>225 mg</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>50 mg</td>
</tr>
<tr>
<td>Pristiq</td>
<td>100 mg</td>
</tr>
<tr>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30 mg</td>
</tr>
<tr>
<td>Cymbalta</td>
<td>60 mg</td>
</tr>
<tr>
<td></td>
<td>90 mg</td>
</tr>
<tr>
<td></td>
<td>120 mg</td>
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<tr>
<td>SSRIs</td>
<td>Fluoxetine</td>
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<tr>
<td></td>
<td>20 mg</td>
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Side-Effects of Antidepressant Medications

- Constipation
- Anxiety
- Nausea
- Agitation
- Dizziness
- Dry mouth
- Headache
- Drowsiness
- Weight gain
• Bupropion SR, XL (WELLBUTRIN)
  – 100-200 mg BID (SR)
  – 150-450 mg/d (XL)
• Mirtazapine (REMERON), 15-45 mg/d
• Trazodone, 50-200mg (for sleep)
• Buspiron (Buspar) 5-15mg TID
<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>
</tr>
<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>
</tr>
<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>
## SSRI Drug to Drug Interactions

<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, ramelteon</td>
</tr>
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<tr>
<td>CYP450 2C9/19</td>
<td>Fluoxetine, Fluvoxamine</td>
<td>Phenytoin, S-Warfarin, TCAs (demethylation), tolbutamine, diazepam, methadone</td>
</tr>
<tr>
<td></td>
<td>Sertraline, Vilazodone</td>
<td></td>
</tr>
<tr>
<td>CYP450 2D6</td>
<td>Fluoxetine, Paroxetine</td>
<td>Codeine, 1C antiarrhythmics, TCAs (hydroxylation), antipsychotics, beta-blockers</td>
</tr>
<tr>
<td></td>
<td>Vilazodone</td>
<td></td>
</tr>
<tr>
<td>CYP450 3A4</td>
<td>Fluvoxamine, Fluoxetine,</td>
<td>BZD (triazolo-), CBZ, TCAs (demethylation), pimozide, ramelteon, methadone</td>
</tr>
<tr>
<td></td>
<td>Sertraline, Vilazodone</td>
<td></td>
</tr>
</tbody>
</table>
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
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

- Venlafaxine (Effexor®)
- Duloxetine (Cymbalta®)
- Desvenlafaxine (Pristiq®)
- Levomilnacipran (Fetzima®)
• **Venlafaxine (Effexor®)**
  – 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®)**
  – 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.
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

- Aplenzin®, 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
• **Trazodone (Desyrel®, Oleptro®)**
  – Classified as Serotonin Antagonist/Reuptake Inhibitors (SARIs)
    • 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
• Medications
• Various Psychotherapies
  – Cognitive Behavioral
  – Supportive
  – Family
  – Group
  – Educational
Depressive Disorder Management Algorithm

- **Stage 1**
  - Selective serotonin reuptake inhibitors (SSRIs),
    - Celexa, Lexapro, Luvox, Paxil, Prozac, Zoloft, Brintellix and Viibryd
  - Selective serotonin & norepinephrine inhibitors (SNRIs)
    - Cymbalta, Effexor, Fetzima, Khedezla, and Pristiq
  - Other; Bupropion (Wellbutrin)

- Response proceed to Continue phase
- Partial Response proceed to Augmentation
- No Response move to Stage 2
Stage 2
- Select Another medication (same or different class)
- Selective serotonin reuptake inhibitors (SSRIs), Celexa, Lexapro, Paxil, Prozac, Zoloft, Brintellix and Viibryd
- Selective serotonin & norepinephrine inhibitors (SNRIs) Cymbalta, Effexor, Fetzima, Khedezla, and Pristiq
- Other: Other; Bupropion (Wellbutrin)

- Response proceed to Continue phase
- Partial Response proceed to Augmentation, Lithium, Atypical antipsychotics-mood stabilizers, Buspirone, Thyroid hormone, Remeron
- No Response move to Stage 3
Stage 3
Select another class of medication
Selective serotonin reuptake inhibitors (SSRIs),
Celexa, Lexapro, Paxil, Prozac, Zoloft, Brintellix and Viibryd
Selective serotonin & norepinephrine inhibitors (SNRIs)
Cymbalta, Effexor, Fetzima, Khedezla, and Pristiq
Other: Other; Bupropion (Wellbutrin)

Response proceed to Continue phase
Partial Response proceed to augment with Lithium, Lamotrigine, Atypical antipsychotics-mood stabilizers, Latuda, Remeron
No Response proceed to Stage 4
Stage 4
- Combination antidepressants
- SSRI+TCA
- Bupripione+SSRI
- Venlafaxin+SSRI
- Bupropione+Vanlafexin
- Deluxotaine+SSRI
- No response-proceed to
- Stage 5
- ECT

Study have shown that one-third of patients who had not previously responded to treatment with the SSRI were able to attain remission after augmentation with Bupropion or Buspirone or cognitive behavioral therapy (CBT).
Medication treatment:

- Start with SSRIs in doses higher than for depression
  - Citalopram (Celexa) 10-20mg
  - Escitalopram (Lexapro) 10-25 mg. Once Daily
  - Sertraline (Zoloft) 50-150 mg. Once Daily
  - Paroxetine CR (Paxil CR) 25-37.5 Once Daily
  - Celexa, Lexapro, Paxil, Prozac, Zoloft
  - Or

- SNRIs in usual doses
  - Venlafaxine XR (Effexor XR) 75-225 mg Daily
  - Or
  - Buspirone (Buspar) 5-15 mg TID Alone or adjunct to above.
  - Note: often 6-8 weeks before evident response.
  - Or

- Psychotherapy: Referral to outside or co-located professional for cognitive behavioral
  - psychotherapy may be effective as adjunct or in lieu of medication.
• SSRIs in doses higher than that for treatment of depression
  • Paroxetine CR(Paxil CR) 25-37.5 mg Once Daily
  • Escitalopram (Lexapro) 20-25 mg Once Daily
  • Sertraline (Zoloft) 50-200 mg Once Daily

• Cognitive Behavioral Therapy may assist in helping the patient examine and modify persistent thought patterns that contribute to symptoms.
• Therapeutic approaches that address self esteem have been found helpful
Obsessive Compulsive Disorder

- SSRIs in doses greater than those for depression.
- Luvox has OCD indication
- Or
- Clomipramine (Anafranil) titrate from starting dose of 25 mg daily up to final dose of 150-250mg Once Daily. Increase as tolerated.
- Sedation may require H.S. dosing.

- Traditional behavioral or Cognitive Behavioral Therapy have been found to be
- useful adjunctive therapies
Questions or Comments

Thank You

References are available for the material used in the slides for education purpose