DEPRESSION

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EPIDEMIOLOGY

Prevalence

- Occurs in 5%-9% of adult primary care population: 5%-9%
- Twice that in the community as a whole
- Present differently in primary care setting versus patients in mental health centers
  - Less likely to report psychological distress initially
  - More likely to describe physical symptoms: pain, physical dysfunctioning, etc.
- Always consider depression as part of the differential diagnosis with any of the following
  - If can't diagnose a medical condition over time
  - Series of complaints which do not correlate with lab studies
  - Patient who is not responding to treatment

Economic - Epidemiologic Issues

- 4th leading disease burden world-wide; affects 1 in 5 people
- Financial toll exceeded 44 billion in 1990
- Suicide risk in primary care patients treated with antidepressants 43/100,000 person years
- Implicated in cardiovascular disease and cancer

Risk factors

- **Women's rate is 2-3 times more prevalent** vs men throughout life
  - Women: 6-11%; men: 2.6-5.5% men
  - Higher rate of depression in women arises at age 15 yrs or earlier
  - Noted cross culturally
  - Felt to be true difference vs women's higher likelihood to report symptoms
  - Various explanations offered: biological, psychological and social factors
  - Higher incidence seen primarily in patients with high-anxiety depressions
- Previous depression
- History of depression in first-degree relatives
- Substance abuse
- Medical illness
- Stressful life events - still warrant diagnosis and treatment

CLASSIFICATION OF DEPRESSION

- Depression grouped with affective disorders (altered mental status and mood)
- Clinical presentation variable
    - Mood disorders: panic attacks, phobia, dysthymia
    - Physical manifestations common
        - Vegetative symptoms, sleep disturbance
        - Symptoms may be life threatening

DSM IV CLASSIFICATION OF DEPRESSION

1. Major affective disorders (endogenous depression)
2. Bipolar disorder (manic-depressive illness)
3. Chronic affective disorders (dysthymic disorder)
4. Cyclothymic disorder (less severe, chronic mood swings)
5. Organic brain syndrome (organic cause)
6. Adjustment disorder with depressed mood (time limited, situational)

COMMON COMPLAINTS PRESENTING AS DEPRESSION

Fatigue
Insomnia
Headache
Chronic pain
Dizziness
Palpitations
Abdominal cramping
Bloating, heartburn
Numbness
Loss of appetite
Premenstrual syndrome

MECHANISM OF ACTION AND GENERAL PRINCIPLES

- Possibly associated with increased relative concentration of dopamine and serotonin
- Antidepressants effect neurotransmitter specific receptors
- Electroconvulsant therapy has similar mechanism
    - Reduces number of postsynaptic B receptors
    - Down-regulation of receptors

- Most agents take several weeks to become effective
    - Result in immediate biochemical events
    - No effect for several weeks due to changes in postsynaptic receptors
- Side effects with older agents have limited their use
    - Tricyclics: significant sedation; narrow therapeutic index (cardiotoxicity)
    - MAO inhibitors: extensive lethal drug interactions (rarely used currently)
- Certain treatment resistant patients may benefit from a different class of agents
- Newer agents more tolerated and widely used as first line agents

DIFFERENTIAL DIAGNOSIS OF DEPRESSION

Bipolar disorder
Dementia
Schizophrenia and schizoaffective disorder
Somatoform disorder
Substance abuse disorder
Personality disorder
Anxiety disorder
Attention deficit hyperactivity disorder (ADHD)
Organic disease (thyroid, anemia, endocrine, etc.)

CLASSIFICATION OF DEPRESSIVE SYNDROMES

Major Affective Disorders

Major depression (unipolar depression)
Severe and episodic with prominent neurovegetative presentation
Atypical presentations may include chronic pain, hypochondriasis, or cognitive difficulties
May be accompanied by psychotic features

TREATMENT: antidepressant plus psychotherapy

Bipolar disorder (manic-depressive illness)

Severe and episodic, with a history of a manic episode
Depressed phase is clinically identical to major depression
May be accompanied by psychotic features

TREATMENT: mood stabilizing agent (plus possibly an antidepressant in depressed phase) plus psychotherapy

Chronic Affective Disorders

Dysthymic disorder
Chronic and less severe, with fewer neurovegetative symptoms
Frequently accompanied by personality disorder

TREATMENT: Psychotherapy plus trial of antidepressant if neurovegetative symptoms are distressing

Cyclothymic disorder

Less severe, chronic mood swings

TREATMENT: mood stabilizing agent plus psychotherapy

Organic Brain Syndrome

Organic affective disorder
Depression or mania due to an organic cause

TREATMENT: manage underlying medical problem; a trial of antidepressant if necessary

Adjustment disorder with depressed mood

Time limited, in response to identifiable precipitant, without neurovegetative symptoms sufficient for major depression

TREATMENT: psychotherapy plus a trial of antidepressant if neurovegetative symptoms are distressing

VARIANTS OF DEPRESSION

Major Depressive Episode - DSM-IV-PC Criteria

- Typical primary care symptoms and complaints:
  Decreased energy, insomnia, weight loss, unexplained medical complaint
- Primary care version of DSM-IV: developed to address time pressures and primary care
- Requires consideration and R/O as first step in evaluating symptoms of depression
  - General medical conditions
  - Substance use/abuse
  - Other mental disorders
- Consider major depressive episode if mood or anhedonia persists over 2 weeks

- Criteria for consideration **
  1. Presence of specific symptoms of depression
     - At least 5 of the following symptoms present during same 2 week period
     - Symptoms present nearly every day
     - Symptoms represent a change in previous functioning
     - At least one symptom must be either depressed mood or anhedonia *

     * Anhedonia: loss of interest or pleasure in acts or events which would normally be pleasurable

     SYMPTOMS

     - Depressed mood (can be irritable in children and adolescents)
     - Marked diminished interest or pleasure in all or most activities
     - Significant weight loss (when not dieting) or weight gain
     - Insomnia or hypersomnia
     - Psychomotor agitation or retardation
     - Fatigue or loss of energy
     - Feelings of worthlessness or excessive/inappropriate guilt
     - Diminished ability to think or concentrate
     - Recurrent thoughts of death, recurrent suicidal ideation without a specific plan or suicide attempt or a specific plan for committing suicide

  2. Symptoms not better accounted for by mood disorder secondary to
     - General medical condition
     - Substance-induced mood disorder
     - Bereavement (normal reaction to death of loved one)

  3.. Symptoms not better accounted for by psychotic disorder
     e.g. schizoaffective disorder

** American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed - Primary Care Version. Washington, DC: American Psychiatric Association, 1995.

Dysthymic Disorder

- Chronic low-grade depression
- Do not have to meet all criteria for major depression but must be symptomatic at least 2 years
- Cognitive symptoms more common vs vegetative symptoms (opposite of depressive disorder)
    - Appetite disturbances
    - Sleep disturbances
    - Sexual functioning disorders
- Less dramatic presentation; can be challenging to diagnose
    D/DX: introversion or shyness
- Persons are relatively functional
- May affect person's relationships and livelihood
- May be different degrees of same disorder as major depression

Bipolar Disorders

- Periodic swings between abnormally low and high moods
- Incidence: 5-15% of all adult cases of depression
- Depression tends toward vegetative nature: lethargy, apathy
- Alternates or is mixed with **mania or hypomania** (milder form of mania)
- Mania alone can justify the diagnosis on assumption that depression is inevitable
- Characteristics of mania - not just elation
    - General activation with intensified, overreactive emotions
    - Irritable or fearful

- Suspect where presentation is lethargy and apathy vs reporting symptoms
    Symptoms: sadness, guilt or worthlessness
- Manic phase: revved-up obvious presentation
- Distinguishing mild mania
    - Can be confused with energetic, effervescent personality
    - Change in "up" characteristics over time
    - Decreased need for sleep vs decreased ability to sleep
- Possible link between **seasonal affective disorder** has been postulated
        SAD is also postulated
- Postpartum depression may signal bipolar disorder (esp postpartum psychotic depression)
    - Postpartum period is high risk for bipolar disorder
    - Childbirth is high risk for bipolar disorder

- **Cyclothymia**: varying mood states each lasting days to months
    - Depression, irritability, cheerfulness, relative normality
    - Begins early adolescence or adulthood; precedes bipolar disorder
- Lithium is drug of choice - sometimes use SSRI

Atypical depression

- Often in young patients
- Overeating, oversleeping, weight gain (vs usual anorexia and insomnia)
- Mood may be reactive to circumstances vs continual dysphoria
- Oversensitivity to interpersonal relationships-rejection
- Report heaviness in arms and legs
- Anxiety, phobias, symptoms of sympathetic arousal

Double Depression

- Dysthymia superimposed on episodes of major depression
- More prevalent in women

Psychotic depression

- Depressive episodes with psychotic features
- Psychosis more likely to develop after several episodes of non-psychotic depression
- Once psychotic features emerge, likely to reemerge with subsequent episodes
- Ask re psychotic symptoms: delusions, hallucinations
    - Pt may not consider symptoms abnormal
    - Pt may attempt to conceal symptoms
- Typical delusional themes: loss, death, guilt, serious physical illness
- Agitation is common

SCREENING FOR DEPRESSION

Screening instruments useful if provider feel uncomfortable re direct questions re emotions

SCREENING INSTRUMENTS AND SYSTEMS

DSM-IV-PC

- Derived from Diagnostic and statistical Manual of Mental Disorders, 4th ed (DSM-IV)
- Paperback aimed at primary care providers - does not contain patient forms
- Emphasizes disorders most commonly seen in primary care
- Avoids psychiatric jargon .

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. - Primary Care Version. Washington, DC. American Psychiatric Association; 1995

Primary Care Evaluation of Mental Disorders (PRIME-MD) best known instrument

- Mood disorders - 4 Other diagnostic areas
  Depression, generalized anxiety, panic disorder, ETOH abuse somatoform disorders and eating disorders
- 2 stage diagnostic system developed by Pfizer Inc
    - Patient questionnaire - one page completed before seeing provider
    - Guided interview by health care provider
    - Structured interview formed divided in 5 diagnostic modules
- Accuracy
    - 88% between PRIME-MD and independent mental health professional
    - 48% of those well known to provider were not previously diagnosed

Spitzer RL, Williams JB, Kroenke, K et al. Utility of a new procedure for diagnosing mental disorders in primary care: the PRIME-MD 1000 study. JAMA, 1994; 272:1749-1756.

Inventory to Diagnose Depression (IDD)

- Self-rating scale useful to diagnosing major depression in primary care
- Takes 10 minutes for patient to finish and a minute to score
- 6th grade reading level

The Mood and Feelings Questionnaire (MFQ)

- Developed to improve detection of depression in children and adolescents
- Versions for parents and children
- Psychiatric review of symptoms (PROS):
    - Series of questions for rapid screening
    - Questions can be remembered via mnemonics

Modified Dartmouth COOP Functional Health Assessment Charts

- Functional disability accompanies all types of depressions
- Functional assessment can be helpful
- Patients report their feelings, social activities, and feelings of pain via responding to cartoon-like pictures

Beck's Depression Inventory

Quantifies degree of dysphoria

Informal Questioning

- Suitable for people who feel comfortable talking about emotional issues
- Provider uses own screening questions and follow-up queries
- Permits closer attention to patients response and style of response
- Allows for differing responses pending on the patient's previous answer
- Permits attention to patients style of symptom attribution
- Caution: may often play down their own symptoms - "normalizers"
    - Less likely to detect depression vs "somatizers" or "analyzers"
- Always ask about suicide: no substitute for simply asking the question
    - Can lead up to question if uncomfortable with direct approach
    - Always ask about a plan

EVALUATING FOR PRESENCE OR ABSENCE OF PHYSICAL ILLNESS

-**"Masked depression":** varied physical symptoms which could suggest depression
    - Insomnia, fatigue, headache, low back pain, eating problems
    - Some populations less inclined to verbalize subjectively; more likely to somatize
        - Non-western cultures or traditional cultures
        - Rural cultures
        - Less educated persons
        - Elderly even in non-rural, Western cultures
- Evaluate for **comorbid physical illness which is precipitating depression** - See Table 1
- Evaluate whether presence of serious illness could be influenced by depression
    - Example: non-compliance with treatment regimen
    - Intensity of sadness should lessen over time otherwise consider depression
- **Psychological symptoms** or disorders may mask depression
    - Difficulty concentrating
    - Substance abuse; personality disorder
    - Marital/family conflicts
    - Poor school performance; absenteeism from work; lack of motivation
    - Social withdrawal
    - Mild cognitive dysfunction
    - Dementia syndrome of depression: Subcortical demential resembling primary dementia
- **R/O medical disorders**: See Table 1
    - Usual ROS: thyroid dysfunction; brain lesion, etc.
    - Usual physical exam
        - Check vitamin esp B12 levels for abnormal neuro exam
        - Calcium abnormalities associated with depression
- Possible relationships between medical disorders and depression
    - Medical disorder causes depression
    - Medical disorder precipitates the depression in genetically predisposed persons
    - Medical disorder causes depression psychologically (direct response to disease)
    - No causal relationship

TABLE 1: MEDICAL CONDITIONS ASSOCIATED WITH DEPRESSION OR MANIA

Neurologic - Parkinson's disease - Huntington's disease - Traumatic brain injury - Stroke - Dementias - Multiple sclerosis	**Metabolic Disease** - Electrolyte imbalance - Renal failure - Vitamin deficiencies - Vitamin excesses - Acute intermittent porphyria - Wilson's disease - Environmental toxins - Heavy metals	**GI Disease** - Irritable bowel syndrome - Chronic pancreatitis - Crohn's disease - Cirrhosis - Hepatic encephalopathy
Endocrine Disorders - Hypothyroidism - Hyperthyroidism - Cushing's disease - Addison's disease - Diabetes mellitus - Parathyroid dysfunction	**Cardiovascular Disease** - MI - Angina - Coronary artery bypass surgery - Cardiomyopathies	**Pulmonary Disease** - COPD - Sleep apnea - Reactive airway disease
Malignancies and Hematologic Diseases - Pancreatic carcinoma - Brain tumors - Paraneoplastic effects of lung cancers - Anemias	**Autoimmune Disease** - Systemic lupus erythematosus - Fibromyalgia - Rheumatoid arthritis	

ELDERLY PATIENTS

- Higher risk of depression
- Diagnosis easily missed esp if multiple medical problems
- Provider may erroneously assume depression to be matter of course
- Treating depression provides additional benefits to elderly with medical problems
    - Enables better coping mechanisms for physical disabilities
    - Better compliance to medical regimen
- Medical conditions may predispose to depression
    - Direct causation possible
    - Secondary to medication side effects

        Beta blockers, anticonvulsants, barbiturates, benzodiazepines, corticosteroids, digitalis, histamine H2-receptor antagonists
- **Differentiating depression from dementia** in the elderly is crucial - See Table 2

- Dementia and depression in elderly can be intertwined
    - 20-25% Alzheimer's patients have major depression
        - Neurobiologic prodrome? Manifestation of neuronal loss?
        - Psychologic response to cognitive decline?
    - Depressed elderly can manifest depression as memory and concentration deficits which resemble may dementia
    - Symptoms may present as energy deficits, anorexia, insomnia vs mood changes
    - Trial of antidepressants may help clarify issue

- Guidelines for Differentiation in the Elderly

    - With confused elderly, assume delirium first
        - Often treatable
        - Risk of mortality esp if misdiagnosed
    - Consider reversible dementia where can R/O delirium
        - Vitamin B deficiencies
        - Thyroid disease
        - Infections

DEPRESSION VS DEMENTIA

DEPRESSION	**DEMENTIA**
- Abrupt onset - Short duration - Previous psychiatric hx Including undiagnosed depressive episodes - Complaints of memory loss - "I don't know" answers - Fluctuating cognitive loss - Equal memory loss for recent and remote events - Depressed mood (if present) occurs first	- Insidious Onset - Long duration - No previous psychiatric history - Often unaware of memory loss - Near-miss answers - Stable cognitive loss (although loss is progressive over time) - Memory loss greatest for recent events - Memory loss occurs first

Espino, DV (1998). Diagnostic approach to the confused elderly patient. American family physician, 57(6). 1358-1366.

CHILDREN AND ADOLESCENTS

- Children as young as 3 can be diagnosed with depression
- Possible diagnostic clues
    - Irritability
    - Failure to maintain weight
    - Decreased school performance
    - Loss of interest in friends and play
    - Reduced self-esteem

- Bipolar disorders occur with higher frequency in children/adolescents vs adults
    - Hyperactivity; psychomotor slowing
    - Family history of bipolar disorder

- Distinction bipolar vs depression important as different medications indicated
    - Antidepressant therapy can induce hypomania
    - Incidence of antidepressant-induced hypomania is higher in children

- Characteristics of early-onset childhood depression
    - Appears to be more severe form of depression
    - High rate of conversion to bipolarity

- Depressed adolescents - variable presentation
    - May hide feelings and feign pleasure in activities
    - May act apathetic re anything or anyone
    - May show extreme irritability

- Evaluation of suicide ideation important in children and adolescents
- Firearm precautions particularly important with depressed children-adolescents

DEPRESSION AND WOMEN

See “Understanding Depression in Women”

DEPRESSION AND INHERITANCE

- Major depression and bipolar disorders have high rates of familial occurrence
- Children of depressed parents more likely to experience major depression
    - Early onset of parental depression carries even higher risk
    - Onset before age 20 associated with 2-3 fold higher rate of illness in adult relatives
- Twin studies support genetic transmission

- Age-period-cohort effect - remains and unexplained phenomenon
    - Risk of mood disorders for family members (and general population) greater for people born in later vs earlier decades of 20 th century
    - Rate of depression and mood disorder increasing in every generation born since 1912
    - Abrupt jump in rate of increase with persons born after 1940

- "Affective disorder spectrum" has been proposed
    - Association noted between bipolar disorders and/or major depression and many psychiatric disorders
    - Dysthymia, cyclothymia, schizoaffective disorder, alcoholism, eating disorders
    - Attention deficit disorders and migraines recent additions to list.

TREATMENT CONSIDERATIONS

- Issues of specialist referral vs primary care treatment
    - Mild uncomplicated depression usually treated in primary care w antidepressants
    - Severe depression or depression with complications warrant referral to specialist
        - Suicide ideation, substance abuse
        - Psychosis, personality disorder
        - Mental retardation or comorbid medical illness

- Issues which may impact course or treatment
    - Precipitating conditions e.g. bereavement
    - Long term predisposing issues e.g. child abuse

- Issues of patient rejecting diagnosis
    - May reflect knowledge deficit
    - May reflect attitude of "there is nothing to be depressed about"
    - Provider needs to discuss nature of illness and altered brain chemistry
    - Provider needs to educate patient and clarify common patient misconceptions
        - Depression reflects personality flaw or failing
        - Educate re familial tendencies of depression
        - Educate re: organic/physiologic basis for depression

- Endogenous versus reactive depression
    - Distinction no longer considered valid - treatment same
    - Reactive depression may trigger depression syndrome
    - Valid to inquire re bereavement or major disappointment
    - Most people w depression severe life event preceding onset

- Psychotherapy
    - Option for mild or moderate depression
    - Increased chance of success if closely related life stressor
    - Severe chronic depression may respond to brief psychotherapy
    - Refer to specialist for assessment if uncertain re suitability for psychotherapy

TREATMENT OPTIONS

- 1993 Agency for Health Care Policy and Research (AHCPR)* published two Clinical Practice Guidelines
    - No 5 Vol 1: Depression in Primary Care: Detection and Diagnosis (93-0550)
    - No 5 Vol 2: Depression in Primary Care: Treatment of Major Depression (93-0551)

    * Division of U.S. Department of Health and Human Services, Rockville MD

- American Psychiatric Association (APA) Practice Guidelines for Major Depressive Disorder in Adults

- Two subsequent consensus conferences in Minnesota and Texas
- AHCPR update (1999) available (800-358-9295)
    Summary at http://www.ahcpr.gov/clinic.deprsumm.htm
    Complete report: http://www.ahcpr,gov/clinic/index/htm#evidence

    TOPICS COVERED

    - 29 newer antidepressants
    - 3 herbal remedies (St. John's wort, valerian, kava-kava)
    - Efficacy of newer pharmacotherapies
    - Relative efficacy of newer agents vs psychosocial therapies
    - Combination therapies
    - Relapse prevention; adherence
    - Efficacy of herbal remedies
    - Treatment of adolescents and children

- Previous treatment goals were 50% symptom improvement
- Current treatment goals: complete return to wellness
- Flexibility is key; there is no "one dose fits all"

- Depression increasingly perceived as chronic disorder and should be managed as such
    - 50% change of recurrence with single episode
    - Need for long term treatment is virtual certainty for 3 or more episodes

- Patient education is crucial: support, concern, guidance, enlightenment (need to dispel myths)
    - Patients often have experienced considerable psychic pain for some time
    - Need encouragement that symptoms represent true disorder which is treatable
    - Advise that benefits of drug therapy are not immediate or dramatic

PHYSIOLOGIC PERSPECTIVES OF ANTIDEPRESSANTS

- Multiple neurotransmitters are active at presynaptic and postsynaptic loci in brain
    - **Histaminergic**
    - **Cholinergic**
    - **Serotoninergic**
    - **Noradrenergic**

- Neurotransmitter effects control both beneficial and adverse effects of medications

- All available equally effective in approximately 2/3 patients - S/E often govern choice
- SSRI largely replaced tricyclics and monoamine oxidase
    - Tricyclics (TCAs) associated with undesirable anticholinergic effects
    - TCAs may be valuable alternative with moderate, severe depression
    - MAOs rarely used due to severe interactions (drug/food) which limit quality of life

- Patients not responding to one antidepressant may respond to another
    - Surprisingly, patients who do not respond to one SSRI often respond to another
    - Some experts add a second drug for augmentation

- Time frame for therapeutic effects
    - All agents may take as long as six weeks to have therapeutic effects;
    - May take longer for maximum benefit

- Agents differ not so much in their effectiveness as in their adverse effects
- All antidepressants can induce mania esp in patients with bipolar disorder
    TCAs more likely to induce mania vs MAOs, bupropion or SSRIs

PSYCHOLOGIC PERSPECTIVES

- All types of depression benefit from psychotherapy
- Current thinking does not mandate therapy as requisite to antidepressant therapy
- Extensive counseling and psychotherapy currently not typically recommended as initial therapy

SPECIFIC TREATMENT INDICATIONS

- Bipolar disorder need treatment with lithium (Eskalith and others) or mood-stabilizing drugs
    - Sometimes respond to SSRI
    - Lithium potentially toxic with narrow therapeutic window - requires monthly monitoring

- Electroconvulsive therapy (ECT) remains effective treatment in some cases
    - Severe delusional depression
    - Elderly patients who may not tolerate drugs
    - Patients who do not respond to drugs

- Depression complicated by psychosis: may require both antidepressants and antipsychotics

CLASSES OF ANTIDEPRESSANTS

1. Tricyclic drugs (Tetracycline drugs)

   Secondary amines

   Desipramine (Norpramin)
   Nortriptyline (Pamelor)
   Protriptyline

   Tertiary amines

   Amitriptyline (Elavil)
   Clomipramine (Anafranil)
   Doxepin (Sinequan)
   Imipramine (Tofranil)
   Trimipramine (Surmontil)

   Dibenzoxazepine derivative

   Amoxapine (Ascendin): See Ayptical Antidepressants

   Tetracyclic drug:

   Maprotiline (Ludiomil)

2. MAO inhibitors

   Isocarboxazid (Marplan)
   Tranylcypromine (Parnate)
   Phenylzine (Nardil)

3. SSRI: Selective Serotonin Reuptake Inhibitors
   Inhibition is of serotonin uptake into the presynaptic neuron *
   * following its release during transmission

   Citalopram (Celexa)
   Paroxetine (Paxil)
   Fluoxetine (Prozac, Sarafem)
   Sertraline (Zoloft)

   Fluvoxamine (Luvox) - indicated only for obsessive compulsive disorder

4. Atypical antidepressants - varying chemical structure

Bupropion (Wellbutrin)
Trazodone (Desyrel), nefazodone (Serzone)
Venlafaxine (Effexor)
Amoxapine (Asendin)
Mirtazapine (Remeron)
Milnacipran (not currently available)
Valproic Acid (Depakote) - mania associated with manic-depressive disorder

5. Lithium salts: bipolar disorder (manic-depression)

Indication: Acute and chronic treatment of affective disorders with manic or psychotic component

Lithium carbonate (Lithonate, Lithobid, Lithotabs)

TRICYCLIC ANTIDEPRESSANTS

- Previously first line therapy; now SSRI used as first line
- Structural similarity to phenothiazines
- Absorbed well orally; very lipophilic with long half-life
- Cause **rapid sedation** in normal individuals
- Metabolized in liver:
  Demethylated metabolites of amitriptyline and imipramine also active
- Antidepressant effect can take up to 6 weeks
- Prototype is **imipramine (Tofranil)**

MECHANISM OF ACTION:

1. Inhibit uptake of norepinephrine and serotonin leading to high levels in synaptic cleft
2. influence the levels of postsynaptic receptors

Results in an increased availability of norepinephrine
- Down-regulation of postsynaptic B adrenergic receptors (delay in onset of action)
- Increased sensitivity of postsynaptic alpha 1 receptors
  - Leads to postural hypotension
  - May lead to eventual up-regulation of these receptors

Drugs effecting neurotransmitter receptors should be discontinued slowly (over weeks)
Slow discontinue process needed due to up or down regulation of receptors
- Increased availability of norepinephrine leads to down-regulation
- Direct blockade postsynaptic alpha receptors leads up-regulation and to postural hypotension

Abrupt withdrawal leads to cholinergic overdrive causing
- Frank mania
- Transient hypomania

OTHER CLINICAL EFFECTS

Strong antimuscarinic activity (atropine-like effects)
- More potent than phenothiazines
- Accounts for **significant side effect profile**

Antihistaminic properties

Serotonin uptake effects - variable

Least effective:
- Desipramine (Norpramin, Pertofrane)
- Maprotiline ((Ludiomil)

Most effect: clomipramine (Anafranil)

CLASS MEMBER DISTINCTIONS

Trimipramine (Surmontil)
- Dibenzazepine - only class member which does not suppress REM sleep
- Antidepressant with anxiolytic and sedative actions
- Mechanism does not involve CNS stimulation or MAO inhibitory effects

Doxepin (Sinequan)
- Commonly used as an hypnotic
- Topical form 5% cream (**Zonalon**) used as antipyretic

Amitriptyline (Elavil) and other class members
- Used off-label as adjuvant therapy **chronic back pain** and chronic pain
- Used off label for **fibromyalgia**
- Used off label for **neuropathic pain**

CLINICAL USES

- Severe depression no longer first line agent (SSRIs generally first line choice)
- **Enuresis:** imipramine (Tofranil)
- Panic disorders, phobias, anxiety-produc'g syndromes
- Obsessive-compulsive disorders
- Bulimia (binging and purging)
- **Chronic pain** and **neuralgias**
  - Commonly used as adjuvant therapy for back pain and other chronic pain
  - Fibromyalgia
- Obsessive-compulsive disorder: Clomipramine (Anafranil)

SIGNS OF TOXICITY AND OVERDOSE

EARLY: dilated pupils, tachycardia, increased reflexes, hyperactivity, insomnia and sweating

OVERDOSE: hyperpyrexia, hypotension, cardiac toxicities, coma

TREATMENT: physostigmine (Antilirium) - AChE inhibitor; activated charcoal and support

INTERACTIONS

- Drug interactions are numerous
- Avoid with drugs than increase neurotransmitter levels or act as central stimulants
  MAO, cocaine, tyramine-containing foods, appetite suppressants
- Avoid with B 2-agonists
- Drugs which increase levels of tricyclics
  - Cimetidine or other drugs which inhibit liver metabolism
  - Glucocorticoids, oral contraceptives, salicylates, thyroxine

- Drugs which decrease levels of tricyclics
  - Drugs which induce P450 enzyme metabolizing system
  - Chronic ETOH use, anticonvulsants, barbiturates
- Increase sedation of other sedatives: barbiturates, benzodiazepines, chloral hydrate
- Increase antimuscarinic action of other drugs
  H2-blockers, phenothiazines, Anti-Parkinsonian agents (benztropine - Cogentin)
- Increase cardiotoxicity of quinidine and cardiac stimulants (e.g. isoproterenol)
- Increase anti-clotting effect of coumarin anticoagulants
- Decrease effectiveness of certain anti-HTN (down-regulate alpha2 receptors)
  - Guanethidine: prevent reuptake
  - Clonidine

ADVERSE EFFECTS

- Can be quite severe; SSRI have gained favor due to better profile
- **Anticholinergic** and antihistaminic (H1) actions
  - Dry mouth, constipation
  - Contraindications: BPH, narrow-angle glaucoma, certain arrhythmias
  - No concomitant admin w MAO inhibitors (hyperpyrexia, convulsions, coma)
  - Orthostatic hypotension (alpha-adrenoreceptor blockade; reflex tachycardia)
  - Anorgasmia: common and under-reported
  - Obstructive jaundice (uncommon) and agranulocytosis (rare)

- **Cardiac toxicity** - narrow therapeutic index - mild overdose can be fatal
  - Arrhythmias
  - Congestive heart failure
  - Myocardial infarction

- No Parkinson-like effect (although fine tremor may develop)
- Rarely may precipitate suicidal ideation (or anxiety) as depression lifts
- Nausea (weight loss) common in early treatment (dose related; rarely require d/c)
- **Sexual dysfunction** (also present with SSRI)
- Lowered seizure threshold (this property also present with bupropion - Wellbutrin)
- Weigh gain common from increased appetite

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI)

- Biogenic amine uptake inhibitor; well absorbed orally
- **First-line therapy** antidepressant;
- Pregnancy category: varies with agent
  - **Pregnancy category B**: sertraline, fluoxetine, paroxetine
  - Pregnancy category C: fluvoxamine, citalopram
- **Fewer side effects**
- Fluoxetine (Prozac) is prototype (all are similar); also has longest half-life
- Affect CNS serotonin metabolism
- Require 3-4 weeks of continuous use before clinical improvement is evident
- Effectiveness equals TCA for mild to moderate depression
  - Fewer side effects
  - Controversy as to whether as effective for severe depression

- Many are energizing or "activating" unlike sedation of TCAs
- Life threatening reaction if used with MAOs (2 week wash-out; 5 weeks with fluoxetine)
- Some agents inhibit liver cytochrome P-450 enzymes
  - Slow hepatic metabolism and prolonging effects of warfarin, phenytoin, others
  - Fluoxetine (Prozac), paroxetine (Paxil), fluvoxamine (Luvox)
- Use in pregnancy does not increase risk birth defects; some perinatal complications
- Class members likely have similar action; Various members have specific indications
  - **Citalopram (Celexa**): depression
  - **Fluvoxamine (Luvox)**: obsessive-compulsive disorder
  - **Paroxetine (Paxil)**: depression, obsessive-compulsion, panic disorder, social anxiety
  - **Fluoxetine (Prozac**)
    Depression, obsessive-compulsive disorder, bulimia nervosa, premenstrual dysphoric disorder (as Sarafem)
  - **Sertraline (Zoloft):** Depression, obsessive-compulsive disorder, panic disorder

SIDE EFFECTS

- Activating agents can exacerbate agitation, anxiety, insomnia
  - Motor restlessness (tremors) initially
  - Initial insomnia
  - Initial concerns about suicidal ideation proved unfounded
- Paradoxical sedation in up to 20% patients
- Little risk of classic TCA effects (orthostatic hypotension, anticholinergic effects, cardiotoxicity)
- **Sexual dysfunction** (reversible) occurs in most patients
  - Impotence in men; decreased lubrication in women
  - Decreased libido, anorgasmia in both sexes
- Weight gain from appetite stimulation (less than with TCAs)
- Headache, nausea and diarrhea common initially
- SSRI withdrawal syndrome: generally discredited by most authorities

DISTINGUISHING CHARACTERISTICS OF SPECIFIC CLASS MEMBERS

Fluoxetine (Prozac)

- Metabolized to norfluoxetine: as active as parent compound
- Both have long half-lives (1 week or more) - need long wash-out (5 wks) if MAO
- Approved for depression, obsessive-compulsive disorder and bulimia
- Evaluated for use as a weight-loss agent (not effective)
- May be more agitating than other class members (increased risk suicide ideation)
- Indicated for **postmenstrual dysphoric disorder (PMDD**) as **Sarafem**
- Manufacturer promotes less likelihood of SSRI withdrawal syndrome (long half-life) the existence of which syndrome is not well accepted by experts

Fluvoxamine (Luvox)

- Approved only for **obsessive-compulsive disorder** (used in higher doses)
- Decision not to seek other indications is likely economic
- Side effects includes toxic epidermal necrosis in addition to the usual side effects
- Metabolized in liver to inactive compounds; half life 16h
- Inhibits certain P450 isozymes thus
    - Increase serum concentration of some benzodiazepines (alprazolam)
    - Increase warfarin, propranolol, theophylline

Sertraline (Zoloft)

- Much shorter half-life than fluoxetine
- Many who fail on fluoxetine do well on sertraline
- Less P450 interactions: selling pt as per drug reps

Paroxetine (Paxil):

- May be somewhat more sedating than other class members

ATYPICAL ANTIDEPRESSANTS

- Varying chemical structures and classes
- Varying mechanism of action; all effect one or more neurotransmitters
- Usually not first-line due to higher side-effect profile and/or less effectiveness

Venlafaxine (Effexor, Effexor XR)

- Inhibits uptake of both **norepinephrine** (greater effect) and **serotonin**
- Structurally unrelated to any of other available antidepressants

MECHANISM AND PHARMACOKINETICS

- Pharmacology is **dose dependent**
    - Low doses: inhibits serotonin reuptake (similar action to SSRI)
    - Medium dose: inhibits norepinephrine reuptake
    - High dose: weakly inhibits dopamine reuptake
- Well absorbed orally, metabolized in liver
- Some studies suggest higher response rate
- No effect on adrenergic, muscarinic, or histaminergic receptors (unlike TCA)

DOSING

- Dose-response curve is broad
- One major metabolite is active leading to short half life of 11 hours must take bid
- Dosing: start at 37.5; gradually titrate upward to 75 mg to 150 mg bid

INTERACTIONS

- Weak inhibitor of CYP2D6 but toxicities from cytochrome P450 not reported
- Use with MAOIs results in serotonin syndrome

ADVERSE REACTIONS:

Low doses has adverse event profile similar to SSRI

Nausea, dizziness, somnolence, insomnia, constipation, **sexual dysfunction**, sweating, dry mouth, nervousness, anorexia, asthenia, others

Mild elevated BP (diastolic) occurs in up to 13% of patients

- Dose related affect
- Most common with doses greater than 200-300 mg/d
- Patients on antihypertensive meds do not experience further rise in BP

Low affinity for H1 histamine, antimuscarinic and alpha1 adrenergic receptors hence virtually devoid of these effects

Discontinuation syndrome has been noted (up to 78% patients)
Gradual tapering is recommended

OVERDOSE

- Tachycardia and decreased level of consciousness
- Brief self-limiting seizures - most patients survive overdose

Trazodone (Desyrel)

- Not structurally related to any of the heterocyclic antidepressants
- Similar efficacy to TCAs but generally better tolerated
- Does not lower seizure threshold

MECHANISM

- Complex and not fully understood
- Potent inhibitor of serotonin-2 receptor
    - Blocks serotonin uptake
    - Down-regulates 5-HT2 receptors postsynaptically
- Little effect on serotonin or norepinephrine reuptake
- High affinity (antagonist) for alpha1 receptor (probably accounts for some side effects)
- Down regulates adrenergic receptors especially presynaptic alpha2 receptors

DOSING: gradually titrate upward to 200-600 mg hs

INTERACTIONS

- Metabolized by cytochrome P450 system
- Possibly interferes with warfarin

ADVERSE EFFECTS

- **Sedating**: particularly helpful for insomnia or intolerance to anticholinergic effects
- Blocks antihypertensive action of clonidine
- Arrhythmogenic and hypotensive effects
- No anticholinergic or antihistaminic effects

- **Priapism** which should be considered medical emergency - **avoid use in males**
    - Sudden and protracted erection
    - Treatment via removal of cavernosal blood
    - Irrigate w NS and then inject phenylephrine
    - May require epinephrine injection in corpus spongiosum for reversal
    - Can result in permanent impotence if not corrected
- **Postural hypotension**, light headedness and dizziness are all frequent
- Gastric upset and lack of energy are common
- Other side effects: Indigestion, nausea, headaches

PRECAUTIONS

- Use cautiously in patients with cardiovascular disease
    - Nonsustained ventricular tachycardia
    - Other dysrhythmias
- Serotonin syndrome reported with other drugs known to precipitate it

OVERDOSE:
- Relatively safe; no reported deaths; supportive care
- Drowsiness, ataxia, nausea, vomiting, dry mouth

Nefazodone (Serzone)

- Congener of trazodone; unlike trazodone, does not cause priapism
- **Not associated with sexual dysfunction** (unlike many other antidepressants)

MECHANISM:

- Inhibits serotonin reuptake with some unique properties
  - Blocks 5-HT2 receptors (unique) vs SSRI which stimulates it
  - Mediates 5-HT-1A transmission (unique)
- Some norepinephrine reuptake blockade capabilities
- Minimal alpha1 adrenergic antagonism (reduced alpha1, alpha2 antagonist activity)

PHARMACOKINETICS:

- Metabolized by cytochrome P450 system
- Increase serum carbamazepine to toxic levels; possible digoxin toxicity
- No change: warfarin, cimetidine, phenytoin, theophylline

INDICATION: depression

DOSING: requires gradual dosing titration (starter packs) and bid dosing
- Initially 200 mg daily in two divided doses
- Increase in increments of 100-200 mg in 2 divided doses at 1 week intervals
- Range 300-600 per day in divided doses

PRECAUTIONS

- Pregnancy category C
- Cardiovascular or cerebrovascular disease
- Predisposition to hypomania
- Mania/hypomania, suicide patients, seizure disorders, hepatic cirrhosis

INTERACTIONS

- Caution with drugs metabolized by CYP34A (simvastatin, lovastatin, atorvastatin)
- May potentiate buspirone, haloperidol, cyclosporin, digoxin

ADVERSE EFFECTS

- Overall good side effect profile
- Nausea and somnolence most common
- Other common effects
  Dry mouth, dizziness, constipation, asthenia, light headedness, blurred vision
  Sexual dysfunction less common than with other antidepressants

OVERDOSE: Generally non-lethal

Bupropion (Wellbutrin, Wellbutrin SR)

- Phenylethylamine with structural similarities to amphetamine
- May be especially helpful in patients who do not respond to SSRIs
- Possibly the antidepressant of choice for bipolar depression (rarely causes manic switch)
- Has been associated with **risk of seizures**
    - Sustained release form reduces risk of seizures to that of other antidepressants
    - All forms are contraindicated for patients with seizure or eating disorders
- No cardiotoxicity
- Only antidepressant that **does not interfere with sexual function** (may enhance activity)
- Sometimes used as **adjuvant therapy with SSRI** to counteract sexual dysfunction
- Used for **smoking cessation** as **Zyban** (decreases craving for smoking)

MECHANISM

- Down-regulating postsynaptic beta-noradrenergic receptor
- No antihistaminic activity and no antimuscarinic activity

DOSING:

SR: start with 150 mg SR q am; titrate upward 150-200 mg SR BID
Non-SR: 100 mg qd to bid x 3 days then increase to 100 tid (6 hrs apart)

INTERACTIONS:

- **Avoid use with drugs (or regimens) which lower seizure threshold**
    DRUGS: Quinolone antibiotics, theophyline, antidiabetics, anoretics, CNS stimulants, systemic steroids, antidepressants, antipsychotics
    REGIMENS: opiate or cocaine addiction, alcohol abuse, sedative withdrawal
- Caution with drugs metabolized by CYP206 (TCA, SSRI, antipsychotics, B-blockers)
- Metabolic enzyme inducers (carbamazepine, phenobarbital or phenytoin)
- Enzyme inhibitors (cimetidine)

PRECAUTIONS and CONTRAINDICATIONS

- Pregnancy category B
- **Contraindicated with seizures** or **lowered seizure threshold**
- Contraindicated in patients with schizophrenia or epilepsy
- Cautious use in patients with kidney or liver dysfunction (accumulation toxic metabolites)

ADVERSE EFFECTS

- Rash on face and breasts of women (centripetal rashes)
- May **precipitate seizures** in susceptible individuals (lowers seizure threshold)
- Seizure side effects is dose related
- May precipitate psychotic episode in susceptible individuals
- CNS stimulation (agitation, anxiety, insomnia, seizures, tremor, dizziness)
- Ataxia, mania/hypomania, psychosis, weight change, dry mouth, headache, migraine,
- GI effects, edema, rash, urinary frequency, sweating, tinnitus, myalgia

Mirtazapine (Remeron)

CLASS: noradrenergic and specific serotoninergic antidepressants

MECHANISM: Increased release of serotonin and norepinephrine
- Inhibiting presynaptic alpha2 receptors
- Effect is to disinhibit both serotonin and norepinephrine transmission
- Blocks serotonin-2 and serotonin-3 receptors which are responsible for anxiety-stimulating and GI side effects seen with SSRIs
    - Mediates 5 HT-1A transmission; blocks 5-HT2 and 5 HT3 receptors
    - Receptors affected may account for both its antidepressant and anxiolytic effects

INDICATION: depression

DOSING: Start at 15 mg hs; gradually titrate upward to 30-40 mg q hs

INTERACTIONS

- Little is known re metabolism or potential interaction with other drugs
- Appear to be weak inhibitors of cytochrome P450 system - more studies indicated
- One episode of serotonin syndrome in a patient switched from fluoxetine
- MAOIs (serious or fatal)
- Potentiates alcohol, diazepam and other CNS depressants
- Caution with antihypertensives
- Drugs metabolized by and/or that inhibit CYP450

PRECAUTIONS:

- Pregnancy category C
- Hepatic or renal dysfunction
- Predispositions to or conditions that could be exacerbated by hypotension
- Diseases that effect metabolism or hemodynamic response
- Seizure disorder. Suicidal ideation. Immunocompromised or elderly patients

ADVERSE REACTIONS

- Somnolence, increased appetite, weight gain, dizziness, nausea
- Dry mouth, constipation, asthenia, flu syndrome, edema, CNS effects, others
- Rare: agranulocytosis, elevated cholesterol and triglycerides, elevated transaminases

OVERDOSE ISSUES

- Few cases reported
- Ingestions of up to 30 X maximal dose resulted in sedation and drowsiness (sometimes requiring intubation)
- No cardiac conduction abnormalities or seizures

Milnacipran

- Noradrenergic and specific serotonergic antidepressant (similar to mirtazapine)
- Prevents reuptake of norepinephrine and serotonin; no effect on postsynaptic receptors
- Not currently marketed in US
- Lower incidence of nauseas and anxiety vs SSRI but higher dysuria, headache, dry mouth

Amoxapine (Asendin):

- Class: dibenzoxazepine (subclass of TCA)
- Antidepressant with mild sedative action
- **Antipsychotic-like drug** with selectivity for inhibition of norepinephrine uptake
- Not an antipsychotic but **substantive neuroleptic activity**

INDICATION:

- Depression with neurotic or reactive depressive disorders \
- Depression accompanied by anxiety or agitation
- Indicated for endogenous and psychotic depression
- Reserved for **psychotic depression**
  - **Side effect profile limits use**
  - Useful for treatment of delusional (psychotic) depression
  - Carries the highest rate of successful suicide

MECHANISM

- Clinical action not well understood
- Reduced uptake of norepinephrine and serotonin; blockade on dopamine receptor
- Blocks dopamine receptors

DOSING: 200-300 mg/d (3 weeks is adequate period of trial if dose is 300 mg)

INTERACTIONS: tricyclics or monoamine oxidates inhibitors (lethal interactions)

PRECAUTIONS:

- Pregnancy category C
- Caution with patients predisposed to suicide
- Manic-depressive patients may experience **shift to manic phase**
- Schizophrenic patient may develop **increased psychosis**

ADVERSE EVENTS

- Serious side effects limit use
- Infrequently used: **serious extrapyramidal adverse effects**
- **Tardive dyskinesia** (irreversible) limits its use
- Has been associated with potentially fatal **neuroleptic malignant syndrome**
- Extreme caution with seizure disorder
- Usual neuroleptic side effects plus cardiotoxicity
- Anticholinergic effects
  Avoid with patients having urinary retention, angle-closure glaucoma or increased intraocular pressure
- Cardiovascular disorders warrant close monitoring
- Manic depressives may experience shift to manic phase

MONOAMINE OXIDASE (MAO) INHIBITORS

- Inhibit mixed-function oxidase systems - cytochrome P450 (example)
- MAO-catalyzed reaction
- Drug actions can be quite complex
    - Breakdown of endogenous and exogenous compounds
    - May have many adverse effects not related to inhibiting MAO
- Onset of antidepressant effect is 2-3 weeks
- **Very infrequently used:** adverse side effect profile and dangerous **food/drug interactions**
    - "Atypical depression (anxiety, hyperphagia, hypersomnolence)
    - Narcolepsy

CURRENT AGENTS

Phenelzine (Nardil) - a hydrazide
Tranylcypromine (Parnate) - a tranylcypromine (structurally similar to amphetamines)

MECHANISM

- May increased levels of norepinephrine and serotonin
- Irreversibly inhibits MAO by covalently attaching
- Tranylcypromine (parnate) has amphetamine-like action (causes release of norepinephrine)
- Classes of MAOs)
    "A" - primarily metabolizes norepinephrine and serotonin
    "B" primarily metabolizes dopamine
    Drugs appear to have a preference for MAO "A"

INTERACTIONS

Interact with **tyramine-containing foods** and **drugs** to produce **hypertensive crisis** *

- Sympathomimetic amines (OTC preps, decongestants, anorectal preparations)
- Amphetamines, narcotic analgesics (morphine, meperidine, etc)
- Methyldopa, levodopa
- SSRI or TCAs **

* Vasoactive amines not catabolized but enter bloodstream, taken up by nerve terminals
** Must have several week wash-out period to avoid **serotonin syndrome**

Low-tyramine diet is required
Seizures, hyperpyrexia, circulatory collapse

Death can occur from **single exposure** to vasoactive amine
Sudden, severe headache
Stiff neck
Hyperpyrexia and profuse sweating
Extreme hypertension
Cardiac arrhythmias
Mydriasis, neuromuscular irritability

SEROTONIN SYNDROME

Hyperpyrexia, shivering
Myoclonus rigidity, hyperreflexia
Confusion, agitation, restlessness
Coma, autonomic instability
Nausea, diarrhea, low-grade fever
Rhabdomyolysis and death

FOODS TO BE AVOIDED

Beer, broad beans, canned figs, fermented cheeses, yogurt, chicken livers, chocolate, herring, processed or dry meats, red wines, vermouth** yeast, caviar, prepared meat, ripe bananas, hydrolyzed protein (soup, gravy, sauces), sauerkraut, smoked-pickled fish

** White wine, vodka, gin whiskey is permitted

TREATMENT FOR INTERACTION-INDUCED CRISIS

Hypertensive crisis: IV alpha-adrenergic antagonist (phentolamine)
Hyperpyrexia: external cooling
Calcium channel blockers may be of use (excellent antidotes)

OTHER DRUG INTERACTIONS

Enhanced effect: general anesthesia, narcotics, oral hypoglycemics

ADVERSE EFFECTS

Sleep disturbances:
Insomnia, daytime sedation, aberrant changes to sleep-wake cycle, suppression of REM
CNS stimulation: agitation, hyperthermia, seizure
Amphetamine-like effect: tremor, heightened locomotion, mild euphoria
Anticholinergic effects: blurred vision, dry mouth, constipation
Sexual dysfunction: inhibition of ejaculation
Other: myoclonic jerks, paresthesias of extremities, rashes

LITHIUM CARBONATE

Lithium carbonate (Lithonate, Lithobid, Lithotabs)

- Originally used for manic states; commonly used in manic-depression
- Mechanism not clearly understood
- **Requires monthly blood levels**
    - Maintain at equal or less than **1.2 meq/L to avoid toxicity**
    - Need for frequent blood monitoring becomes major compliance issue
- Majority of patients experience side-effects at therapeutic doses albeit most describe as mild
- **Extreme caution with diuretics** - result in toxic levels (see pharmacokinetics)

PHARMACOKINETICS

- Quickly absorbed with oral administration; distributes to all body tissues
- Brain concentration: 50% of plasma levels
- Concentrated in bone, thyroid and brain; majority excreted in urine
- Only 75 % excreted kidneys is reabsorbed via competing with Na reabsorption
- Conditions leading to **Na+ retention/fluid retention result in increased lithium** reabsorption and **decreased sodium reabsorption**
    - Potential for toxic lithium levels
    - Caution with use for CHF, liver cirrhosis, etc.
- Caution with diuretics: increase Na+ excretion, <u>increase lithium absorption</u>

MECHANISM OF ACTION

- Not well understood; no kinow physiologic role for lithium ion in th body
- Appears to interfere with stimulus-secretion coupling in CNS (possibly via effect on G proteins)
- <u>Lithium ions inhibit phospholipase and phosphatase action</u>

  Decreased intracellular availability of 2nd messengers inositol triphosphate and diacylglycerol which are involved in raising intracellular calcium levels and activation of protein kinase C

- Serotonin effects
    - Enhances neurotransmission
    - Does not affect post synaptic serotonin receptor sensitivity
- May block dopamine-induced behavior
- Enhances acetylcholine effects

POSSIBLE MECHANISM OF ACTION OF LITHIUM

Interferes with stimulus-secretion coupling via inhibiting phospholipase and its actions
Inhibits generation of second-messengers inositol triphosphate and diacylglycerol
Enhances serotonin functioning
Blocks dopamine-related behaviors
Cholinergic-enhancing effects

CLINICAL USES

- Treatment of affective bipolar disorder (manic-depressive)
- Patients benefit from maintenance therapy
- Decrease frequency and magnitude of mood swings
- Therapeutic effect seen after 1-2 weeks of administration
- Initially may add anxiolytic or antipsychotic agent particularly if psychosis is present
- Low doses (max 900 mg/day) as potentiator of other antidepressants
- Prophylactic use for bipolar patients

BIPOLAR (MANIC DEPRESSIVE) ILLNESS

Less common than unipolar disorder (1% of general population)
Men and women affected equally
Acute episodes recur about every 3-9 years
Manic phase: serious clinical situation; often requires hospitalization
Depressive phase: treatment decisions same as for unipolar depressed
Compliance can be an issue - patients often prefer manic phase
Patient is more likely to switch to mania during treatment of depression
TCAs may induce rapid cycling in some bipolar patients
Lithium carbonate only medication FDA approved as mood stabilizer

ADVERSE EVENTS

Narrow therapeutic index
Therapeutic range is 0.6 to 1.0 mEq/L
Serious toxicities occur beyond therapeutic range
Toxic levels: **severe renal damage** and **CNS toxicity**
Encephalopathy, coma
Baseline thyroid and renal function plus regular monitoring q 4-6 months
Side effects may not be dose related
Tremor, edema, nausea/vomiting, diarrhea, psoriasis, weight gain, acne, mental dulling, hypothyroidism, nephrogenic diabetes insipidus/polyuria, weakness, ataxia, dizziness, confusion

Hypothyroidism develops in 25% of patients (diffuse goiter; increased TSH)
Polydipsia, polyuria with elevated ADH also common
- May cause direct stimulation of ADH release
- Increase sens of distal renal tubules to ADH
- Cause nephrogenic diabetes insipidus (rare)
- Unknown mech for causing diabetes insipidus

ALTERNATIVES TO LITHIUM

Carbamazepine (Tegretol) - used where patient is resistant to lithium

- Anticonvulsant used off-label for prophylaxis of bipolar disorder
- Used in patients intolerant or non-responsive to lithium salts
- Sometimes used in combination with lithium salts
- Structurally similar to TCA but has different actions
    - Does not effect norepinephrine uptake
    - Does not affect postsynaptic B-receptor numbers
    - Appears to inhibit norepinephrine release (stimulation adenosine receptors)
- Adverse effects are dose related: Sedation, confusion, ataxia

Valproic acid (Depakene)

Indication: Mania associated with bipolar disorder

The only anticonvulsant which has received FDA approval for acute mania