Antidepressants/Antipsychotics Serotonin Syndrome/ Neuroleptic Malignant Syndrome/ Malignant Hyperthermia

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CME® Procedures

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Objectives

- Review basic epidemiology, pathophysiology, and clinical presentation of major depressive disorder (MDD) and schizophrenia
- Discuss the antidepressant and antipsychotic agents available and differentiate them based on their mechanisms of action, pharmacokinetics, clinical uses, drug interactions and adverse effects
- Explain the pathophysiology, clinical manifestations, and treatment options in the setting of serotonin syndrome, neuroleptic malignant syndrome and malignant hyperthermia

Major Depressive Disorder (MDD)

- A common, disabling disorder that defies attempts to "feel better"
- MDD can have significant impact on mood, thinking, physical health, work and relationships
- Epidemiology
  - At least 17.3 million adults over the age of 18 experience at least one episode of depression
  - 8.1% of individuals over 20 yo in the Us experience symptoms of depression in any given 2 week period
  - Women are twice as likely to experience MDD
  - Per the WHO, MDD is the leading cause of disability worldwide

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MDD - Pathophysiology

- Likely multifactorial
- Possibly "involves complex interaction of genetic predisposition, psychological stressors, and underlying pathophysiology"
  - First degree relatives of patients with MDD are ~2 – 4x more likely to develop MDD
- No accepted unifying theory for the pathophysiology of MDD
  - Biogenic amine and receptor hypothesis:
    - A deficit of norepinephrine (NE), dopamine (DA), or serotonin (5-HT) at the synapse is the cause of depression
    - However, patients with depression do not always have decreases levels of NE, DA or 5-HT

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MDD - Clinical Presentation

- At least 5 of the following symptoms have been present within the same two-week timeframe and is different than previous functional status (not related to the direct effects of physiologic substance abuse)
  - **Depressed mood***
  - **Diminished interest/lack of pleasure with activities***
    - ***One of these symptoms must be present**
  - Increase or decrease in appetite and/or weight
  - Increase or decrease in sleep
  - Increase or decrease in psychomotor activity
  - Fatigue and/or loss of energy
  - Feelings of worthlessness
  - Diminished ability to think or make decisions; worsened concentration
  - Recurrent thoughts of death, suicidal ideation or suicide attempt

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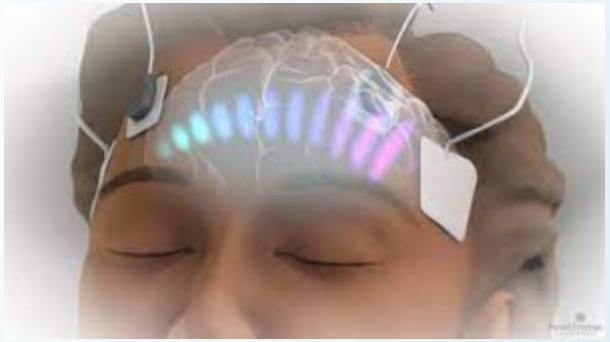
MDD Treatment – Nonpharmacologic

- Psychotherapy
  - Initial treatment option for mild-to-moderate depression
  - Can be useful in severe depression in combination with pharmacotherapy



- Electroconvulsive therapy (ECT)
  - Response rate ~80%; >50% in patients that failed pharmacotherapy
  - May be beneficial in MDD that is complicated by psychosis, severe suicidality, refusal to eat, pregnancy or contraindications to pharmacotherapy
- Transcranial magnetic stimulation
- Physical exercise
  - Mild-to-moderate depression

MDD Treatment – Pharmacologic

Multiple classes available

- Even within the same class of agents, there are important pharmacologic difference between medications

Classes include:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Tricyclic antidepressants (TCAs)
- Serotonin agonists and serotonin multimodal drugs
- Norepinephrine and serotonin multimodal drugs
- Monoamine oxidase inhibitors (MAOIs)

Schizophrenia

- Challenging disorder often requiring lifelong treatment
- Manifests as positive psychotic symptoms (hallucinations/delusions) and disorganized thinking
- Often, accompanied by:
  - Cognitive impairment - Abnormalities in thinking, reasoning, attention, memory, and perception
  - Impaired insight and judgment
  - Negative symptoms – loss of motivation, loss of emotional range (flat affect), decrease in spontaneous speech
- Many patients with schizophrenia experience both poor social and functional outcomes
- 4th leading cause of disability among adults and is associated with lower rates of employment, marriage and independent living compared to population norms

Schizophrenia – Epidemiology and Etiology

- 0.7% of the world population suffers from schizophrenia
  - Symptoms typically present in late adolescence or early adulthood
- Prevalence is the same for men and women
  - Symptoms appear earlier in men
    - First hospitalization typically occurring 15 – 24 years in men vs 25 – 34 years in women
- Etiology unclear; appears to have a genetic component
  - First-degree relatives of patients with schizophrenia have a 10% chance of developing the disorder
  - If both parents are diagnosed, the risk increases to 40%
- When a genetic variability is present, environmental factors may trigger expression of the illness
  - Intrauterine exposure to significant stress, viral or bacterial infections
  - Certain drugs of abuse (ie marijuana) may trigger susceptible individuals

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Schizophrenia – Pathophysiology

- Dopamine hypothesis
  - Oldest theory that suggests psychosis due to excessive dopamine in the brain
  - Medications that decrease dopamine improve psychotic symptoms
- Likely more complicated with the presence of both hyperdopaminergic and hypodopaminergic brain regions in schizophrenia ➔ **Dysregulation hypothesis**
  - Hyperdopaminergic symptoms in mesolimbic pathway account for the positive symptoms of psychosis
  - Hypoactivity of the mesocortical pathway can account for the negative symptoms
- May also be associated with dysregulation of glutamate neurotransmitter systems and malfunctioning NMDA receptors

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Schizophrenia – Clinical Presentation

- Positive, negative and cognitive symptoms already addressed
- Can also be uncooperative, suspicious, hostile, anxious or aggressive
- Often associated with poor hygiene and impaired self-care
- 4 – 5x more likely that the general population to abuse cigarettes and illicit drugs
- Schizophrenia is a clinical diagnosis
  - No psychological assessments , brain imaging or lab testing available to confirm the diagnosis
  - Requires ruling out other causes of psychosis and meeting specific diagnostic criteria

Schizophrenia - Treatment

- Antipsychotic medications are at the cornerstone of treatment
  - Should be started as soon as psychotic symptoms are recognized
  - Often lifelong treatment required because nonadherence and discontinuation are associated with high relapse rates
- Psychosocial support helps improve functional outcomes
  - Help patients cope with the challenging aspects of their illness and is usually beneficial as an aid to medication for remission and recovery

Antidepressants/ Antipsychotics

Antidepressants

Antidepressants

- Account for 16 of the top 200 prescription drugs in the US
- In addition to being used for MDD, can also be used for generalized anxiety disorder, bipolar disorder, post-traumatic stress disorder, obsessive-compulsive disorder, eating disorders, etc.

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Fluoxetine
- Sertraline
- Paroxetine
- Fluvoxamine
- Citalopram
- Escitalopram

SSRIs

- First line pharmacotherapy for most depression and anxiety disorders
  - MDD, generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD)
- Mechanism of Action
  - Inhibit post-synaptic reuptake of serotonin by blocking the serotonin transporter protein (SERT) resulting in increased serotonin concentrations in the synapse
- Each SSRI has a unique pharmacologic profile
  - Paroxetine has anticholinergic effects
  - Fluoxetine antagonizes 5-HT2c receptors, which may make it useful in bulimia
- Patients who do not respond to one SSRI may do well on a different SSRI
  - Typically, at least two different SSRIs are tried before switching the class of medications

SSRIs – Adverse Effects

- Sexual dysfunction
  - Can lead to nonadherence
  - Can try waiting for symptoms to subside, reducing the dose, allowing a drug-free period, adding an adjunctive therapy or switching agents
- Central Nervous System (CNS) stimulation
  - Nervousness, insomnia
- GI upset (nausea/diarrhea)
  - Often self-limiting
- Weight gain

SSRIs - Pharmacokinetics

- Fluoxetine is a potent inhibitor of CYP2D6; moderate inhibitor of CYP2B6 and CYP2C9 ➔ drug interactions!
- Fluoxetine has an active metabolite (norfluoxetine) and can inhibit its own metabolism; has a prolonged half-life 3 – 6 days (norfluoxetine up to 16 days)
  - Long washout period if transitioning to another class of agents (~6 weeks)
  - Due to long half-life, less chance for withdrawal symptoms than the other SSRIs
- Paroxetine half-life ~21 hours; more significant anticholinergic effects
  - Withdrawal syndrome common
- Sertraline half-life 25 hours; few CYP450 interactions
  - May be more likely to cause GI symptoms
- Citalopram and Escitalopram (S-enantiomer of citalopram) are well-tolerated
  - Citalopram can cause QTc prolongation

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Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

- Venlafaxine
- Desvenlafaxine
- Duloxetine
- Milnacipran
- Levomilnacipran

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SNRIs

- Often first or second-line agents for depressive and anxiety disorders
- Mechanism of Action
  - Inhibit post-synaptic reuptake of serotonin by blocking the serotonin transporter protein (SERT) resulting in increased serotonin concentrations in the synapse
  - Inhibit the norepinephrine transporter (NET)
  - Venlafaxine and desvenlafaxine have primarily serotonin reuptake inhibitor activity with dose-related norepinephrine reuptake inhibition
  - Duloxetine has balanced serotonin and NE reuptake inhibition
    - Also used commonly for neuropathic pain related to diabetes
  - Levomilnacipran has more NE reuptake inhibition than serotonin
- Can be used off-label to treat various forms of chronic pain
  - Are thought to work by increasing engagement of descending pain systems that suppress ascending pain transmission and regulate pain homeostatically
  - Usually requires lower doses than for depression; suggests the mechanism for treatment of these two conditions is different

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SNRIs – Adverse Effects

- May increase BP due to increased noradrenergic activity
  - Have shown statistically significant rises in SBP/DBP but not usually clinically significant increases
- Venlafaxine/desvenlafaxine
  - Nausea that may require lower doses and taking medication with food
- Duloxetine
  - Potential hepatic injury; avoid in alcohol use disorder or chronic liver disease

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Bupropion

- A NE and DA reuptake inhibitor (NDRI) used in MDD and smoking cessation
  - May also be used as nonstimulant treatment for ADHD
  - First line alternative to SSRIs for MDD
    - Lacks the sexual side effects of SSRIs
- Mechanism
  - Structurally related to amphetamine with without concerns for dependency
  - Effects on NE and DA reuptake inhibition are weak but bupropion is an efficacious antidepressant
  - Generally activating and may be especially useful at improving energy, alertness, and other depression-relates symptoms

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Bupropion

- Adverse Effects
  - Seizures (0.4%)
    - Lowers seizure threshold
  - Insomnia/nightmares
  - Decreased appetite
  - Stimulant-like effects that can exacerbate comorbid anxiety
  - Ataxia
  - Myoclonus
  - Relative contraindication for MAOIs given potential hypertensive effects
- Bupropion has NO anticholinergic effects, does NOT cause postural hypotension and lacks significant on cardiac conduction

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Serotonin Multimodal Drugs

- Vortioxetine
- Vilazodone
- Trazodone
- Nefazodone

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Serotonin Multimodal Drugs

- Mechanism of Action
  - Vortioxetine and Vilazodone
    - Inhibit the SERT serotonin transporter protein
    - Partial agonists at the 5-HT_{1A} receptor
    - Vortioxetine also acts as an antagonist as the 5-HT_3 and 5-HT_7 receptor

  - Trazodone
    - Originally indicated for MDD; now more commonly used for insomnia (nondependency forming)
    - Some SRI activity but primarily works through serotonin receptor modulation
      - 5-HT_{2A} antagonist and weak 5-HT_{1A} partial agonist
      - Likely also has weak histamine (H1) receptor agonism and potent α_1 antagonism

  - Nefazodone
    - Chemically related to trazodone with fewer α_1 –adrenergic blockade
    - Some SRI activity
    - 5-HT_{2A} antagonist and weak 5-HT_{1A} partial agonist
    - Also weakly inhibits NE and DA reuptake
    - Antihistaminergic activity

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Serotonin Multimodal Drugs

- Adverse Effects
  - Vortioxetine and Vilazodone
    - Similar to SSRIs
  - Trazodone
    - Priapism, dry mouth and orthostasis related to α_1 antagonism
    - Cardiac dysrhythmias (rare)
    - May show up as a false positive for MDMA on a urine drug screen
  - Nefazodone
    - Priapism (likely less common than with trazodone)
    - Sedating
    - Nausea
    - Dry mouth
    - Orthostasis
    - Hepatotoxicity

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Buspirone

- Serotonin Agonist
  - Indicated for the short-term treatment of generalized anxiety disorder (GAD)
- Mechanism of Action
  - Partial agonist of serotonin receptors, particularly 5-HT1A
  - Leads to decreased serotonin turnover and anxiolytic effects
  - NO effects on GABA
    - No cross-reactivity with BZDs, barbiturates or alcohol
- Slow onset of effect (1 – 2 weeks)

Tricyclic Antidepressants (TCAs)

- Amitriptyline
- Amoxapine
- Clomipramine
- Desipramine
- Imipramine
- Nortriptyline

Tricyclic Antidepressants

- Prior to the availability of SSRIs and SNRIs, TCAs were the mainstay of treatment for MDD
- Primary NE reuptake inhibitors
  - Secondary amines → desipramine and nortriptyline
- Also include drugs with NET and SERT inhibition or primary SERT inhibition
  - Tertiary amines → amitriptyline, imipramine and clomipramine
- Some direct action on serotonin receptors

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Tricyclic Antidepressants

- Mechanism of Action
  - Antidepressant effect likely produced by blocking the reuptake of serotonin and/or NE at presynaptic terminals, increasing the availability of the neurotransmitters
- Antidepressant effects usually emerge after 2 – 3 weeks of treatment
- Chronic administration of the agents is associated with:
  - Decreased sensitivity of post-synaptic β_1 and serotonin 2 receptors and of presynaptic α_2 receptors
  - Increased sensitivity of postosynaptic α_1 receptors
- Tend to be more sedating due to antihistaminergic potency
  - Tertiary TCAs more sedating than the secondary TCAs
- Also used in the treatment of chronic pain
  - Neuropathic pain and fibromyalgia
  - May potentiate endogenous opioids in the CNS and may have anti-inflammatory properties

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Tricyclic Antidepressants

- Been supplanted as first-line agents for MDD due to significant adverse effects
- Adverse effects related to anticholinergic, antiadrenergic, and antihistaminergic properties
  - Anticholinergic effects
  - CV effects
  - CNS effects

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Tricyclic Antidepressants

- Anticholinergic effects
  - Dry mouth
  - Blurred vision
  - Tachycardia
  - Urinary retention
  - Slowed gastric emptying
  - Ileus
  - Delirium in the elderly

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Tricyclic Antidepressants

- CV effects
  - Orthostatic hypotension
  - Tachycardia
  - Depress conduction of cardiac impulses through atria/ventricles
    - Prolong the P-R interval, widen the QRS complex and flattening or inversion of the T wave
    - Benign in majority of patients

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Tricyclic Antidepressants

- CNS effects
  - Sedation
    - Amitriptyline and doxepin produce the most
  - Weakness
  - Fatigue
  - Clomipramine can lower the seizure threshold
  - May enhance the CNS-stimulating effects of enflurane
  - Fine tremor (~10% of patients)
- Can be fatal in overdose due to narrow therapeutic window
  - Check plasma drug concentrations if concerns for toxicity

Tricyclic Antidepressants

- Tolerance
  - During chronic therapy, tolerance to anticholinergic effects and orthostatic hypotension can develop
  - Often fails to develop tolerance to desirable effects
- Taper TCAs down prior to discontinuation
  - Can cause a mild withdrawal syndrome
    - Malaise, chills, cold-like symptoms and skeletal muscle aching

Tricyclic Antidepressants

- Drug Interactions
  - Principally metabolized by CYP1A2
  - Sympathomimetics
    - Due to NE reuptake blockade, patients may have a downregulation of beta-receptors
    - May require increased doses
  - Anticholinergics
    - May cause additive effects
  - Antihypertensives
    - Rebound hypertension after abrupt discontinuation of clonidine may be accentuated/prolonged

Tricyclic Antidepressants

- Drug Interactions
  - Opioids
    - Augment the analgesic and ventilatory depressant effects of opioids in animals
  - Monoamine oxidase inhibitors (MAOIs)
    - Potentially fatal serotonin syndrome

TCA Overdose

- Life-threatening
  - Can progress from an alert state to unconsciousness rapidly
- Most common cause of mortality is intractable myocardial depression or ventricular cardiac dysrhythmias
- Presenting signs/symptoms:
  - Agitation and seizures
  - Can also cause depression of ventilation, hypotension, hypothermia and coma
  - Also present with anticholinergic effects
    - Mydriasis, flushed/dry skin, urinary retention and tachycardia
  - QRS complex >100 msec

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TCA Overdose

- Comatose phase can last 24 – 72 hours; cardiac dysrhythmias can occur for up to 10 days
  - Continued ECG monitoring necessary
- If comatose, ensure airway secured
- Treat seizures with BZDs
  - May require sustained treatment with antiepileptic drugs like phenytoin
- Alkalinization with sodium bicarbonate or hyperventilation can reverse drug-induced cardiotoxicity
  - Can use lidocaine or phenytoin for sustained suppression of arrhythmias
- Can consider gastric lavage and activated charcoal if ingestion within hours

Pharmacologic Treatment of Tricyclic Antidepressant Overdose

Symptom	Treatment
Seizures	• Diazepam • Sodium bicarbonate • Phenytoin
Ventricular arrhythmias	• Sodium bicarbonate • Lidocaine • Phenytoin
Heart Block	• Isoproterenol
Hypotension	• Crystalloid fluid resuscitation • Sodium bicarbonate • Vasopressors/Inotropes

Monoamine Oxidase Inhibitors (MAOIs)

Serotonin, NE and dopamine enzyme inhibitors

- Phenelzine
- Isocarboxazid
- Moclobemide
- Selegiline

Serotonin, NE and dopamine multimodal drugs

- Tranylcypromine

MAOIs

- Block the enzyme that metabolizes biogenic amines, increasing the availability of neurotransmitters in the CNS and peripheral nervous system
- Historically, used commonly due to potent psychopharmacologic properties in depressive disorders
  - Now uses less commonly due to adverse effects, lethality in overdose, drug and food interactions, and lack of simplicity in dosing
  - However, remain a valuable tool for patients who do not respond to other antidepressants; many will respond to MAOIs
- Patients must follow a specific diet to avoid tyramine-rich foods that can result in systemic hypertension
  - Monoamine oxidase-A is found in the GI tract and liver and active to metabolize bioactive amines like tyramine

Monoamine Oxidase Enzyme System

- Monoamine oxidase (MAO) is a flavin-containing enzyme found on outer mitochondrial membranes
- MAO functions via oxidative deamination to inactivate several monoamines, including:
  - Serotonin
  - Dopamine
  - NE
  - Epinephrine
- Divided into 2 subtypes: MAO-A and MAO-B
  - MAO-A preferentially deaminates serotonin, NE, dopamine and epinephrine
    - About 60% of human brain MAO activity
  - MAO-B preferentially deaminates phenylethylamine

MAOIs

- Mechanism of Action
  - MAOIs act by forming a stable, irreversible complex with the MAO enzyme, esp in cerebral neuronal MAO
  - Therefore, the amount of neurotransmitter available for release from the CNS increases
    - More serotonin, NE, dopamine
    - Not limited to the CNS so the concentration of monoamines increases in the SNS

MAOIs

- Adverse Effects
  - Most common – orthostatic hypotension
  - Decreased libido
  - Paresthesia
  - Weight-gain
  - Peripheral edema
  - Hepatitis (rare)
  - Phenelzine has anticholinergic effects/sedation
  - Tranylcypromine has mild stimulant effects
    - Insomnia and transient increases in BP
    - Instead of weight gain, may suppress appetite

MAOIs – Dietary and Drug Restrictions

Prohibited Food

- Aged cheese
- Cured, smoked, or processed meats
- Preserved, salted or picked fish
- Liver
- Fermented soy products
- Yeast extracts
- Fava or other broad beans
- Dried or overripe fruit
- Red wine, draft or homebrewed beer, some liqueurs

Prohibited Drugs

- Serotonin reuptake inhibitors
  - SSRIs
  - SNRIs
  - Many TCAs
- Cold or allergy medications
- Nasal decongestants
- Sympathomimetic drugs
- Opioids
  - Esp meperidine
- Linezolid (Zyvox®)
  - Weak MAOI

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MAOI overdose

- Reflected by signs of excessive sympathetic nervous system activity
  - Tachycardia
  - Hyperthermia
  - Mydriasis
- Can also present with seizures and coma
- Treatment – supportive care
  - Dantrolene may be used for skeletal muscle rigidity and associated symptoms of hypermetabolism

Incidence of Adverse Effects for the Antidepressants

Drug	Sedation	Weight Gain	Weight Loss	GI Upset	Sexual dysfunction
Bupropion	+	+	++	+++	+
Citalopram	+	+	+	++++	++++
Duloxetine	+	+	+	+++	++++
Escitalopram	+	+	+	++	++++
Fluoxetine	+	+	+	++++	++++
Fluvoxamine	++	+	+	++++	++++
Mirtazapine	+++	++	+	+	+
Nefazodone	++	+	+	++	+
Paroxetine	++	+	+	++++	++++
Sertraline	+	+	+	++++	++++
Venlafaxine	++	+	+	++++	++++
Vilazodone	+	+	+	++++	++
Vortioxetine	+	+	+	++++	+

+ minimal, ++ low, +++ moderate, ++++ high

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Antipsychotics

Antipsychotics

- Dopamine antagonists (particularly at the D2 receptor) have long been considered the central property of agents used to treat psychosis
- In addition to the treatment of schizophrenia, also useful for bipolar disorder, depression with psychotic features, certain organic psychoses, Tourette disorder, certain movement disorders, and n/v
  - Used commonly off-label in the ICU for ICU delirium
- Commonly divided into first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA)
  - FGA: Primarily dopamine blockers
  - SGA: Dopamine blockers with serotonin antagonism and other actions

Antipsychotics – Mechanism of Action

- As a class, antipsychotic activity comes primarily from their shared dopamine antagonist activity
- Dopamine is believed to act via 4 pathways in the brain
  - Mesolimbic
    - Primary site of action
  - Mesocortical
    - May contribute to the negative cognitive and affective symptoms of schizophrenia
  - Nigrostriatal
    - Blockade underlies extrapyramidal side effects
  - Tuberoinfundibular
    - Contributes to endocrine functions of the medications
- All antipsychotics achieve maximum clinical efficacy over a period of weeks
  - Emphasizes the importance of distinguishing the acute receptor antagonist effects from the chronic effects

Antipsychotics

First Generation

- Chlorpromazine
- Thioridazine
- Fluphenazine
- Perphenazine
- Haloperidol
- Pimozide
- Loxapine

Second Generation

- Clozapine
- Risperidone
- Olanzapine
- Quetiapine
- Aripiprazole
- Ziprasidone
- Lurasidone
- Brexpiprazole
- Cariprazine
- Paliperidone

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First Generation Antipsychotics (FGA)

- Now infrequently used compared to the second-generation agents
  - SGAs have additional serotonin (5-HT_{2A} antagonism), which has presumed greater benefit for the cognitive and affective aspects of psychotic disorders and a lower risk of extrapyramidal side effects
- Haloperidol and chlorpromazine still used commonly in emergency situations
- A landmark study found no difference in efficacy between perphenazine and SGAs
- Also, have antiemetic properties due to their interaction with dopaminergic receptors in the chemoreceptor trigger zone of the medulla
  - Most effective in preventing opioid-induced n/v

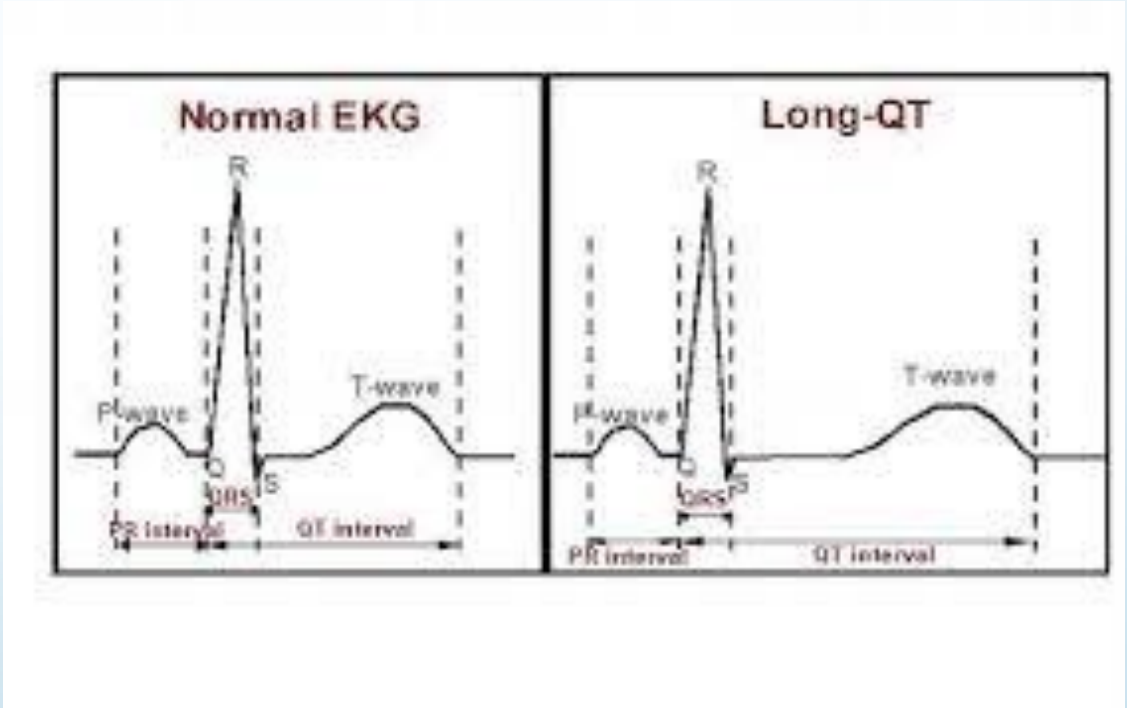
FGAs - Pharmacokinetics

- Have a high therapeutic index and relatively flat dose-response curve
  - Remarkable safety over a wide dose range
  - Even large overdoses are unlikely to cause life-threatening ventilatory depression
- Do NOT produce physical dependence
  - Abrupt discontinuation can cause skeletal muscle discomfort
- Display erratic and unpredictable absorption after PO administration
- Highly lipid soluble → accumulate in well-perfused tissues like the brain
- Metabolism
  - Principally by oxidation in the liver followed by conjugation and are pharmacologically inactive
  - Excreted primarily in the urine; lesser extent in bile
- Typical elimination half-lives are 10 – 20 hours → once daily dosing

FGAs – Adverse Effects

- Adverse effects seen more commonly in the FGAs than the SGAs but can occur in both classes

- Adverse effects include:
  - Extrapyramidal symptoms (EPS)
  - Neuroleptic malignant syndrome (NMS)
  - CV effects
    - Prolonged QTc
    - Hypotension
  - Endocrine effects
  - Sedation
  - Obstructive jaundice
  - Hematologic toxicity
  - Hypothermia
  - Decrease in seizure threshold
  - Skeletal muscle relaxation



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FGAs – Extrapyramidal Symptoms (EPS)

- Acute dystonic reactions occur in ~2% of treated patients and are most likely to occur within the first 72 hours of therapy
  - Responds dramatically to diphenhydramine 25 – 50 mg IV
- More common in young men and in patients taking high potency D2 antagonist medications
- Can also cause drug-induced akathisia (restlessness, urges to move and inability to tolerate inactivity), drug-induced parkinsonism (tremor, masked facies, and skeletal muscle rigidity)
- Tardive dyskinesia may occur with chronic exposure
  - May occur in 20% of patients who receive D2 antagonist drugs for >1 year
  - Elderly women and females are at greater risk
  - Manifestations include abnormal involuntary movements affecting the tongue, facial and neck muscles, upper and lower extremities, truncal musculature and occasionally skeletal muscle groups involved in breathing and swallowing
  - Two FDA approved medications now available for treatment: deutetrabenazine and valbenazine

FGAs – CV effects

- QTc prolongation
  - General risk of psychotropic medications in the setting of anesthesia
  - Sudden death during treatment with haloperidol has been attributed to drug-induced QTc prolongation
  - Several classes of noncardiac medications commonly used in anesthesia can also prolong the QTc in some patients
    - Propofol, isoflurane, sevoflurane, succinylcholine, neostigmine, atropine, glycopyrrolate, metoclopramide, methadone, macrolide and quinolone antibiotics, SSRIs, 5-HT3 receptor antagonists and dopamine antagonists
- Hypotension
  - Acute administration of chlorpromazine causes a decrease in systemic BP resulting from
    - 1) depression of vasomotor reflexes mediated by the hypothalamus or brainstem
    - 2) peripheral α–adrenergic blockade
    - 3) direct relaxant effects on vascular smooth muscle
    - 4) direct cardiac depression
  - Sufficient enough to blunt or prevent the pressor effects of epinephrine

FGAs – Endocrine Effects

- Increase prolactin levels by disrupting the normal dopaminergic inhibition of prolactin secretion
  - Can also cause galactorrhea and gynecomastia
- Amenorrhea is possible (rare)
- Corticosteroid secretion is decreased due to diminished corticotropin release from the anterior pituitary
- Chlorpromazine can impair glucose tolerance and insulin release in some patients
- Hypothalamic effects may lead to weight gain and possible abnormalities in thermoregulation
  - Hypothermia

Second-Generation Antipsychotics (SGAs)

- AKA "Atypical" antipsychotics
- In addition to D2 receptor antagonism, the drugs include prominent antagonism at the 5-HT2A receptor as well as other serotonin receptors
- SGAs come with similar overall risks and adverse effects of the FGAs although relative risk may be reduced
  - Thought to have decreased extrapyramidal symptoms
- Metabolic risks appear to be greater with the SGAs; higher rates of CV morbidity
  - Weight gain, hypercholesterolemia, and insulin resistance
  - May have direct impacts on glucose homeostasis

Clozapine

- The most effective antipsychotic medication; often beneficial when other treatments fail
  - The only medication for schizophrenia proven to decrease suicidality
- Has relatively little D2 antagonist activity
  - Has additional antagonist activity at 5-HT_{2A}, 5-HT_{2C}, 5-HT_{6}, and 5-HT_{7} receptors
  - May also include $GABA_{B}$ receptor agonism
- Does not appear to have a risk of tardive dyskinesia or extrapyramidal symptoms
- Why not first line?? Multiple potential medical complications
  - Agranulocytosis (~1% of patients)
    - Requires patients, pharmacies and physicians to be registered with a central clozapine Risk Evaluation and Mitigation Strategy (REMS) program
    - Patients must undergo weekly blood count monitoring for the first 6 months with continued routine monitoring thereafter
  - Clozapine-associated myocarditis
    - CRP and troponins are tested weekly during the initiation and titration period
  - Low grade fever
  - Mild sinus tachycardia
  - Excessive salivation despite anticholinergic properties

Olanzapine

- Structurally and pharmacologically similar to clozapine
- Frequently used first-line in acute care settings for agitated psychosis or bipolar mania where is can be given as a PO tablet, ODT, and IM injection
- Similar to clozapine, it can be heavily sedating and lead to hypotension initially
  - Warning with concomitant IV BZDs for an increased risk of cardiorespiratory suppression and death
- Associated with the highest risk of weight gain and metabolic syndrome
- Can disrupt thermoregulation and leave patients more susceptible to heat injury
- PK
  - Elimination half-time 30 – 50 hours; can be slower in women and the elderly
  - Metabolized by CYP1A2 and 2D6

Risperidone and Paliperidone

- Risperidone is one of the most widely used SGAs and is available as a long-acting injectable
  - Long-acting injectables are helpful in situations of nonadherence
- One of the most effective SGAs and is the most "first-generation-like SGAs" due to its high D2 potency
  - May have a greater risk of EPS than the other atypicals
- In addition to its dopamine and serotonin antagonism, risperidone also is a potent antagonist at α_1 and α_{2A} and α_{2C} receptors, which may account for the possible adverse effect of hypotension
- Risperidone and Paliperidone have elimination half-lives of 20 – 30 hours and are the most commonly associated SGAs with prolactin increase and gynecomastia

Aripiprazole, Brexpiprazole, and Cariprazine

- Differ from other SGAs → D2 receptor partial agonist/antagonists along with partial agonism or antagonism at multiple serotonin receptors, including 5-HT_{1A}, 5-HT_{2A-C}, and 5-HT_7
- Aripiprazole is one of the most common SGAs likely due to its balance of efficacy and tolerability
  - Less likely to cause weight gain or sedation and is frequently used in mood disorders
    - Indicated for all phase of bipolar disorder and as an adjunctive agent for MDD
- Risk of akathisia typically associated with higher starting doses or too-rapid dose escalation as well as the potential emergence of compulsive risk behaviors
  - Gambling, shopping or sexual behavior
  - May reflect partial D_3 agonism
- Aripiprazole is less likely to cause QTc prolongation or hyperprolactinemia

- PK
  - Aripiprazole, brexpiprazole, and cariprazine have elimination half-lives of 3 – 5 days
  - Substrates of CYP2D6 and 3A4

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Ziprasidone and Lurasidone

- Ziprasidone
  - Antagonizes D2 and to a lesser extent D3 receptors, antagonizes 5-HT2A receptors and a partial antagonist at 5-HT_{1A} and 5-HT_{2C} receptors
  - Moderately effective with a minimal metabolic effect compared to the other SGAs
  - Higher association with QTc prolongation
  - Intestinal absorption depends strongly on food

- Lurasidone
  - Also antagonizes D2 and D3 receptors as well as 5-HT_{2A}, 5-HT_7 and α_{2C} receptors
  - Also has partial agonist activity at 5-HT_{1A} and is minimally active at 5-HT_{2C}, potentially limiting its effects on appetite and weight
  - Frequently causes significant akathisia, particularly with initiation or rapid titration
  - Absorption also highly influenced by concomitant food intake
  - Half-life 20 – 40 hours; primarily metabolized by CYP3A4

Quetiapine

- Has 5-HT2A antagonism that is more potent than its D2 receptor antagonism
  - D2 receptor antagonism may be minimal at lower doses
- Notably has an active metabolite (norquetiapine) with potent NET inhibition ➔ considered to be a dopamine, serotonin and NE multimodal drug
- The EPS risk is the lowest of any antipsychotic drug with the exception of clozapine
  - Often the antipsychotic of choice when EPS is a concern (ie psychosis associated with Parkinson's disease)
- Significantly sedating at low doses likely due to significant antihistamine activity
- May cause orthostatic hypotension due to α_1 antagonist activity
- Elimination half-life ~7 hours
  - May be taken more than once a day or use ER formulation

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Incidence of Adverse Effects for First Generation Antipsychotics

	Relative Potency	EPS	Sedation	Anticholinergic Side Effects	CV Side Effects	Seizure Effects/QTc prolongation
Chlorpromazine	100	++	++++	+++	++++	++
Thioridazine	100	++	++++	++++	++++	+++
Perphenazine	8 – 10	+++	++	++	++	+
Trifluoperazine	2 – 5	+++	++	++	++	+
Fluphenazine	2	++++	++	++	++	+
Haloperidol	2	++++	+	+	+	++

+ very low, ++ low, +++ moderate, ++++ high

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Incidence of Adverse Effects for Second Generation Antipsychotics

	Anticholinergic Side Effects	EPS at Clinical Doses	Dose-Dependent EPS	Orthostatic hypotension	Prolactin Elevation	QTc Prolongation
Clozapine	+++	+	o	+++	o	+
Risperidone	+/-	+	++	++	+++	+/-
Olanzapine	++ (higher doses)	+/-	+	+	+	+/-
Quetiapine	+	+/-	o	++	+/-	+
Ziprasidone	+/-	+/-	+	+	+	+
Aripiprazole	+/-	+	+	+	o	+/-
Lurasidone	+/-	+	+	+	+/-	+
Haloperidol (FGA)	+/-	++	+++	++	+	+

o absent, +/- minimal, + mild or low risk, ++ moderate, +++ severe

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Incidence of Adverse Effects for Second Generation Antipsychotics

	Sedation	Seizures	Weight Gain	Glucose Dysregulation	Lipid Abnormalities
Clozapine	+++	++	+++	++	+++
Risperidone	+	+/-	++	+	+
Olanzapine	+	+/-	+++	++	+++
Quetiapine	++	+/-	++	+	++
Ziprasidone	+	+/-	+	+/-	+/-
Aripiprazole	+	+/-	+	+/-	+/-
Lurasidone	+	+/-	+	+/-	+/-
Haloperidol (FGA)	+	+/-	+/-	+/-	+/-

o absent, +/- minimal, + mild or low risk, ++ moderate, +++ severe

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Serotonin Syndrome
Neuroleptic Malignant Syndrome
Malignant Hyperthermia

Serotonin Syndrome (SS)

- Attributed to toxic levels of synaptic and extracellular serotonin
- Rare but serious complication of serotonin reuptake inhibitors (SRIs)
- Classic triad for symptoms:
  - Neuromuscular excitability
  - Autonomic nervous system excitability
  - Mental status changes
- In severe cases, life-threatening hyperpyrexia and rigidity may lead to rhabdomyolysis, multiorgan failure, and disseminated intravascular coagulation (DIC)

Serotonin Syndrome – Neuromuscular Excitability

- Hyperreflexia
- Clonus
- Myoclonus
- Opsoclonus
- Rigidity

Serotonin Syndrome – Autonomic Changes

- Diarrhea
- Tachycardia
- Hypertension
- Fever
- Diaphoresis
- Flushing
- Mydriasis

Serotonin Syndrome – Mental Status Changes

- Insomnia
- Agitation
- Anxiety
- Confusion
- Coma

Serotonin Syndrome

- Clonus is most sensitive and specific sign of serotonin syndrome
- Typically results from the combination of different classes of serotonergic medications
  - Most dangerously an SRI with an MAOI
  - Concern with linezolid (antibiotic with weak MAOI activity) and other SRIs
  - Methylene blue in combination with SRI can cause serotonin syndrome
  - Other agents include: lithium, tramadol, fentanyl, dextromethorphan, amphetamine, methamphetamine, methylphenidate, phentermine, cyclobenzaprine,
- Rarely results from the use of a single serotonergic agent at therapeutic doses
  - Occurrence in ~15% of SRI overdoses
- The rigidity and hyperpyrexia appear to reflect excessive stimulation of 5-HT2A
  - Causative agents are generally those that broadly increase extracellular serotonin, including serotonin precursors, stimulants of serotonin release, SRIs or MAOIs

Crit Care Med. 2012; 40: 2662 – 2670.
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Box 3. Drugs associated with serotonin syndrome (105, 106, 118–120)

Monoamine oxidase inhibitors[a]: tranylcypromine, phenelzine, isocarboxazid, moclobemide, nialamide, iproniazid, clorgiline, and toloxatone (antidepressants); pargyline and selegiline (antiparkinsonian agents); procarbazine (antineoplastic); linezolid and furazolidone (antibiotics); Syrian rue (harmine and harmaline—various uses)

Selective serotonin reuptake inhibitors: fluoxetine, sertraline, paroxetine, fluovoxamine, citalopram, escitalopram

Serotonin–norepinephrine reuptake inhibitors: venlafaxine, duloxetine, milnacipran

Tricyclic and other antidepressants: clomipramine, imipramine, trazodone

"Mood stabilizers": lithium, valproate

Opiates: meperidine, fentanyl, methadone, tramadol, dextromethorphan, dextropropoxyphene, pentazocine

Other antimicrobials: ritonavir

Antiemetics: ondansetron, granisetron, metoclopramide

Antihistamines: chorphenamine, brompheniramine

Antimigraine drugs: "triptans" (controversial) (120)

Supplements/herbal products: L-tryptophan, 5-hydroxytryptophan, *Hypericum perforatum* (St. John's wort), ginseng

Stimulants: amphetamine, 3,4-methylenedioxymethamphetamine ("Ecstasy")

Psychedelics: lysergic acid diethylamide, 5-methoxy-diisopropyltryptamine

[a]Note that the listed monoamine oxidase inhibitors have various uses within and outside of medicine. Thus, we specify their usual indications here.

Crit Care Med. 2012; 40: 2662 – 2670.

Serotonin Syndrome and the OR

- Serotonin syndrome is of particular concern in the OR and ICU as serotonergic agonists may have been administered in the OR reflecting the many serotonergic agonists in common use during anesthesia
- Symptoms usually occur within hours of introduction of the causative medication
- Prompt recognition is critical to limiting associated morbidity

Serotonin Syndrome – Treatment

- Discontinue all serotonergic medications and prompt initiation of supportive care
  - Benzodiazepines
  - IV fluids
  - Cooling, paralysis and ventilation in life-threatening cases
    - Antipyretics (APAP) are not helpful
- Possible treatment option: cyproheptadine
  - A potent antihistamine with serotonin antagonist and anticholinergic effects
    - May antagonize 5-HT2A receptors
  - Reserve for patients with agitation despite discontinuation of serotonergic medications, adequate sedation and supportive care
  - Dosing: 12 mg once followed by 2 mg every 2 hours until clinical response
    - Maintenance: 4 – 8 mg every 6 hours as needed
    - Max dose: 32 mg/day
- Chlorpromazine and atypical antipsychotics could be an alternative treatment IF neuroleptic malignant syndrome has been ruled out
- Avoid bromocriptine; can precipitate SS

Crit Care Med. 2012; 40: 2662 – 2670.
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Neuroleptic Malignant Syndrome (NMS)

- Occurs in 0.2 – 1% of all patients on antipsychotic drugs
- Dopamine receptor blockade plays a role in this syndrome
  - Occurs in the setting of dopamine antagonist drugs as well as with abrupt withdrawal of levodopa therapy
- Risk factors for NMS:
  - Youth, male gender, dehydration, iron deficiency, catatonia, organic brain disease, and intercurrent illness
- Typically, occurs over 24 – 72 hours

Box 2. Drugs associated with neuroleptic malignant syndrome (113)

Typical antipsychotics: pimozide, droperidol, haloperidol, fluphenazine, trifluoperazine, thiothixene, perphenazine, loxapine, molindone, mesoridazine, thioridazine, chlorpromazine

Atypical antipsychotics: clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole

Other dopamine blockers: metoclopramide, prochlorperazine, promethazine

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Neuroleptic Malignant Syndrome (NMS)

- Characteristic symptoms:
  - Hyperthermia
  - Generalized hypertonicity of skeletal muscles
    - May be so severe that it affects the chest wall expansion requiring mechanical ventilation
    - May also lead to myonecrosis leading to increased CK levels, rhabdomyolysis, myoglobinuria and renal failure
  - Instability of the autonomic nervous system manifesting as alterations in systemic BP, tachycardia, and cardiac dysrhythmias
    - May precede the other symptoms
  - Fluctuating levels of consciousness
- Mortality may be >5% due to ventilatory failure, cardiac failure/dysrhythmias, renal failure and thromboembolism

NMS – Treatment

- Primarily supportive
  - Discontinue dopamine antagonist treatments
  - ICU monitoring
  - Correct electrolyte derangements
  - IV fluids
  - Cooling
  - Treatment of agitation and CNS arousal with IV BZDs
    - For milder cases: Lorazepam 1 – 2 mg IV every 4 – 6 hours

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NMS – Treatment

- Can consider administering dopamine agonists like bromocriptine or amantadine to reverse parkinsonian symptoms like rigidity
  - Dosing:
    - Bromocriptine
      - Initial 2.5 mg PO BID or TID
      - Max dose 45 mg/day
      - Should be continued for 10 days after resolution of NMS as patients can have a recurrence if discontinued prematurely
      - May cause psychosis, hypotension, and vomiting → use alternative if this occurs
    - Amantadine
      - 200 – 400 mg PO daily in two divided doses

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NMS – Treatment

- Consider dantrolene
  - A skeletal muscle relaxant that can reduce symptoms, speed recovery and reduce mortality in patients with NMS who have extreme hyperthermia and muscle rigidity
  - Can give BZDs and dopamine agonists in conjunction with dantrolene
    - Do NOT give CCBs as they can lead to CV collapse
  - Dosing
    - Initial 1 – 2.5 mg/kg IV
    - Can give 1 mg/kg IV q6h if hyperthermia or rigidity improves after the first dose
    - If good response, can be tapered and switched to an oral preparation after the first few days
    - Like bromocriptine, should be continued for 10 days following the resolution of symptoms
  - Adverse effects: Respiratory and hepatic impairment
- Electroconvulsive therapy (ECT) can be considered if supportive care and pharmacotherapy are ineffective after 2 days
  - Has been effective in pharmacotherapy-resistant cases

Crit Care Med. 2012; 40: 2662 – 2670.
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Table 2. Characteristics of neuroleptic malignant syndrome and serotonin syndrome (105, 106)

			Identical Features		Overlapping Features			Distinct Features		
Condition	Precipitated by	Onset	Vital Signs	Mucosa	Skin	Mental Status	Muscles	Reflexes	Pupils	Bowel Sounds
Neuroleptic malignant syndrome	Dopamine antagonist	Variable, 1–3 days	Hypertension, tachycardia, tachypnea, hyperthermia (>41°C)	Sialorrhea	Pallor, diaphoresis	Variable: stupor, coma, alert mutism	"Lead-pipe" rigidity in all muscle groups	Hyporeflexia	Normal	Normal or decreased
Serotonin syndrome	Serotonergic drug	Variable, <12 hrs	Hypertension, tachycardia, tachypnea, hyperthermia (>41°C)	Sialorrhea	Diaphoresis	Variable: agitation, coma	Increased tone, especially in lower extremities	Hyperreflexia, clonus (unless masked by increased muscle tone)	Dilated	Hyperactive

Crit Care Med. 2012; 40: 2662 – 2670.

Malignant Hyperthermia (MH)

- A rare genetic hypermetabolic disease
  - 1:15,000 pediatric patients
  - 1:40,000 adult patients
- Characteristic signs/symptoms most commonly seen following exposure to inhaled general anesthetics or succinylcholine
  - AKA the triggering agents
- May occasionally present more than 1 hour after emergence from the anesthetic and rarely occurs without exposure to a known triggering agent
- All ages and both sexes may be affected
  - Majority of cases reported in young males
  - Almost no reports in infants
  - Few reports in the elderly
- Upper Midwest appears to have the greatest incidence of MH in the US

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MH – Pathophysiology

- A halogenated anesthetic agent alone can trigger an episode of MH
  - However, in many of the early reported cases, patients received both succinylcholine AND a halogenated anesthetic agent
  - Succinylcholine is not used as commonly in the OR as it once was --> ~1/2 of cases in the past decade were associated with a volatile anesthetic alone
- About 50% of patients who experience an episode of MH have had al least one previous uneventful exposure in the past where they received a triggering agent
  - → WHY DOES MH FAIL TO OCCUR AFTER EVERY EXPOSURE TO A TRIGGERING AGENT??
    - Answer unclear

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Drugs Known to Trigger Malignant Hyperthermia

Inhaled General Anesthetics

- Halothane
- Isoflurane
- Desflurane
- Sevoflurane

Depolarizing Muscle Relaxant

- Succinylcholine

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MH – Pathophysiology

- Biochemical causes of MH
  - Likely related to an uncontrolled increase in intracellular calcium in skeletal muscle
  - The sudden release of calcium from the sarcoplasmic reticulum removes this inhibition of troponin, resulting in sustained muscle contraction
  - Marked increases in adenosine triphosphatase enzyme activity results in an uncontrolled hypermetabolic state with significantly increased oxygen consumption and carbon dioxide production, producing a severe lactic acidosis and hyperthermia

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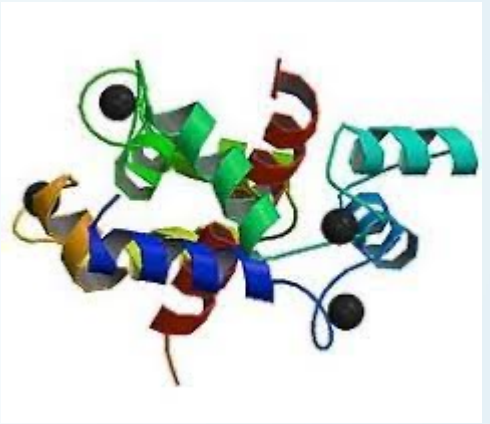
MH – Pathophysiology



- Genetics
  - Most patient with an episode of MH have relatives who have had a similar MH episode
  - The complexity of genetic inheritance patterns in families suggest that MH is not associated with a specific genetic mutation but rather a variety of different mutations
  - Major focus of research is on the gene for the ryanodine (Ryr_1) receptor, which is located on chromosome 19
    - Ryr_1 is a calcium channel responsible for calcium release from the sarcoplasmic reticulum and plays an important role in the depolarization of muscle
    - MH thought to result from abnormalities in this channel

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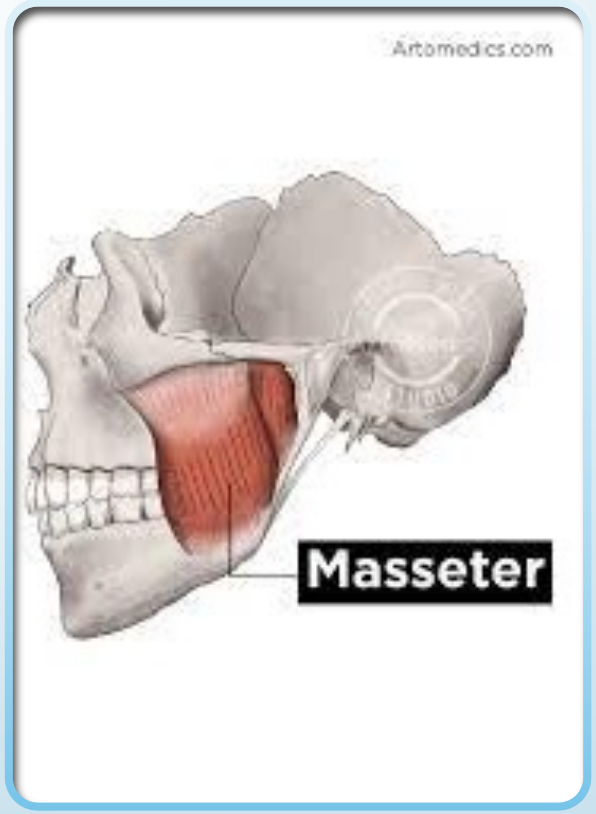
MH – Additional Risk Factors

- Susceptibility to MH may be increased in patients with musculoskeletal diseases
  - Central-core disease
  - Multi-minicore myopathy
  - King-Denborough syndrome
- Duchenne and other muscular dystrophies, nonspecific myopathies, heat stroke, and osteogenesis imperfecta have been associated with MH-like symptoms in some reports
  - Association is controversial
- Several reports of MH occurring in patients with a history of exercise-induced rhabdomyolysis
- Any patient who develops masseter muscle rigidity during anesthesia induction should be considered potentially susceptible to MH



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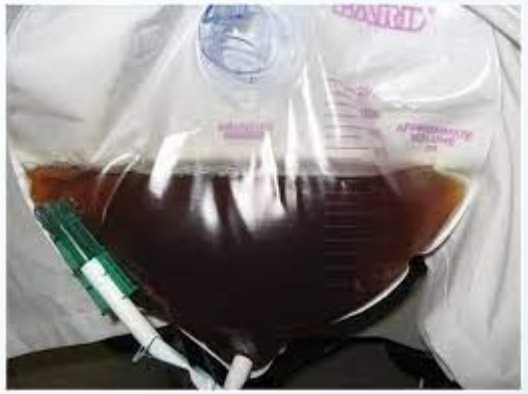
MH – Clinical Manifestations

- Early signs during anesthesia
  - Muscle rigidity
    - Not always present
  - Tachycardia
  - Unexplained hypercarbia
    - May result in tachypnea if NMBs not used
  - Increased temperature
    - Core temperature may rise as much as 1°C every 5 minutes



- ≥2 of these signs significantly increase the likelihood of MH
- Overactivity of the sympathetic nervous system leads to tachyarrhythmias, hypertension, and mottled cyanosis
  - Hypertension may be rapidly followed by hypotension if cardiac depression occurs
- Dark-colored urine may signify myoglobinemia and myoglobinuria

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MH – Clinical Manifestations

- Laboratory testing
  - Mixed respiratory and metabolic acidosis with a marked base deficit
  - Hyperkalemia
  - Hypermagnesemia
  - Reduced mixed-venous oxygen saturation
  - Ionized calcium levels are variable
    - May initially increase then eventually decrease
  - Increased serum myoglobin
  - Increased creatine kinase (CK)
    - If >20,000 IU/L, diagnosis is strongly suspected
  - Increased lactic dehydrogenase (LDH)
  - An unanticipated doubling or tripling of end-tidal CO_2 is an early and sensitive indicator of MH

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MH – Clinical Presentation

- Later manifestations if patient survives the initial presentation
  - Acute kidney failure
  - Disseminated intravascular coagulation (DIC)
  - Cerebral edema
  - Seizures
  - Hepatic failure
- Most MH-related deaths are due to DIC and organ failure due to delayed or no treatment with dantrolene

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Signs/Symptoms of Malignant Hyperthermia

Markedly Increased Metabolism

- Increased CO_2 production
- Increased O_2 consumption
- Reduced mixed venous oxygen tension
- Metabolic acidosis
- Cyanosis
- Mottling

Increased Sympathetic Activity

- Tachycardia
- Hypertension
- Arrhythmias

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Signs/Symptoms of Malignant Hyperthermia

Muscle Damage

- Masseter spasm
- Generalized rigidity
- Increased serum creatinine kinase
- Hyperkalemia
- Hypernatremia
- Hyperphosphatemia
- Myoglobinemia
- Myoglobinuria

Hyperthermia

- Fever
- Sweating

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MH – Treatment

- First and most importantly → stop all triggering agents!
  - Even trace amounts from soda lime, breathing tubes and breathing bags can be detrimental
- Hyperventilate with 100% oxygen to counteract the effects of uncontrolled CO_2 production and increased oxygen consumption
- Start dantrolene therapy immediately
  - Mainstay of therapy
  - Safety and efficacy of IV dantrolene mandate its immediate use in this potentially life-threatening situation

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Dantrolene

- Mechanism of Action
  - A hydantoin derivative that directly interferes with muscle contraction by binding to the Ryr_1 receptor channel and inhibiting calcium ion release from the sarcoplasmic reticulum
- Dosing
  - 2.5 mg/kg IV every 5 minutes until the episode is terminated
  - Max dose 10 mg/kg

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Dantrolene

- Two formulations available
  - "Conventional" dantrolene (Dantrium®; Revonto®)
    - 20 mg lyophilized powder to be dissolved in 60 mL sterile water
      - 75 kg patient would need 187.5 mg (2.5 mg/kg x 75 kg) ➔ 10 VIALS NEEDED
    - Must shake well until clear
    - Can be considerably time-consuming in a life-threatening situation
  - Newer formulation available (Ryanodex®)
    - 250 mg can be reconstituted in 5 mL
    - Shake well; suspension is orange-colored
    - $$$
    - May be an attractive option for the initial dose
- Both formulations can be administered by rapid IV injection for crisis doses
  - Maintenance doses of Revonto® should be administered over 1 hour
  - Ryanodex® follow-up doses should be administered over ≥1 minute

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Comparison of Dantrolene Formulations

Revonto®

- One vial contains 20 mg
- Mix vial with 60 mL sterile water
- Contains 3000 mg mannitol
- Solution pH ~9.5
- Shelf life 3 years
- Cost ~$60/vial

Ryanodex®

- One vial contains 250 mg
- Mix vial with 5 mL sterile water
- Contains 125 mg mannitol
- Solution pH ~10.3
- Shelf life 2 years
- Cost ~$2500/vial

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Dantrolene

- Effective half-life is ~6 hours
- After initial control of symptoms, dantrolene should be continued at a dose of 1 mg/kg IV every 6 hours for 24 – 48 hours to prevent relapse
  - MH can recur within 24 hours after an initial episode
- Also used in patients with neuroleptic malignant syndrome (NMS) and thyroid storm
- Most serious adverse effect is generalized muscle weakness that can lead to respiratory insufficiency or aspiration
  - Has also been associated with hepatic dysfunction
- Can cause phlebitis – administer through central line if available

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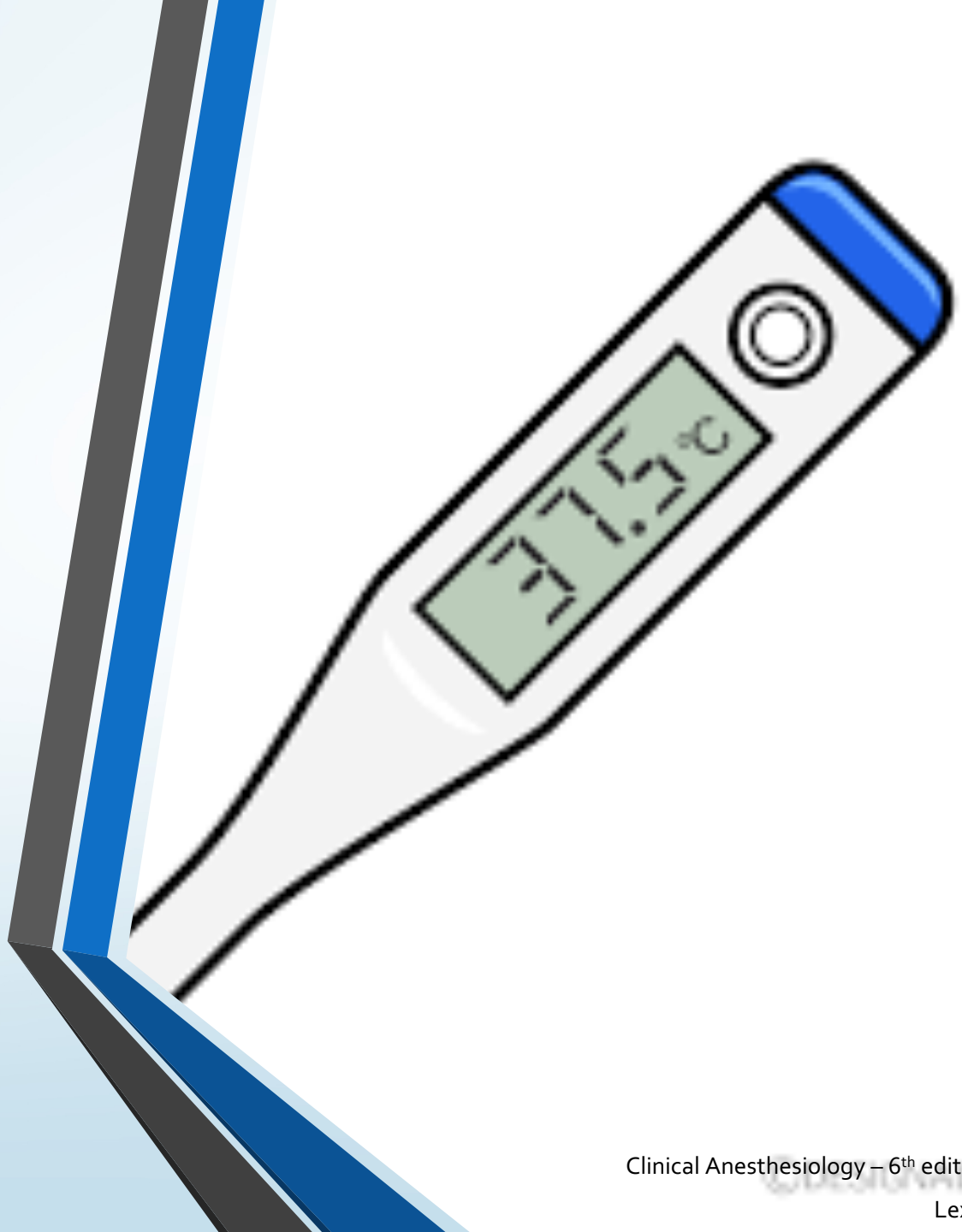
Dantrolene

- General treatment goals:
  - End-tidal CO_2 <45 mmHg
  - Normal minute ventilation
  - Core temperature <38°C
  - HR stable and decreasing
  - Muscular rigidity resolved



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MH – Treatment

- Correction of acid-base and electrolyte imbalances
  - Treat persistent metabolic acidosis with sodium bicarbonate
    - Caution – can worsen hypercarbia
  - Hyperkalemia should be treated with dextrose, insulin and diuresis
    - No useful role for IV calcium salts in MH treatment
    - Avoid calcium channel blockers (CCBs) in patients receiving dantrolene as the combination appears to promote hyperkalemia
    - Furosemide can be helpful for diuresis and prevention of kidney failure
      - Dantrolene contains mannitol (3 gm per 20 mg bottle) so loop diuretics preferred
- Cooling
  - If fever present, cooling should be initiated immediately
  - Surface cooling with ice packs over major arteries
  - Cold air convection
  - Cooling blankets
  - Iced saline lavage of open body cavities
  - Hypothermic cardiopulmonary bypass if other measures fail

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MH Immediate Treatment Protocol

Discontinue	Discontinue volatile anesthetic and/or succinylcholine. Notify surgeon and call for help.
Mix	Mix dantrolene with sterile water and give 2.5 mg/kg IV ASAP.
Administer	Administer sodium bicarbonate for metabolic acidosis.
Institute	Institute cooling measures (cooling blanket, cold IV solution, etc.)
Treat	Treat severe hyperkalemia with 25 – 50 gm IV dextrose and 10 – 20 units regular insulin IV
Administer	Administer antiarrhythmics as needed if needed despite correction of hyperkalemia and acidosis
Monitor	Monitor end tidal CO_2, electrolytes, arterial blood gases (ABGs), CK, serum myoglobin and core temperature
Call	If necessary, consult on-call physicians at 24-hour MHAUS hotline **(1-800-644-9737)**

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Prophylaxis and Post-Anesthesia Care

- Dantrolene should ALWAYS be available wherever general anesthesia is provided
- Do NOT prophylactically administer dantrolene if a nontriggering agent is used
  - There are NO reported cases of MH-susceptible patients experiencing MH after receiving a nontriggering anesthetic during uneventful surgery
- If procedure was uneventful with a nontriggering anesthetic, patient can be discharged from the PACU or ambulatory surgery unit when the standard criteria are met

Clinical Anesthesiology – 6th edition, 2018.

Safe Agents To Use in MH-Susceptible Patients

- Propofol
- Etomidate
- BZDs
- Ketamine
- Methohexital

- Droperidol
- Nitrous oxide
- Nondepolarizing NMBs
- All local anesthetics

Clinical Anesthesiology – 6th edition, 2018.

How can you distinguish NMS from MH?

A distinguishing feature is the ability of nondepolarizing NMBs to produce flaccid paralysis in patients with NMS but NOT MH

Crit Care Med. 2012; 40: 2662 – 2670.
Pharmacology & Physiology in Anesthetic Practice – 6th ed. 2022.

Differential diagnosis of hyperthermia in the intraoperative and immediate post-operative periods

- Malignant hyperthermia
- Neuroleptic malignant syndrome (NMS)
- Thyroid storm
- Pheochromocytoma
- Drug-induced hyperthermia
- Serotonin syndrome
- Iatrogenic hyperthermia
- Brainstem/hypothalamic injury
- Sepsis
- Transfusion reaction

Clinical Anesthesiology – 6th edition, 2018.

Diagnosis Comparison

Diagnosis	Inciting Agent	Time course	Fever	Physical Examination
Serotonin Syndrome	Serotonergic agonists	< 12 hours	>41°C	Mydriasis, drooling, sweating, hyperactive reflexes, agitation, coma
Anticholinergic Syndrome	Muscarinic antagonists	< 12 hours	<39°C	Mydriasis, dry mouth and skin, normal reflexes, delirium
NMS	Dopamine antagonists	1 – 3 days	>41°C	Normal pupils, drooling, pallor, lead-pipe rigidity, hyporeflexia, alert mutism, coma
MH	Volatile anesthetics or succinylcholine	Immediate to 24 hours after administration	To 46°C	Normal pupils, mottled sweaty skin, total body rigidity, hyporeflexia, agitation

Pharmacology & Physiology in Anesthetic Practice – 6th ed. 2022.

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