58. AntiPsychotics – Schilling

59. Pharmacological Treatment of Unipolar Depression, Anxiety Disorders – Part I – Battaglia (To be Posted Later)

60. Pharmacological Treatment of Unipolar Depression, Anxiety Disorders – Part II – Battaglia (To be Posted Later)

61. Pharmacology of Sedative-Hypnotics & Other Drugs Used to Treat Sleep Disorders – Part I – Battaglia (To be Posted Later)

62. Pharmacology of Sedative-Hypnotics & Other Drugs Used to Treat Sleep Disorders – Part II – Battaglia (To be Posted Later)

63. Drugs of Abuse, Tolerance & Dependence – Bakowska

64. Pediatric PsychoPharm – Treatment of ADHD – On-Line Only (slides posted)

65. Drugs to Treat Rheumatoid Arthritis & Gout - Clipstone
ANTIPSYCHOTIC DRUGS

KEY CONCEPTS AND LEARNING OBJECTIVES:

1) Name the 4 well-defined dopamine systems/tracts

2) Describe what happens when each of the 4 dopamine systems/tracks have:
   A. less than 65% of their dopamine receptors blocked
   B. between 65% and 80% of their dopamine receptors blocked
   C. have more than 80% of their dopamine receptors blocked

3) Explain how high potency & low potency “typical” antipsychotic drugs are similar to each other and are different from each other.

4) Describe the mechanism of actions of:
   A. The high & low potency first generation (typical) antipsychotic prototypes
   B. The second generation (atypical) antipsychotic prototype
   C. The second generation (atypical) antipsychotic Aripiprazole (Abilify)

5) Identify which side effects are caused by which neurotransmitter system receptors being blocked by an antipsychotic drug

6) Recall the common side effects for:
   A. High potency first generation antipsychotics
   B. Low potency first generation antipsychotics
   C. Second generation antipsychotics
   D. Clozapine (Clozaril)

7) Recall the rare but dangerous side effects for:
   A. High potency first generation antipsychotics
   B. Low potency first generation antipsychotics
   C. Second generation antipsychotics
   D. Clozapine (Clozaril)

8) Propose which antipsychotic medication to prescribe to a specific patient based on a description of a patient’s history and clinical presentation

9) Explain what the “Metabolic Syndrome” is and what medical problems it may cause/contribute to.

IMPORTANT DRUGS

| Chlorpromazine (Thorazine)** | Risperidone (Risperidal)** |
| Haloperidol (Haldol)** | Aripiprazole (Abilify)** |
| Prototye drugs** | Clozapine (Clozaril)** |

| Olanzapine (Zyprexa) | Paliperidone (Invega) |
| Quetiapine (Seroquel) | Asenapine (Saphris) |
| Ziprasidone (Geodon) | Lurasidone (Latuda) |
| Ilooperidone (Fanapt) |
II. Pathophysiology/Disease state

Dopamine Hypothesis

Hyperactivity of Dopamine (DA) neurotransmitter pathways → Schizophrenia

Evidence
1. Typical Anti-psychotics-block DA receptors
2. Drugs, such as cocaine, amphetamines, levodopa, which ↑ Dopamine activity → psychosis
3. Increased Dopamine receptors in patients with schizophrenia
4. Treated schizophrenic patients have less Dopamine breakdown products than untreated schizophrenic patients (the dopamine system in treated patients is no longer hyperactive, less dopamine, less dopamine breakdown products)
Dopamine Hypothesis Limitations
- 20 - 40% of schizophrenic pts fail to respond adequately to treatment w/ antipsychotics
- ~30% of pts treated w/ typical antipsychotics relapse each year
- First Generation Antipsychotics (FGA’s) are more effective against positive symptoms than negative symptoms.

III. Description of Drugs used to treat Disease

First Generation Antipsychotics (FGA’s)
Also called: Conventional antipsychotics, Typical Antipsychotics, Neuroleptics, Major Tranquilizers

Phenothiazines
- Chlorpromazine (Thorazine**)-low potency
- Thioridazine (Mellaril)
- Fluphenazine (Prolixin)
- Trifluoperazine (Stelazine)
- Perphenazine (Trilafon)

Thioxanthines
- Thiothixene (Navane)

Butyrophenones
- Haloperidol (Haldol)**-high potency

Second Generation Antipsychotics (SGA’s)
Also called: Atypical antipsychotics

- Risperidone (Risperdal)**
- Olanzapine (Zyprexa)
- Aripiprazole (Abilify)**
- Clozapine (Clozaril)**

Prototypes**
IV. Drug Indications - FDA approved

Adults
- Schizophrenia (acute & maintenance treatment)
- Bipolar disorder (acute mania treatment, maintenance treatment, bipolar depression treatment)
- Agitation associated with schizophrenia or bipolar disorder

Children & Adolescents
- Schizophrenia, Autism

Common use: Psychosis treatment
- Schizophrenia
- Mood disorders - Bipolar disorder, Major Depression
- Medical Illness - Dementia, Delirium, Substance abuse

V. Pharmacodynamics - mechanism of action; what the drug does to the body

Each antipsychotic drug has a different level of affinity for the different neurotransmitter receptors; so different medications have different side effects, or different levels of the side effects, in patients.

<table>
<thead>
<tr>
<th>Drug Affinity</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
<th>Quetiapine</th>
<th>Olanzapine</th>
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<tr>
<td>Alpha1</td>
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<tr>
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<td>--</td>
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<td>6</td>
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<td>8</td>
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<tr>
<td>H1</td>
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<td>8.5</td>
<td>7.7</td>
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<tr>
<td>5-HT2A</td>
<td>10</td>
<td>10</td>
<td>7.5</td>
<td>9</td>
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<tr>
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<td>6.1</td>
<td>7.7</td>
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<tr>
<td>5-HT2A:D2 affinity ratio</td>
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<td>32</td>
<td>25</td>
<td>20</td>
<td>100</td>
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Atypical Antipsychotic Drug Affinities at Various Neurotransmitter Receptors
(Value expressed as pKi = -logKi; higher number means higher affinity)

5-HT2A:D2 affinity ratio >20:1 for atypical antipsychotics (100:1 for clozapine)

Therapeutic Window for Treatment

Treatment of psychosis—block >60-65% of dopamine D2 receptors in the Mesolimbic tract

A substantial EPS risk—block >80% of the dopamine D2 receptors in the Nigrostriatal tract
Risk of ↑Prolactin—block >80% of the D2 receptors in Tuberoinfundibular tract

What mechanism of action allows for greater than 65% dopamine receptor blockage in the mesolimbic system but less that 80% dopamine receptor blockage in the nigrostriatal system? How do the drugs work to hit this therapeutic window?
1. Serotonin-Dopamine Antagonism hypothesis
   - Mesolimbic tract, Nigrostriatal tract, & Tuberoinfundibular tract
     5-HT2A blockade enhances DA release in basal ganglia (from nigrostriatal DA system);
     This DA competes with the antipsychotic medication for DA2 receptors;
     Result: blockage of > 65% receptors but < 80% of receptors (therapeutic window).
     Consequence is antipsychotic efficacy (>65% mesolimbic tract DA2 receptors blocked), but
     reduced EPS (<80% nigrostriatal tract DA2 receptors blocked) &
     reduced hyperprolactinemia (<80% tuberoinfundibular tract DA2 receptors blocked)

   - Mesocortical
     5-HT2A blockade may normalize cortical function (possibly by enhancing DA release and
     acetylcholine release in frontal cortex), thereby reducing negative symptoms/cognitive deficits

2. Hit & run concept
   Lower potency DA2 blockade by atypical antipsychotics has also led to “hit and run” concept;
   i.e. atypical drug-induced blockade of DA2 receptors is not as long-lasting as with typical drugs so is
   present long enough for therapeutic effect but not long enough to be disruptive and cause side effects

Partial Agonism & Aripiprazole (Abilify)
   Partial agonist
     - rheostat analogy; the receptor (light) is partially on (neither completely on nor completely off)
   Partial agonist sits on the receptor like an antagonist & blocks the receptor from other stimulation;
     changes the receptor conformation slightly; G protein organization changes slightly & there is a small
     signal

   In low neuroreceptor stimulation environments
     Causes a little agonist activity (the cell is not completely off)
     In low dopamine receptor stimulation environment, aripiprazole binds to the DA2 receptor with
     high affinity (potent) & has a partial agonist effect

   In high neuroreceptor stimulation environments
     Exerts antagonist action (the cell is not completely on)
     In high dopaminergic environment aripiprazole has the effect of an antagonist

Dopamine system stabilization idea (i.e. not too much, not too little); supported by observation that
clinical efficacy of atypical antipsychotics may be seen at DA2 occupancy levels below those achieved by
typical antipsychotics
Aripiprazole is the first Dopamine-Serotonin System Stabilizer

VI. Pharmacokinetics-what the body does to the drug
   Bioavailability IM > PO
     PO, incomplete GI absorption, 1st pass effect
   Peak plasma level
     IM: ~ 30 min vs. PO: ~ 1-4 hrs
   90% protein bound; unbound passes through blood brain barrier
   Half-life about 20 hours, steady state 4-7 days
### VII. Important side effects: Common & Rare

<table>
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<tr>
<th></th>
<th>Chlorpromazine (Low potency)</th>
<th>Haloperidol (High potency)</th>
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<tr>
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<tr>
<td>Extrapyramidal (EPS/TD); Increased prolactin</td>
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<td>+++</td>
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<td><strong>Muscarinic-M1-Anticholinergic</strong></td>
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<td>0</td>
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<td><strong>Adrenergic-Alpha1-related</strong></td>
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<tr>
<td>Orthostasis</td>
<td>+++</td>
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<td>Sedation, weight gain</td>
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<table>
<thead>
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<th>Risperidone (Risperdal)</th>
<th>Ziprasidone (Geodon)</th>
<th>Quetiapine (Seroquel)</th>
<th>Olanzapine (Zyprexa)</th>
<th>Clozapine (Clozaril)</th>
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<tr>
<td>Sedation</td>
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<td>+</td>
<td>++</td>
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</table>

Prominent atypical drug-related effects
- **Suicide:** Clozapine (clozaril) appears to lower the risk of suicide
- **Discontinuation for any reason over long term (≥2 yrs):**
  - Olanzapine (Zyprexa) & Clozapine (Clozaril) have lowest rates of discontinuation
- **EPS/TD:**
  - Risperidone (Risperdal)-acts more like a typical antipsychotic at higher doses (≥6 mg/day);
  - Asenapine (Saphris)-increased risk of EPS
- **QTC elongation:**
  - Ziprasidone (Geodon) > Quetiapine (Seroquel) > Risperidone (Risperdal)
- **Sedation:**
  - Clozapine > Olanzapine > Quetiapine > Risperadone/Paliperidone
- **Metabolic Syndrome:** Weight gain, Hyperglycemia, Diabetes Mellitus, Dyslipidemia
  - All SGA’s can result in significant weight gain; are differences among the medications.
  - Clozapine > Olanzapine >> Quetiapine >> Risperadone/Paliperidone >>
  - Asenapine/Ziprazodone/Aripiprazole/Lurasidone

Among patients with Schizophrenia, the risk factors for cardiovascular disease are far higher than the general population. Evidence suggests that SGA antipsychotics are associated with metabolic disturbances that can further increase this risk. The rate of cardiovascular disease is the primary reason patients with schizophrenia’s life expectancy is about 20 years shorter than the general public.
Rare Side Effects
All antipsychotics: Neuroleptic Malignant Syndrome (no difference in risk among antipsychotics)
Clozapine: Agranulocytosis in 1-2% of patients. Requires weekly blood monitoring;
Increased risk of seizures

FGA’s & SGA’s: ↑ Mortality in elderly pts with Dementia; death from stroke and related
disorders is greater than placebo.

VIII. Important drug-drug interactions
- May increase (↑) levels of various antipsychotics:
ciprofloxacin (Cipro®), erythromycin, ritonavir (Norvir®),
fluoxetine (Prozac®), fluvoxamine (Luvox®),
- May decrease (↓) levels of various antipsychotics:
carbamazepine (Tegretol®), phenobarbital, phenytoin (Dilantin®), rifampin (Rifadin®)

- Combining clozapine and carbamazepine (Tegretol®) may increase the risk of agranulocytosis.

IX. Contraindications
No absolute contraindications.
Drugs of Abuse

Instructor: Joanna C. Bakowska, Ph.D., Assistant Professor, Department of Pharmacology

Reading Assignment: Basic & Clinical Pharmacology, B.G. Katzung, 9th Ed, Chapter 32

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Explain the basis underlying the conceptualization of addiction as a disease.

2. Discuss the differential diagnostic criteria for drug abuse vs dependence.

3. Describe the mechanism of action within the central nervous system of major drugs of abuse.

4. Illustrate the signs and symptoms of over dosage caused by the major drugs of abuse and appropriate therapeutic interventions.

5. Analyze the options for pharmacotherapy of major drugs of abuse.
Drugs of Abuse

Date:  Feb 24th, 2014 – 8:30 AM

Instructor: Joanna C. Bakowska, Ph.D., Assistant Professor, Department of Pharmacology

Reading Assignment: Basic & Clinical Pharmacology, B.G. Katzung, 12th Ed. Chapter 32

KEY CONCEPTS AND LEARNING OBJECTIVES

1. To understand the basis underlying the conceptualization of addiction as a disease.

3. To understand the differential diagnostic criteria for drug abuse vs dependence.

5. To know the mechanism of action within the central nervous system of major drugs of abuse.

6. To know the signs and symptoms of overdosage caused by the major drugs of abuse and appropriate therapeutic interventions.

7. To know the signs and symptoms of opioid withdrawal.

8. To know the options for pharmacotherapy of opioid abuse/dependence and alcohol dependence.
Drugs of Abuse

1. Introduction

1.1 Why medical students need to learn to recognize a substance abuse problem regardless of your specialty

1. You will be encountering individuals with drug problems in your practice
   a. 15.6% of adults (29 million) used illegal drugs in 2007
   b. Two-thirds of those who abuse or are dependent visit a primary care physician or emergency department every 6 months
2. Failure to consider substance use as a contributor to the clinical picture will compromise treatment

1.2 Drugs of Abuse
   A. Psychomotor stimulants – cocaine, amphetamines
   B. Opiates and Opioids – heroin, morphine, codeine
   C. Cannabinoids – marijuana
   D. Alcohol
   E. Sedatives – benzodiazepines
   F. Nicotine
   G. Hallucinogens – LSD, mescaline “club drugs”

1.3 Substance abuse disorder based on DSM-V
   Dependence
   - abuse
   - craving
   - legal problems

1.4 Criteria for Substance Abuse Disorder by DSM-V
   1. Tolerance
   2. Withdrawal (marker of physiological [physical] dependence)
   3. Use of larger amounts than intended
   4. Persistent desire, inability to control use
   5. Excessive time spent obtaining, using, recovering
   6. Normal activities given up or reduced
   7. Use despite knowledge of problems drugs cause

1.5 Withdrawal (marker of physiological dependence)
   1) Signs and symptoms emerge when use of the drug is stopped
   2) Signs and symptoms are reversed when drug is administered again
   Tolerance
   a) decreased effect with repeated use of the drug
b) need to use more to have the same effect

1.7 Tolerance due to decreased effect with repeated use of the drug (constant amount of the drug)

1.8 Tolerance – increased dose of the drug needed to have the same effect (shift to right in dose-effect curve).

1.9 Drug dependence

• Drug dependence (addiction) is compulsively using a substance, despite its negative and sometimes dangerous effects

• Drug dependence results in:
  a) withdrawal syndrome emerge when use is stopped
  b) tolerance

1.10. Mesolimbic dopamine system- a major target of addictive drug

1. General neurobiological theory of reinforcement (most clearly established for stimulants)

   a. Ability of a drug to control behavior (be abused) is related to the release of dopamine in the mesolimbic dopaminergic pathway (VTA⇒nucleus accumbens⇒prefrontal cortex), termed the “pleasure center” or “reward center”

   b. Inhibitory inputs onto dopamine neurons come from GABA-ergic neurons present within the VTA or as a feedback loop from the nucleus accumbens

2. Given evidence of these brain changes, addiction/dependence has come to be considered a disease

   a. Disease rooted in neuropathology produced by the repeated administration of the drug (pharmacological insult)

   b. Pathological changes in brain function are in circuits that regulate how a person interprets and behaviorally respond to motivationally relevant stimuli

A.1 Psychostimulants: Cocaine and Amphetamines

Cocaine

1. Derived from Erythoxylon coca, which is a cultivated plant from South America
2. Isolated in 1855 by Niemann in Germany
3. First human experiments conducted by Freud on himself were published in 1884
4. Regulated by Pure Food and Drug Act of 1906 and Harrison Narcotic Act of 1914

Amphetamines

1. Synthetic phenylethylamine synthesized in 1800s
2. Marked to treat asthma and narcolepsy and later for obesity
3. Used extensively by military during WWI and left over supplies led to epidemic use in several countries.
A2. Site of action of Cocaine and Amphetamines in Presynaptic Neurons

Cocaine

Cocaine – inhibits the action of dopamine transporters

Amphetamine – inhibits the function of VMAT and impedes the filling of synaptic vesicles, cytoplasmic DA increases – leads to reversal of DAT direction and increase of extracellular DA concentration

A3. Behavioral and physiological effects (sympathomimetic-mimicking the effects of the sympathetic nervous system)

1. Euphoria, arousal, well-being, increased energy and activity, decreased appetite, self-confidence, reduces feelings of fatigue and boredom, “rush” often described as orgasmic
2. Increases in heart rate and blood pressure, bronchodilation, pupillary dilation

A4. Pharmacokinetics of Cocaine

1. Rapidly absorbed into the brain and short-acting.
2. Onset, magnitude of effect (differences in potency), and duration depend upon route of administration
3. If smoked or taken iv, peak arterial blood levels are reached in 15 sec.
4. Acute effects last less than 30 min, resulting in binge use.
5. Half-life varies from 40-80 min, requiring repeated administration to maintain blood levels
6. Rapidly metabolized by cholinesterases into benzoylecgonine and eegonine methyl ester, the former being what is measured in urine tests and which can remain present for up to 36 hr and perhaps even longer. Cocaine metabolites can also be measured in saliva, hair, and breast milk.
7. Cocaethylene is formed in the body when cocaine is ingested with alcohol; it is pharmacologically active and enhances the effects of cocaine
A5. Consequences of Long term use of psychostimulants
Results either in
1) Sensitization – increased drug response (low-doses and intermittent exposure)
2) Tolerance – decreased drug response

Impairment of neurocognitive functions
- visuomotor performance, attention
Increased risk of infections to viral hepatitis and HIV
Physical dependence is controversial
Increased risk of developing autoimmune or connective tissue diseases such as lupus, Goodpature’s syndrome, Stevens-Johnson syndrome

A6. Overdose signs and symptoms
1. Hyperactivity, agitation, diaphoresis, dilated pupils, tremor, tachycardia, hypertension, hyperpyrexia, stereotypical behavior, chills, nausea/vomiting, weight loss, muscle weakness, tactile hallucination, chest pain, cardiac arrhythmia, confusion, dyskinesia, seizures, paranoia, coma
2. These can be exacerbated with co-administration of alcohol (formation of cocaethylene)
3. Death can occur secondary to myocardial infarction, cerebrovascular accident, cardiac arrhythmias, seizures or respiratory depression

A7. Withdrawal (peaks at 2-4 days) Signs
1. Anxiety, agitation, fatigue, depression, nightmares, headache, sweating, muscle cramps, hunger, craving

A8. Detection of Use
1. Look for symptoms noted above
2. Urine tests (2 to 4 days)
3. Other clues: AIDS, hepatitis, track marks, abscesses, bacterial endocarditis, chronic respiratory symptoms

A9. Treatment of Cocaine Withdrawal
1. Acute withdrawal-symptomatic treatment
   - Bromocriptine (dopamine agonist) – ameliorates dopamine deficiency state of cocaine withdrawal
   - Benzodiazepines (lorazepam) - in patients with severe agitation and sleep disturbance

2. Long-term addiction
   a) No FDA-approved pharmacological therapies
   b) Cognitive-Behavioral Therapies – two components
      - Functional analysis – to identify the patient's thoughts, feelings, and circumstances before and after the cocaine use to understand reason for using cocaine
      - Skills Training to help cocaine users to cope with intrapersonal and interpersonal problems
B. **Opioids (morphine, codeine, heroin, oxycodone)**

B1. **History**
1. Opium is derived from extracts of the juice of the opium poppy, *Papaver somniferum*, and has been used since 3400 BC to relieve suffering, largely pain and asthma.
2. Morphine, isolated from opium in early 1800s, and codeine is derived from opium. There are semi-synthetic (e.g., heroin, hydromorphone [Dilaudid®]) and synthetic (e.g., fentanyl [Sublimaze®]) drugs with morphine-like effects and together all are called **opioids**, which includes naturally occurring brain neuropeptides (e.g., endorphins).

B2. **Mechanisms of action**
1. Opioids exert their pharmacodynamic effects through three principal opioid receptors: **mu, delta and kappa**
2. Opioids cause disinhibition of mesolimbic dopaminergic system.
3. The dependence producing properties of opioids are mediated through the mu receptors.

B3. **Patterns of Abuse**
1. Oral, intravenous, subcutaneous (skin popping), smoking, snorting (becoming more prevalent because of fear of AIDS) and intravenous.

B4. **Patterns of Use**
1. Heroin’s effects last about 3-5 hrs.
2. Average addict uses 2-4 times/day
3. **Tolerance** develops which results in a gradually increasing frequency/quantity of use. **Physical dependence** also develops.

B5. **Signs of Opioid Overdoes**
1. Unconsciousness
2. Miosis
3. Hypotension
4. Bradycardia
5. **Respiratory depression**
6. **Pulmonary edema**

B6. **Pharmacokinetics**
1. Tolerance to one opioid is usually associated with tolerance to other opioids (cross-tolerance).
2. Heroin is a pro-drug that is rapidly converted into 6-monoacetylmorphine by esterases present in the blood, brain and every tissue.
2. 6-monoacetylmorphine is further metabolized to morphine which contributes to the duration of effect of heroin
3. Withdrawal begins 12 hours after last dose, peaks at 1½ - 3 days, and is mostly over by 5-7 days
4. Lingering symptoms can persist for months (“Protracted Abstinence Syndrome”) and are associated with relapse.
5. Withdrawal is profoundly painful and unpleasant though not life-threatening

B7. **Withdrawal** (7-10 days, uncomfortable but not medically complicated)
1. Anxiety and dysphoria
2. Craving and drug-seeking
3. Sleep disturbances
4. Nausea, *vomiting* and *diarrhea*
5. Lacrimation
6. Rhinorrhea
7. Yawning
8. **Sweating**, chills, gooseflesh (“cold turkey”)
9. **Mydriasis** (excessive dilation of the pupil)
10. Cramps
11. Hyperpyrexia
12. Involuntary movements (“kicking the habit”)

B8. Treatment of Opioid Addiction
- Pharmacotherapy
- Many individuals are not treated with medications (drug free)
  - Self-help groups such as Narcotics Anonymous
  - Inpatient detoxification facilities/residential
  - Individual therapy rare largely due to sociodemographic characteristics of users
  - Dependence on prescription opioids presents a new challenge for treatment

B9. Goals of Pharmacotherapy
- “Cure” of withdrawal or overdose
- To improve the holding power of outpatient treatment
  **To reduce drug craving**
  - To create a “window of opportunity” during which patients can receive psycho-social intervention to decrease the risk of relapse
  - To serve as short or long-term maintenance agents for patients who can’t function without them, but can lead productive lives with them

B10. Treatment approaches of opioid overdose and withdrawal syndrome
- Treatment of overdose of opioids
  - Naloxone (m-opioid receptor antagonist)
- Treatment of opioid dependence
B11. Treatment of Opioid Dependence with Naltrexone

Naltrexone [Vivitrol]

**µ-opioid agonist with long half-life**

- FDA approved 1984 – opioid dependence
- Orally absorbed, high receptor affinity
- Heroin self-administration no longer rewarding
- Avoid in patients with liver failure

B12. Treatment of Opioid Overdose

- **Naloxone [Narcan, Nalone]**
  - **µ-opioid antagonists** with very high affinity –
  - Fast acting (2 min) but the duration of action (about 45 min) is much shorter than heroin
  - Therefore, individuals treated for overdose with these antagonists must be kept under observation for the duration of the opioid drug’s effects to determine if additional antagonist treatment is needed

B13. Treatment with Methadone

- Methadone – agonist to m-opioid receptor with long half-life (15-60h)
  - Oral administration
  - Lasts at least 24 hrs
- Methadone: Prevents withdrawal symptoms and cravings, has a cross-tolerance with other opioids
- Can only be dispensed in federally licensed clinics
  - Requires almost daily clinic visits even for individuals with long term success

B14. Treatment with Buprenorphine

- Buprenorphine is a partial m-opioid receptor agonist
  - has less potential for respiratory depression (hard to overdose)
- It has both high affinity for receptors (competes easily) and dissociates slowly (long acting so withdrawal is minimized)
- Marketed in a formulation with naloxone (Suboxone) to decrease potential for iv abuse
- If buprenorphine is initiated prior to the onset of acute withdrawal signs, it may lead to abrupt withdrawal syndrome resulting from displacement of full agonists (e.g. heroin) for the mu-opioid receptor by a buprenorphine
C. Marijuana

C1. History
1. Like other drugs of abuse derived from natural plant products, marijuana has been used for 1000s of years
2. **Delta-9-tetrahydrocannabinol** (THC) is active constituent

C2. Mechanism of action
1. THC activates a cannabinoid receptor in the VTA to initiate its action, a relatively new scientific finding
2. There are two cannabinoid receptors with CB1, not CB2, most likely mediating the abuse-related effects of THC
3. Cannabinoids cause disinhibition of mesolimbic DA system.

C3. Acute Effects of Marijuana
- Sedation, relaxation
- Mood alteration, sense of well-being
- Altered perception and time estimation
- Impaired judgment, memory, and concentration
- Increased appetite (“munchies”)
- Increase heart rate, dry mouth
- Injection of the conjunctiva (“red eyes”)

C4. Adverse Effects of Marijuana Use
1. Panic, delirium, psychosis (often paranoid)
2. Long-term use: Amotivational syndrome, inattention, poor judgment, distractability, impaired social relationships but results from field and laboratory studies are often inconsistent
3. **Tolerance** occurs but whether or not physical dependence develops in humans remains an open question (but has been demonstrated in mice)
4. Many believe it is a “gateway” drug, i.e., its use leads to initiation of use of other drugs of abuse

C5. Treatment of Marijuana Abuse is Symptomatic
- Anxiolytics for anxiety and panic
- Antipsychotics for delirium and paranoia
- Cognitive behavioral therapy for dependence
- No pharmacotherapies but discovery of CB1 receptor and development of an antagonist is promising

D. Alcohol
- Health care cost of alcohol problems - $186 Billion
- Alcohol dependence is a complex disorder in which many factors act together to produce the illness
- Approximately 50% of the risk is attributed to genetics
May arise in individuals without family history of alcohol dependence as a result of environmental factors

D1. Subtypes of Alcohol Dependence

Type A Alcohol Dependence
- Late onset (>25 years old)
- Few familial alcohol-dependency antecedents
- Slower disease progression
- Milder form of alcohol dependence
- Important environmental influence
- Minimal criminality

Type B Alcohol Dependence
- Early onset (≤25 years old)
- Paternal type B alcohol dependence
- More severe form of alcohol dependence
- Little environmental influence
- Frequent criminality
- Frequent presence of personality disorder

D2. Disease Associated with Chronic Alcohol Use

Primary Diseases
- Alcohol poisoning
- Alcoholic heart disease (cardiomyopathy)
- Alcoholic gastritis
- Alcoholic liver cirrhosis
- Alcoholic nerve disease (polyneuropathy)
- Alcoholic psychoses

Secondary Diseases
- Cancer (lip, mouth, pharynx, esophagus, larynx, liver, stomach)
- Diabetes
- Gastrointestinal disease
- Heart disease (hypertension, stroke)
- Liver disease
- Pancreatitis (acute, chronic)

D3. Effects of Acute Alcohol on Neural Circuits I

Dopamine and Opioid Systems
- Indirectly increases dopamine levels in the mesocorticolimbic system
  - Associated with positively reinforcing effects of alcohol
- Indirect interaction with opioid receptors results in activation of opioid system
  - Associated with reinforcing effects via µ-receptors

D4. Effects of Acute Alcohol on Neural Circuits I

GABA and Glutamine Systems
- Increases the effects of GABA, the major inhibitory neurotransmitter in the brain
• Inhibits the effects of glutamate, the major excitatory neurotransmitter in the brain

Chronic exposure of alcohol leads to a compensatory
1) Reduction in the levels of GABA-gic receptors
2) Up-regulation of NMDA receptor

Sudden reduction in chronic alcohol intake results in overactivation of NMDA system

D5. Treatment Stages of Alcohol Dependence

Stage 1: Identification
- obtain history of current and past alcohol use and family history of alcohol problem
  - use standardized screening tests (e.g., 4-question CAGE)
  - evaluate patients in terms of the DSM-IV criteria for alcohol abuse and dependence and determine whether patient wants to abstain

Stage 2: Detoxification/Withdrawal
- Mild or severe withdrawal symptoms
  mild withdrawal symptoms - agitation, anxiety, insomnia, nausea
  severe withdrawal symptoms – autonomic hyperactivity, seizures, delirium tremens
- relieve immediate symptoms of withdrawal – benzodiazepines – indirect agonist for GABA receptors (reverses effect of alcohol) Benzodiazepines with long half-life have less chance of recurrent withdrawal. Diazepam has a long half-life Larazepam has as shorter half-life but not metabolized by liver – good for patients with cirrhosis

Stage 3: Rehabilitation
- restructure life without alcohol
- relapse prevention – psychotherapy, pharmacotherapy

Stage 4: Aftercare
- AA meetings, family support

D6. Symptoms of Alcohol Withdrawal
1) minor withdrawal (6-36 hrs)- due to CNS hyperactivity – Hyperarousal mild anxiety, headache, sweating, GI upset, insomnia, nausea
2) Seizures (6-48 hrs)
  3% of chronic alcoholics can develop tonic-clonic seizures, some develop status epilepticus (seizures without regaining consciousness for 30 min)
  Can be life threatening
3) alcoholic hallucinations (12-48 hrs)
  visual, auditory, tactile – can last for months
4) delirium tremens (48-96 hrs after the last drink, can last 1-5 days)
D7. Delirium Tremens (DT) – 48-96 hrs
- Caused by withdrawal from long-term alcohol consumption
- 5% of alcohol withdrawal leads to DT (mortality can be up to 35% when untreated)
- Caused by withdrawal from benzodiazepines

Symptoms
- Confusion, disorientation, visual hallucinations
- Uncontrollable tremors of the extremities
- Severe autonomic instability (fever, tachycardia, hypertension)

Treatment
- Pharmacotherapy is symptomatic and supportive
- Benzodiazepines, such as diazepam (Valium), lorazepam (Ativan)

D8. FDA-Approved Pharmacotherapies for Alcohol Dependence

Disulfiram – Alcohol Aversion Therapy
Naltrexone – Opioid antagonist
Acamprosate – restores balance between neuronal excitation and inhibition

D9. Disulfiram
- Inhibits aldehyde dehydrogenase
- When taken with alcohol, increased levels of [acetaldehyde] leads to nausea, dizziness, headache, hypotension, vomiting
- Decreases desire to drink alcohol but does not increase abstinence
- Increased risk of hepatotoxicity

D 10. Naltrexone [ReVia]
- Opioid antagonist
- Blocks release of dopamine from Nucleus Accumbens
- Avoid Naltrexone with Disulfiram – both are potential hepatotoxins
- Avoid Naltrexone in patients dependent on opioids- it will precipitate acute withdrawal syndrome

D. 11 Acamprosate
- Restore balance between neuronal excitation and inhibition (mechanism unknown)
- Minor side effects: diarrhea, allergic reactions, irregular heartbeats
- Dose adjustment in patients with moderate renal disease (creatinine clearance 30-50 mL/min)
- Contradicted in severe renal disease (creatinine clearance < 30 mL/min)

E. Anti-depressants: Benzodiazepines
Therapeutic Uses of Benzodiazepines
- Benzodiazepines are the most commonly prescribed sedative-hypnotics
- Severe anxiety, panic attacks and phobias (because of their anxiolytic properties)
- Insomnia
- In muscular disorders - effective muscle relaxants
  - Alcohol withdrawal
  - Epilepsy – anticonvulsant

E1. Benzodiazepine Withdrawal Syndrome

- Anxiety, agitation
- Increased sensitivity to light and sound
- Muscle cramps
- Sleep disturbance
- Dizziness
- Mycolonic jerks

Withdrawal Management

Treatment with diazepam (Valium)
- benzodiazepine with a long-half life
- gradually tapering off the drug over a period of months

F. Nicotine

- Is among the most addictive drugs, accounts for 440,000 deaths yearly
- Selective agonist of the nicotinic acetylcholine receptor (nAChR)
  - that is normally activated by acetylcholine
- Nicotine acts on nAChR receptors, stimulate dopaminergic neurons
  - in the VTA and increases the release of dopamine in the nucleus accumbens

Treatment

- Nicotine patches, nasal spray, nicotine lozenge
- Varenicline
  - non-nicotine medication – partial agonist that binds subunits of
    nicotine acetylcholine receptors. Because it stimulates the receptors, it
    relieves cravings and withdrawal symptoms during abstinence from smoking
    - binds to the nAChR receptors with greater affinity than nicotine –
      thus reduces the pharmacologic reward from cigarette smoking

G. Hallucinogens

- Causes change of sensation, illusions, called – mind-bending drugs
- The drugs do not induce dependence or addition
- Serotonin receptors 5-HT2A in cortex are molecular targets
- Treatment: for nonpsychotic agitation – anti-anxiety drugs
  - for severe agitation – use antipsychotic drugs

Please see summary slides in PowerPoint presentation
Clinical practice of pediatric psychopharmacology is challenging
+ Over the past 10 years, significant increase in the use of psychotropic medications in the pediatric population.
+ The largest increase was the use of
  • atypical antipsychotics (138.4%)
  • atypical antidepressants (42.8%)

Treatment with psychotropic drugs managed
+ A large proportion of children receive these medications from primary care doctors and pediatric specialists

OBJECTIVES

• To be cognizant of the general pharmacological properties of psychotropic medication for the pediatric population
• To know the clinical indications/usage of psychotropic medications for childhood presentations of psychiatric disorders as recommended by the FDA
• To know the major warnings and precautions associated with psychotropic medications
• To appreciate the evidence based medicine treatment of pediatric psychiatric disorders
For more detailed and up-to-date information on FDA regulations
http://www.fda.gov/medwatch/index.html

**NEUROBIOLOGY OF ADHD**

Conceptualization of etiology

* Underactivity of the catecholamergic system mediated by dysregulation of the dopaminergic(DA) and noradrenergic(NE) CNS systems
NEUROBIOLOGY OF ADHD

+ Dopamine neurotransmission
  × Pathways
    + Tuberoinfundibular
    + Nigrostriatal
    + Mesolimbic
    × Mesocortical (executive functioning)
  × Functions
    × Neurophysiologically dopamine enhances the signal for attention skills

× Stimulants block (inhibition of the neurotransmitter reuptake pump)
  + 1-reuptake of norepinephrine (NE) and of 2-dopamine (DA) in the presynaptic neurons which 3-increase their concentrations (DA) in the intrasynaptic space.

× Atomoxetine (non-stimulant) increases norepinephrine in the synaptic cleft by inhibiting its presynaptic transporter.
  + Children who are CYP2D6 “slow metabolizers” may experience atomoxetine’s serum peak concentrations 5-fold greater than fast metabolizers.
Stimulants have FDA indications for the treatment of ADHD and narcolepsy (2).

MPH and d-MPH are approved for use in patients at least 6 years old.

Amphetamines in children > 3 years old.

Atomoxetine has FDA indication for the treatment of ADHD in individuals at least 6 years old (2).
STIMULUS PRACTICAL CONSIDERATIONS

- Start with MPH or AMPH
- If one stimulant not effective, try the other one
- Short-acting easier to titrate, then may wish to switch to long acting
- Start with long acting if school dose a problem
- Titrate to optimum response
- Example starting dose
  - Methylphenidate 5mg ½ tab BID-TID

Atomoxetine, a suggested second line treatment option for ADHD (4),

- Optimal effective dose of atomoxetine
  - 1.2-1.3 mg/kg/day, administered once daily.

MAJOR WARNINGS AND PRECAUTIONS

- The FDA issued a Black Box Warning reporting sudden death in children prescribed stimulants
  - therefore stimulants should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, and serious heart rhythm abnormalities.
- Precaution:
  - Temporary slowing in growth has also been found in children medicated with stimulants. 
MPH has strong evidence supporting its use as the first line treatment for ADHD.

Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA)
- 14-month multisite trial
- of 4 different treatment strategies for 579 children, aged 7 to 9.9 years (9)

MTA compared the following treatments:
- (a) the fixed-dose of MPH titrated to the child’s “best dose”
- (b) intensive behavioral treatment
- (c) combined MPH and intensive behavioral treatment, and
- (d) standard community care.

All four groups improved,
But children in the MPH and combination groups improved significantly more.

Several studies comparing the safety and efficacy of MPH and Adderall (15, 16, 17).
Adderall was reported to exhibit longer lasting therapeutic effects than MPH (15, 16), but more stomachaches and sad mood.
Swanson et al. (1998) (16) reported that MPH had a faster onset of clinical effect than Adderall (1.8 hours and 3 hours respectively).

Stimulants are available in short (4 hours), intermediate (6-8 hours), and long-acting sustained-release (10-12 hours) formulations.
- A short-acting medication may be added to a sustained-release medication in the late afternoon to maintain ADHD symptom control in the evening.
- It is recommended that stimulants be given seven days per week (20), but patients with decreased appetite, irritability, or sleep problems may discontinue stimulants on weekends and holidays (21).

Weight-based dosing guidelines are available, but effective maintenance dose of stimulants is guided by the clinical response and the side effects.
Red Light, Green Light

- Red Light, Green Light
  + (Complex Rules)
- Simon Says
  + (Mental Flexibility and Self-Control)
- Row, Row, Row Your Boat
  + (Focus, Memory, Flexibility and Self-Control)

"Executive Function"

- Interactive games require high levels of executive function, test a child’s ability to pay attention, remember rules and exhibit self-control — qualities that predict academic success.

Rule of thumb with Pediatric Pharmacology

- Go low (dosing), Go slow (titration/taper)
REFERENCES ARE LISTED IN BOOK CHAPTER


* Slides contributed with direct consent from Shire, U.S.
Drugs Used in the treatment of Rheumatoid Arthritis and Gout

Date: Wednesday, March 5th, 2014 – 10:30-11:30am

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Discuss the rationale behind the use of Analgesics, NSAIDs and glucocorticoids in the treatment of Osteoarthritis.

2. Discuss the relative therapeutic benefit of the use of NSAIDs, Analgesics, Glucocorticoids, DMARDs and Biological Response Modifiers/Biologics in the treatment of Rheumatoid Arthritis.

3. Describe the major indications, mechanism of action, time to effect, major adverse effects and contraindications of the frequently used DMARDs class of drugs used in the treatment of RA.

4. List the less frequently used DMARDs used in the treatment of Rheumatoid Arthritis.

5. Describe the major indications, mechanism of action, major adverse effects and contraindications of the Biological Response Modifier class of drugs used in the treatment of Rheumatoid Arthritis.

6. Identify the classes of drugs used in the treatment of Rheumatoid arthritis that are safe to use in pregnancy.

7. Apply your knowledge of the pharmacology of the major classes of drugs used to treat rheumatoid arthritis to select the most appropriate medication for a specific patient based upon patient-specific criteria.

8. Describe the pathophysiology of Gout; the role of uric acid in the etiology of the disease; and the typical disease course including hyperuricemia, acute gouty attack, intercritical phase and chronic gout.

9. Discuss the rationale for the use of Colchicine and NSAIDs in the treatment of an acute gouty attack.

10. Describe the rationale behind the use of the major drug classes used to treat Chronic Gout.

11. Describe the indications, mechanism of action, major adverse effects and contraindications of the major drug classes used in the treatment of chronic gout.

12. Apply your knowledge of the pharmacology of the major classes of drugs used to treat gout to select the most appropriate medication for a specific patient based upon patient-specific criteria.
Drugs to be covered in this lecture:

Particular emphasis should be placed on the drugs that are highlighted in **BOLD TEXT**.

1. NSAIDs

2. Acetaminophen (Tylenol®/Paracetemol®)

3. Topical Analgesics e.g. Capsaicin

4. Glucocorticoids (Injectable/Oral)

5. Disease-Modifying anti-Rheumatic Drugs (DMARDs)
   
   **Commonly used DMARDs:**
   - Methotrexate (Rheumatrex®)
   - Hydroxychloroquine (Plaquinil®)
   - Sulfasalazine (Azulidine®)
   - Leflunomide (Arava®)

   **Less frequently used DMARDs:**
   - Azathioprine (Imuran®)
   - D-penicillamine (Depen®)
   - Gold salts
   - Cyclosporin A (Sandimmune® & Neural®)
   - Cyclophosphamide (Cytoxan®)

6. Biological-response Modifiers
   - Etanercept (Enbrel®) - TNFa inhibitor
   - Infliximab (Remicade®) - TNFa inhibitor
   - Adalimumab (Humira®) - TNFa inhibitor

   - Anakinira (Kineret®) - IL-1R antagonist
   - Abatacept (Orenica®) - inhibitor of T cell co-stimulation
   - Rituximab (Rituxan®) - anti-B cell agent
   - Tocilizumab (Actemra®) - anti-IL-6R agent
   - Tofacitinib (Xeljanz®) - small molecule inhibitor of immune cytokine receptor signaling

7. Colchicine

8. Uricosuric agents
   - Probenecid

9. Uric Acid Synthesis Inhibitor
   - Allopurinol (Zyloprim®)
   - Febuxostat (Uloric®)

10. Pegloticase
    - PEG-coupled PORCINE URICASE- degrades Uric acid to soluble byproduct
A. Osteoarthritis

Overview
- Most common joint disease affecting 21 million in the US
- Characterized by loss of articular cartilage, bone remodeling and bone hypertrophy
- Most commonly affects the weight bearing joints of the hips, knees and lower back
- Exact cause unknown, but may result from either excessive load on the joints or the presence of abnormal cartilage or bone
- Risk factors include age > 50yrs, joint injury, obesity, high bone density, long-term immobilization of the joint, mechanical stress to the joints (e.g. occupational/sports), and genetics

Symptoms
- Joint soreness after periods of overuse or inactivity
- Stiffness after periods of rest that disappear when activity is resumed
- Redness, tenderness and swelling of the affected joints
- Pain when moving the knee, pain and swelling of the finger joints
- Stiffness and pain in the neck, shoulders, arms or lower back

Pathophysiology
- Cartilage loses its elasticity and is more easily damaged
- Mechanical wear and tear of the cartilage promotes the proliferation of chondrocytes.
- Chondrocytes release proteases and pro-inflammatory mediators
- Proteases degrade the matrix and result in the formation of abnormal cartilage
- Breakdown of the cartilage can cause bones to rub together causing pain
- Inflammation of the cartilage (mild c.f. with RA) causes new bone spurs to form, which causes pain and decreases the mobility of the joint

Treatment

Treatment goals
a) Control pain and other symptoms with medication
b) Improve functionality and quality of life- weight loss, exercise and physical therapy

Medications

1. Analgesics:
- For mild to moderate pain- Acetaminophen is the drug of choice for pain relief with minimal side effects (see below).

2. Topical Analgesics:
- A topical analgesic such as Capsaicin (derived from hot peppers) can be used together with oral acetaminophen for pain relief.
- Capsaicin works by depleting Substance P, which is present in painful joints and is involved in the transmission of pain to the CNS

3. NSAIDs: e.g. Aspirin, Ibuprofen and Naproxen
- For patients with moderate to severe pain and signs of inflammation.
- However use of NSAIDs may be limited by their side effects.

4. Injectable glucocorticoids
- Glucocorticoids can be injected directly into the joint for fast targeted pain relief as an alternative to patients with mild to moderate pain that do not respond to acetaminophen or NSAID treatment.
- ~80% of patients exhibit a therapeutic response
- Injections not given more frequently than once every three months
B. Rheumatoid Arthritis.

Overview
- Chronic inflammatory disease of the joints
- Affects 1.5% of Americans, 9 million physician visits and >250,000 hospitalizations/year
- Systemic autoimmune disease of unknown etiology
- Characterized by inflammation and pain in the joints with progressive joint destruction
- Additional extra-articular involvement of the skin, cardiovascular system, lungs and muscle
- Causes significant disability, deformity and can even precipitate premature death
- Although the exact cause is unknown, disease progression clearly involves the immune system with evidence of both T cell and B cell immune response to self-antigen

Pathophysiology
- Chronic lymphocytic inflammatory infiltration develops in the synovium (joint lining)
- Swelling of the synovium causes pain, warmth, stiffness and redness of the joint
- Rapid proliferation of synovial fibroblasts and infiltrating leukocytes causes the snovium to thicken and invade the local cartilage and bone
- Macrophages and lymphocytes secrete proteolytic enzymes (e.g. collagenase) and inflammatory mediators (e.g. TNF-α, IL-6, IL-1 and prostaglandins) causing further inflammation, the activation of bone-resorbing osteoclasts and ultimately the destruction of bone and cartilage.

B1 Treatment of Rheumatoid Arthritis

B1.1 Treatment goals
- Decrease pain
- Prevent or control joint damage
- Prevent loss of function and preserve quality of life

B1.2 Medications used to treat Rheumatoid Arthritis: An overview

B1.2A Drugs to treat Acute Joint Pain-Symptomatic Relief Only
1. NSAIDs (e.g. Aspirin, Ibuprofen, Naproxen and Celecoxib)
   - Drugs of choice for the reduction of inflammation and pain
   - Patients usually started on an NSAID immediately after diagnosis
   - For symptomatic relief only! - NSAIDs do not affect disease course
   - Choice of NSAID determined by efficacy and side effects
   - If a particular NSAID is ineffective after a 2 week trial an alternative NSAID is warranted

2. Analgesics (e.g. Acetaminophen, Capsaicin or an Opioid analgesic)
   - For symptomatic pain relief
   - Can be combined with a NSAID for improved pain relief and anti-inflammatory effect
   - A topical analgesic such as Capsaicin (derived from hot peppers) can be used together with oral acetaminophen for pain relief. Capsaicin works by depleting Substance P, which is present in painful joints and is involved in the transmission of pain to the CNS

3. Glucocorticoids
   a) Glucocorticoids exhibit both anti-inflammatory and immunoregulatory activity
   b) Can be administered orally, intravenously, or by direct injection into the joint
   c) Useful early in disease while waiting for slow acting DMARDs to work
   - Shown to: Decrease joint tenderness
   - Decrease joint pain
   - Increase grip strength
   - Short term/low dose glucocorticoids are seldom associated with serious side effects
e) The use of chronic glucocorticoid therapy is controversial- there is some evidence for the inhibition of disease progression, although their use is associated with increased side effects

<table>
<thead>
<tr>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>Weight gain</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Increased risk of infection</td>
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f) Withdrawal from long-term glucocorticoid use is difficult, as this can result in increased disease severity due to suppression of the Hypothalamus-Pituitary-Adrenal axis

**B1.2B Drugs that can acto to prevent or control joint damage**

4. **Disease modifying anti-Rheumatic Drugs (DMARDS) (e.g. methotrexate) (SEE BELOW)**
   - To slow joint damage and modify the course of the disease

5. **Biological Response Modifiers (BRM)/Biologics (e.g. TNF inhibitors etc) (SEE BELOW)**
   - Specific recombinant protein drugs that inhibit the immune responses that contribute towards joint inflammation.
   - Shown to slow joint damage and modify the course of the disease

**B2 Disease-Modifying anti-Rheumatic Drugs (DMARDs)**

**Overview**

a) Unlike NSAIDs and corticosteroids, DMARDs can potentially reduce/prevent joint damage
b) DMARDs work to inhibit the overactive immune system that is present in Rheumatoid Arthritis
c) DMARDs should be considered in Rheumatoid Arthritis where the use of NSAIDs/steroids has not prevented ongoing joint pain or other clinical symptoms
d) Use of DMARDs should not be delayed beyond 3 months in these patients
e) DMARDs are slow acting anti-rheumatic drugs that can take several weeks to many months to show efficacy and are typically taken for long periods (i.e. months to years)

**B2.1. Frequently used DMARDs**

1. **Hydroxychloroquine (e.g. Plaquenil®)**
   a) An anti-malarial drug that is moderately effective for mild rheumatoid arthritis
   b) Effectiveness only becomes apparent after 3-6 months
   c) Often combined with other DMARDs e.g. sulfasalazine and methotrexate
   d) Considered safe for use during pregnancy

   **Mechanism of action:** Unclear- thought to inhibit immune responses in a variety of ways
   - inhibition of TLR signaling in dendritic cells and B cells
   - inhibition of antigen presentation to CD4+ T cells

   **Adverse Effects**
   - Nausea, epigastric pain, rash and diarrhea
   - Rare (1/40,000) retinal toxicity has been reported in elderly patients that can result in irreversible visual loss

2. **Sulfasalazine (Azulifidine®)**
   a) Decreases signs and symptoms of disease and slows radiographic evidence of joint destruction (effective in up to 50% of patients).
   b) more toxic than hydroxychloroquine/somewhat less effective than methotrexate
   c) Sulfasalazine is a combination of 5-aminosalicylic acid covalently linked to sulfapyridine that is cleaved by colonic bacteria to its active components- it is thought that sulfapyridine is responsible for the therapeutic effect
   d) Effect can be seen in 1-3 months
e) Does not appear to be a teratogen—therefore unlike methotrexate it is safe during pregnancy
f) Often combined with other DMARDs e.g. hydroxychloroquine

**Mechanism of action:** Unclear, but thought to interfere with T and B cell immune responses, potentially by inhibiting the activity of the NF-kB transcription factor

**Adverse Effects:** Nausea, headache, anorexia and rash are common (~30% of patients)
- Rare – Agranulocytosis with Fever/Rash within 2 weeks of treatment
  - fully reversible following drug discontinuation

3. **Methotrexate** *(Rheumatrex®)******

a) **Drug of choice** for treatment of Rheumatoid Arthritis—especially for patients with active disease
b) Oral methotrexate in low doses (15-27.5 mg/week) decreases the appearance of new bone erosions and improves the longterm clinical outcome – up to 70% of patients experience some response to the drug
c) N.B. the levels of methotrexate used in RA are ~100-1000x lower than used in cancer treatment
d) Effects are apparent after 4-6 weeks
e) Well tolerated >50% of patients continue taking the drug for >3 yrs

**Mechanism of action:** Unclear, but appears to be independent of its anti-proliferative activity. Thought to be due to an indirect effect on the increased production of adenosine, which is known to exhibit immunosuppressive properties

**Adverse Effects**
- Generally well tolerated (>50% of patients continue taking the drug for > 3 yrs)
- MTX is 80-90% renally excreted—side effects more common in patients with renal impairment
  - Common side effects:
    - Dose-dependent hepatotoxicity
    - Not recommended for those with pre-existing liver disease or consuming alcohol
  - Rarer Side effects:
    - Bone marrow suppression
    - Acute pneumonitis occurs in 1-2% of patients
    - Increased risk of lymphoma

- **Contraindicated during pregnancy** (MTX is actually used as an abortifacient)

4. **Leflunomide** *(Arava®)*

a) As effective as either slufasalazine or methotrexate in decreasing symptoms of disease
b) Alternative to those unable to take MTX or for those non-responsive to MTX
c) low cost alternative to expensive TNF inhibitors or for those with a preference for oral vs IV medication
d) Responses evident in 1-2 months

**Mechanism of action:** Oral pyrimidine synthesis inhibitor that inhibits dihydroorotate dehydrogenase and therefore blocks the de novo synthesis of uridine, which leads to cell growth arrest in the G1 phase of the cell cycle. Inhibits both T cell proliferation and the production of autoantibodies by B cells

**Adverse Effects**
- Diarrhea occurs frequently (~10-15% of patients)
- Alopecia, weight gain, rash, increased blood pressure and an increase in liver enzymes can
Severe hepatotoxicity (including several fatalities) have been reported in patients taking both Leflunomide and Methotrexate - Contraindicated during pregnancy - Should not be taken concomitantly with rifampin (anti-tuberculosis medication), as it is known to elevate serum leflunomide levels leading to increased risk of toxicity

B2.2. Less frequently used DMARDs

1. Azathioprine
   a) Orally active purine analog that is cytotoxic to inflammatory cells
   b) Used for patients with refractory Rheumatoid Arthritis and those with systemic involvement, such as rheumatoid vasculitis
   c) Treatment for 3-6 months is required to be effective
   d) Drug is not always well tolerated

   **Adverse effects**
   - Nausea, vomiting, abdominal pains, hepatitis, reversible bone marrow suppression and increased risk of lymphoma

2. Gold salts
   a) Gold compounds (oral/injected intramuscularly) have been used to treat arthritis since the 1960’s
   b) Can induce a complete remission
   c) Sometimes used in patients who cannot tolerate methotrexate
   d) Gold particles are taken up by macrophages and impair their function
   e) Response requires 3-6 months

   **Adverse effects**
   - Stomatitis, dermatitis, proteinuria, thrombocytopenia, leukopenia and bone marrow suppression (RARELY USED NOW DUE TO TOXIC SIDE EFFECTS)

3. Cyclosporin (e.g. Sandimmune®, Neural®)
   a) Approved for use in Rheumatoid arthritis and retards appearance of bony erosions
   b) Acts by inhibiting T lymphocyte activation pathways leading to cytokine production
   c) Maybe useful in patients with refractory arthritis
   d) However, associated with significant nephrotoxicity, neurotoxicity, hepatotoxicity and increased hypertension
   e) Toxicity and costs associated with drug level monitoring limit use

4. Cyclophosphamide (Cytoxan®)
   a) Major metabolite is phosphoramide mustard, which promotes DNA crosslinks and thereby inhibits DNA replication
   b) Acts to inhibit T and B cell function by 30-40%
   c) Is useful in the treatment of severe rheumatoid vasculitis
   d) Long term use is associated with leukopenia, increased risk of infection, cardiotoxicity, alopecia and an increase risk of malignancy, especially bladder cancer.

5. D-penicillamine (Depen®)
   a) Can be effective in patients with refractory Rheumatoid Arthritis
   b) However, more toxic than either methotrexate or sulfasalazine- RARELY USED NOW

*Because of the increased toxicities of these drugs they are now typically only utilized in RA with severe life-threatening extra-articular symptoms such as systemic vasculitis, or in very severe RA that is refractory to other medications.*
B3 Biological Response Modifier/Biologic Drugs

Overview

Biological response modifiers are recombinant protein drugs that are specifically designed to inhibit either cytokines (e.g. TNF-α and IL-1) or cell types (e.g. T cells/B cells) involved in the regulation of the in vivo immune response.

a) Drugs that specifically inhibit the action of TNF-α:
   (i) Etanercept (Enbrel®)
   (ii) Infliximab (Remicade®)
   (iii) Adalimumab (Humira®)

b) Drugs that interfere with the actions of IL-1
   - Anakinra (Kineret®) is an IL-1 blocker

c) Drugs that inhibit T lymphocyte activation/co-stimulation:
   - Abatacept (Orenica®)

d) Drugs that deplete B lymphocytes:
   - Rituximab (Rituxan®)

e) Drugs that block the actions of IL-6
   - Tocilizumab (Actemra®)

f) Drugs that inhibit immune cytokine receptor signaling
   - Tofacitinib (Xeljanz®)

B3.1 The critical role played by TNF-α in the pathogenesis of Rheumatoid arthritis: An overview

<table>
<thead>
<tr>
<th>Activated Endothelial cells</th>
<th>TNF-α</th>
<th>Osteoclast Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte recruitment</td>
<td></td>
<td>Bone resorption</td>
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<tr>
<td>Synoviocyte/Chondrocyte</td>
<td></td>
<td>Joint Inflammation</td>
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<tr>
<td>Cartilage Breakdown</td>
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<td>Cartilage Breakdown</td>
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<tr>
<td>Bone Erosion</td>
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</tbody>
</table>

a) TNF-α is a pivotal cytokine in the regulation of the immune response

b) It is synthesized by macrophages, mast cells and activated CD4+ Th1 cells

c) It activates macrophages increasing their phagocytic activity and the production of cytotoxic molecules

d) It activates the endothelium and promotes the recruitment of leukocytes to site of inflammation

e) It promotes the differentiation of bone-resorbing osteoclasts

f) It induces the proliferation of synoviocytes and their production of proteases & inflammatory molecules

g) It exhibits pyrogenic activity causing fever and acts systemically to cause pain
**B3.2. Anti-TNF-α drugs**

a) **Etanercept (Enbrel®)**
Recombinant protein consisting of two soluble p75 TNF-α receptor moieties linked to the Fc portion of a human IgG1 antibody molecule

b) **Infliximab (Remicade®)**
Chimeric human/mouse anti-TNF-α monoclonal antibody

c) **Adalimumab (Humira®)**
Recombinant fully human monoclonal antibody

---

**Anti-TNF-α drugs: Mechanism of Action.**

All three anti-TNFα drugs work by binding to soluble TNF-α and prevent it from interacting with its cognate receptor expressed on the surface of specific cell types.

---

**Anti-TNF-α drugs: Clinical Use**

a) Anti-TNFα drugs are given either subcutaneously or intravenously and are typically administered weekly/bi-weekly

b) Typical time to effect is 1-4 weeks

c) Clinically shown to:
   i) reduce joint pain and swelling
   ii) decrease the formation of new bone erosions
   iii) slow progression of structural joint damage

d) ~30-60% of patients will exhibit a 20-50% improvement in their symptoms

e) Are used as both monotherapy and in combination with methotrexate. When combined with low dose methotrexate the addition of anti-TNFα drugs have been shown to significantly prevent disease progression versus the use of methotrexate alone

---

**Anti-TNF-α drugs: Common Adverse effects.**

a) Injection site reactions, injection site pain, headache and rash are common, but usually do not require discontinuation of treatment

b) Increased risk of opportunistic infections

c) Can result in the reactivation of latent tuberculosis and Hepatitis B virus

d) Should not be given to patients with either acute or chronic infections

e) Treatment should be discontinued if a serious infection or sepsis develop

f) May rarely be associated with the exacerbation of pre-existing congestive heart failure and the development of demyelinating diseases such as multiple sclerosis, and the appearance of malignancies, especially lymphoma

g) Should not be given to patients with a recent history of malignancy

---

**B3.3 Abatacept (Orenica®)**

a) Is a recombinant protein fusion between the T cell surface molecule CTLA-4 and human IgG1 (CTLA4-Ig)
b) It inhibits T cell activation by binding to the CD80/CD86 (B7) family of co-stimulatory ligands expressed on antigen presenting cells, thereby blocking the delivery of co-stimulation signals to the T cell via the CD28 molecule, which is essential for efficient T cell activation

c) Slows damage to bone and cartilage and relieves both the symptoms and signs of arthritis

d) Effective in patients non-responsive to anti-TNF-α drugs
Pharmacology & Therapeutics
March 5th, 2014
Neil Clipstone, Ph.D.

Drugs to treat RA and Gout

**Adverse effects**
- Increased risk of serious infections - screen for latent TB and HBV
- Not to be given to patients with either acute or chronic infections
- Should not be given in combination with a TNF-α blocker as this increases infections

**B3.4 Rituximab (Rituxan®)**

a) Rituximab is a chimeric humanized antibody that binds to the CD20 molecule expressed on B lymphocytes
b) I.V. infusion of Rituximab depletes B cells from the blood.
   - since B cells are implicated in disease etiology through antigen presentation and formation of autoantibodies their depletion can slow disease progress
c) Clinically shown to decrease signs and symptoms of disease and reduce radiographic evidence of disease progression.
d) Effects not seen for 3 months, although effects may last 6 months - 2 yrs following a single infusion.
e) Effective in patients not responsive to TNF-α inhibitors

**Adverse Effects**
- Increased infections
- Reactivation of latent viruses e.g. CMV, HSV and Hepatitis B&C
- Progressive multifocal leukoencephalopathy (PML-RARE)
  - fatal demyeinating disease associated with reactivation of the JC virus

**B3.5 Anakinra (Kinera®)**

a) Genetically engineered recombinant version of an endogenous IL-1 receptor antagonist (IL-1RA)
b) Competitively inhibits the pro-inflammatory effects of endogenous IL-1
c) A subcutaneous dose of 150 mg/day gives a modest reduction in pain and swelling, but a significant reduction in new bone erosions (due to the effects of IL-1 on synoviocyte-mediated cartilage degradation).
d) Also given in combination with methotrexate

**Adverse effects**
- Local injection site reactions are frequent (~40%) and can lead to discontinuation of the drug
- Only a small increase in infections
- Should not be given to patients with either acute or chronic infections
- Complications (neutropenia and severe bacterial infections) occur more frequently when given together with an anti-TNF-α drug

**B3.6 Tocilizumab (Actemra®)**

a) Chimeric humanized antibody directed against the IL-6 receptor
b) Acts as an antagonist of the IL-6 receptor
c) Used in patients non-responsive to TNF inhibitors

**Adverse Effects**
- Increased risk of BM suppression (Lymphocytopenia, neutropenia, anemia)
- Increased risk of serious infections (including TB and HBV)
- Hepatotoxicity (routine liver monitoring)
- Increased levels of cholesterol
- Increased risk of malignancy (especially in setting of immunosuppression)
### B3.7 Tofacitinib (Xeljanz®)

- **a)** New class of anti-rheumatic drug
- **b)** Small molecule inhibitor that inhibits JAK tyrosine kinases involved in immune cell cytokine signaling.

#### Adverse Effects
- Lymphocytopenia, neutropenia and anemia
- Increased risk of serious infections including TB
- Lipid abnormalities (increased cholesterol)
- Increased liver enzymes

### B4 Treatment strategy in Rheumatoid Arthritis

- **a)** Initial symptomatic treatment for relief of pain and joint inflammation
  - NSAIDs (e.g. Naproxen, Indomethacin)
  - Glucocorticoids (e.g. Prednisone)

- **b)** DMARDs therapy should be initiated within 3 months of diagnosis
  - Hydroxychloroquine + Sulfasalazine is used for mild disease
  - Methotrexate is the drug of choice for active and/or moderate-severe disease

- **c)** NSAID are used in the early stages of DMARD therapy to reduce pain while waiting for the clinical effect of DMARDs to “kick-in”

- **d)** If Methotrexate is ineffective- other DMARDs (e.g. Leflunomide) and/or Biological Response Modifiers either alone or in combination should be tried.

- **e)** Clinical trials have shown that combination therapy with multiple agents is likely to be more effective than monotherapy.
  - e.g. Methotrexate + Hydroxychloroquine and Sulfasalazine
  - Methotrexate + either Etancerpet, Infliximab or Adalimumab

### C. Gout

#### Overview

- **a)** Gout is an extremely painful form of arthritis.
- **b)** It is associated with **HYPERURICEMIA**: **high** serum levels of uric acid (>7 mg/dL)
  - uric acid is a poorly soluble end product of purine metabolism
  - however not all individuals with hyperuricemia will develop gout

- **c)** Hyperuricemia can result from either **over production** of uric acid (10% of patients), or from **decreased excretion** of uric acid by the kidney (~90% of all patients).
d) It affects primarily men in their 30’s and 40’s (frequency 1 in 100) and is associated with obesity, hypertension, hyperlipidemia, type 2 diabetes, a diet rich in purines and the excessive consumption of alcohol. - Historically referred to as the “Disease of Kings”

**Gout: Pathophysiology**

a) Urate crystals are deposited in the joints  
b) Synoviocytes phagocytose urate crystals  
c) Synoviocytes secrete inflammatory mediators- prostaglandins, IL-1 and lysosomal enzymes  
d) Inflammatory leukocytes are recruited into the joint  
e) Recruited macrophages phagocytose urate crystals and release additional inflammatory mediators that promote further recruitment of inflammatory cells  
f) Inflammation causes pain, heat and swelling and damage to the joint

---

**C1. Gout Disease Course**

1. **Initial stage: Asymptomatic hyperuricemia**  
   - only a small percentage of patients with hyperuricemia will go onto develop gout  

2. **Acute Gouty Attack**  
   - rapid onset of an **intense** period of painful swelling in a single joint, most often in the feet (esp. big toe; first metatarsophalangeal joint).  
   - the symptoms of the attack typically resolve within 3-10 days.  

3. **Intercritical Phase**  
   - hyperuricemia without acute symptoms  
   - 10% of patients may never experience another attack  

4. **Chronic Gout**  
   - recurrent attacks of increasing frequency and severity involving additional joints  
   - chronic high levels of urate crystals lead to the formation of **TOPHI** - a deposition of urate crystals around the synovial joint that can induce an inflammatory response resulting in the destruction of cartilage and the synovial lining

---

**C2. Pharmacological strategies for the treatment of gout**

**C2.1. Drugs that relieve the symptoms of the acute gouty attack**

(A) **Colchicine**  
   - traditional treatment,  
   - plant alkaloid that prevents tubulin polymerization into microtubules  
   - blocks leukocyte migration and phagocytosis  
   - anti-inflammatory, but **no** analgesic properties  
   - effective typically only when given during the first 24-48 hrs of the attack  
   - limited by side effects (especially at high doses)- ~80% of patients develop diarrhea/vomiting within 24hrs  
   - overdose can be life threatening due to bone marrow suppression
- because of toxicity now generally relegated to a second line agent

(B) NSAIDs
- commonly used as a replacement for Colchicine
- **all NSAIDs except** Aspirin and Salicylates have been used successfully in the treatment of gout
- effective at reducing pain and disability due to attack
- COX-2 inhibitors should be used when other NSAIDs are contraindicated because of history of GI bleeds or use of blood thinners

C2.2. Drugs that lower plasma uric acid levels by promoting uric acid excretion
- **URICOSURIC AGENTS**

  **Probenecid**
  
  a) Probenecid are both weak organic acids that inhibit anion transporters in the **proximal tubules** of the kidney and **decrease net reabsorption of uric acid** - thereby **promoting uric acid excretion**

  ![Probenecid Diagram](image)

  b) Indicated in patients that **under excrete** uric acid

  c) **Should not** be given until 2-3 weeks **after** the initial attack as drugs can actually **initiate** and/or **prolong** the symptoms of an acute gouty attack (due to disruption of urate homeostasis) - usually prophylactic NSAID treatment is given at the same time to reduce risk of inducing an attack

  d) **Should not** be given to patients that **naturally produce** high levels of **uric acid** due to increased risk of **kidney stones**

  e) To reduce risk of kidney stones urine volume should be maintained at a high level and the urine pH should be kept > pH 6.

**Contraindicated**: Patients with kidney stones and/or renal insufficiency

C2.3. Drugs that lower plasma uric acid levels by decreasing uric acid synthesis

**Allopurinol** (Zyloprim®) and **Febuxostat** (Uloric®)

a) Used in the treatment of chronic gout to block production of Uric Acid

b) structural analogue of **hypoxanthine** that inhibits **Xanthine Oxidase**, an enzyme that catalyses the final two steps in purine degradation
c) particularly useful in patients with:
   - a high level of endogenous uric acid synthesis,
   - Recurrent Kidney stones
   - Renal Impairment
   - Grossly elevated Uric Acid Levels ie. The presence of TOPHI

d) Should **not** be given during an **acute gouty attack** as this can actually worsen symptoms
   *An NSAID is usually prophylactically co-administered at the onset of Allpurinol therapy to reduce the chances of precipitating an acute attack of gout*

**Adverse Effects:**

a) Can induce an acute gouty attack if NSAID prophylaxis not provided
b) Rash, leukopenia, thrombocytopenia & fever can occur in 3-5% of patients
c) Allopurinol hypersensitivity syndrome (<0.1% of patients) **[NOT FEBUXOSTAT]**
   - a rare, but potentially **life threatening reaction** (25% mortality rate)
   - most likely to occur in patients with renal insufficiency + diuretic
   - dosage reduction required in presence of renal impairment
   - symptoms include: Erythematous rash, fever, hepatitis esinophilia
   - and acute renal failure

**Drug Interactions:** 6-mercaptopurine and azathioprine
- purine synthesis inhibitors used in immunosuppression and treatment of leukemia
- metabolized by xanthine oxidase to inactive metabolites
- toxicity is increased in the presence of allopurinol

**C3. Management of Chronic Gout**

a) Hyperuricemia by itself does not indicate that treatment is necessary

b) Treatment is indicated for:
   - Patients with multiple gouty attacks
   - Those that are more susceptible to future attacks e.g. Renal insufficiency
   - Patients with very high levels of uric acid (>12 mg/dL)

**Treatment Goal:** To reduce serum uric acid levels to <6mg/dL

c) Which drug to use is dependent upon whether the patient is either an over producer or an under secretor of uric acid.
   - 24 hr urinary uric acid excretion < 700 mg/dL - Undersecretion - Probenecid
   - 24 hr urinary uric acid excretion >700 mg/dL - Overproduction - Allopurinol

d) Allopurinol is specifically indicated for:
   - Patients with a uric acid kidney stone
   - Patients with renal insufficiency- as uricosuric agents are not effective
   - Patients with TOPHI

e) Effective therapy will require lifelong treatment

**C4. Treatment of drug-resistant chronic gout**

a) New drug Pegloticase (PEG-coupled Porcine Uricase) is an enzyme that degrades insoluble uric acid to more soluble byproduct. Note: Humans lack the Uricase enzyme

b) Reserved for patients that have advanced, actively symptomatic gout that is uncontrolled with other uric acid lowering drugs
   - presence of frequent flares
   - Presence of tophi
   - Contraindication to other gout drugs
<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td></td>
<td>Drug of choice; RA Moderate/Severe</td>
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<tr>
<td>Sulfasalazine</td>
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<tr>
<td>Hydroxychloroquine</td>
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<tr>
<td>Indications:</td>
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**Traditional DMARDs**

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Adverse Effects</th>
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<tr>
<td>Liver disease</td>
<td></td>
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<tr>
<td>Pregnancy and</td>
<td></td>
</tr>
<tr>
<td>Renal impairment</td>
<td></td>
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</tbody>
</table>

**Leukomide**

| Immune responses: | Inhibitors of IL-1β and IL-6, G-CSF, and other cytokines | Moderate/Severe RA |

**Sulfasalazine**

| Adriamycin (very rare) | TNF Blockade | Severe RA |

**Hydroxychloroquine**

| Anti-malarial drug | Anti-malarial drug | Severe RA |

**Methotrexate**

| Risk of lymphoma | Immunosuppression | RA Moderate/Severe |

**Sulfasalazine**

| Adriamycin (very rare) | TNF Blockade | Severe RA |

**Hydroxychloroquine**

| Anti-malarial drug | Anti-malarial drug | Severe RA |

**Methotrexate**

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| Risk of lymphoma | Immunosuppression | RA Moderate/Severe |

**Sulfasalazine**

| Adriamycin (very rare) | TNF Blockade | Severe RA |

**Hydroxychloroquine**

| Anti-malarial drug | Anti-malarial drug | Severe RA |
### Biologics/Biological Response Modifiers

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Indications</th>
<th>MOA</th>
<th>Adverse Effects</th>
<th>Misc.</th>
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</thead>
<tbody>
<tr>
<td><strong>TNF-α inhibitors</strong></td>
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<tr>
<td>Etanercept</td>
<td>Active RA (monotherapy or combine with MTX)</td>
<td>Binds to TNF-α and prevents its interaction with its receptor</td>
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<tr>
<td>Active RA</td>
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<tr>
<td><strong>Biostatic</strong></td>
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<tr>
<td>Adalimumab</td>
<td>Active RA</td>
<td>Binds IL-12/23</td>
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<td>Active RA</td>
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<td><strong>Biologic antibody</strong></td>
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<tr>
<td>Infliximab</td>
<td>Active RA</td>
<td>Humanized anti-TNF mAb</td>
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<tr>
<td>Active RA</td>
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<tr>
<td><strong>Other</strong></td>
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<tr>
<td>Anakinra</td>
<td>Active RA</td>
<td>rIL-1RA, IL-1 receptor antagonist</td>
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<td>Active RA</td>
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<td><strong>Small molecule</strong></td>
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<td>Tocilizumab</td>
<td>Active RA</td>
<td>Humanized anti-IL6R mAb</td>
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<td>Active RA</td>
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<tr>
<td><strong>Abatacept</strong></td>
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<td>Active RA</td>
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<tr>
<td><strong>Tofacitinib</strong></td>
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</table>
### Drugs to Treat Gout

<table>
<thead>
<tr>
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<th>MOA</th>
<th>Adverse Effects</th>
<th>Misc.</th>
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</thead>
<tbody>
<tr>
<td>Acute Gouty Attack</td>
<td>NSAIDs</td>
<td>Inhibits COX-2</td>
<td>GI Toxicity, etc.</td>
</tr>
<tr>
<td>Prophylaxis for other gout medications</td>
<td>NSAIDs</td>
<td>Inhibits COX-2</td>
<td>GI Toxicity, etc.</td>
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<tr>
<td>Inhibits Xanthine Oxidase</td>
<td>Xanthine Oxidase Inhibitors</td>
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<tr>
<td>Decrease uric acid production</td>
<td>Uricosurics</td>
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<tr>
<td>Promotes uric acid excretion</td>
<td>Uricosurics</td>
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<tr>
<td>Decrease uric acid levels</td>
<td>Uricosurics</td>
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<td></td>
</tr>
<tr>
<td>Rash, Nausea, Vomiting</td>
<td>Colchicine</td>
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### Common side effects:
- GI Toxicity
- Nephrotoxicity
- Enzymatic degradation of Insoluble Uric Acid
- Increased toxicity
- High dose/renal failure

### Contraindications:
- Uric acid overproduction
- Renal insufficiency
- Kidney stones
- Allopurinol hypersensitivity

### NSAIDs
- Anti-inflammatory
- Analgesic
- GI Toxicity

### Colchicine
- Acute Gouty Attack
- Rash
- Nausea, Vomiting (80%)

### Uricosurics
- Probenecid
- Rash
- Nausea, Vomiting

### Xanthine Oxidase Inhibitors
- Allopurinol
- Rash
- Nausea, Vomiting
- Gouty attack

### Pegloticase
- Enzymatic degradation of Insoluble Uric Acid
- Risk of CV events

### Xanthine Oxidase
- Allopurinol
- Rash
- Nausea, Vomiting

### MOA
- Enzymatic degradation of uric acid
- Inhibits tubulin polymerization
- Decreases uric acid production

### Adverse Effects
- GI Toxicity
- Renal toxicity
- Etc etc