Antiparasitic Agents

• (1) Aims: High efficacy & prevent resistance
  • Maximum concentration in target organisms for appropriate time to be effective
    • Need to know PK & PD in both host & parasite
  • Need a drug at site of action
    • long enough to be effective, but short enough for safety, & environmental concerns
      – Critical for treatments given externally
Antiparasitic Agents

• (2) Drug distribution in host
  • To appropriate organs/tissues so parasite can absorb the drug from surrounding medium or take it up by ingestion (i.e. blood, mucus, tissue meal) so that therapeutic concentration achieved in parasite
  • Need to know stage of parasite to ascertain presence of target and/or where the stage is in the host
    – e.g. Liver? Blood? Gut?
    – Migrating through sensitive tissue...
  • Need to know parasite’s feeding habits
  • Critical for treatments administered to host orally, parenterally or absorbed through host’s skin

• (3) Selective toxicity / Mechanism of Action (MOA)
  – Agents that affect parasite but not host
    • Need to know qualitative or quantitative biochemical differences between host & parasite
  – Safety margin or therapeutic index:
    • Ratio of dose that will cause no clinical adverse reactions (no toxicity) to host vs dose needed to kill parasite
  – What is unique about the parasite?
    • Ion channels
    • Metabolic pathways, enzymes
    • Chitin in arthropods
    • Growth regulation
    • Phylogenetically...
Antiparasitic Agents

- (4) Prudent or judicious use is required
  - Optimal selection of drug, dose & duration of treatment, along with reduction of the inappropriate & excessive use as a means of slowing the emergence of resistance
  - Therapeutic:
    - Medical treatment of a disease or condition
  - Prophylactic:
    - Prevention of or protective treatment for disease
  - Metaphylactic:
    - Timely mass medication of a group of animals to eliminate or minimize an expected outbreak of a disease

Antiparasitic Drugs

1. Antiprotozoal agents
   - Antimicrobial drugs (e.g. sulfonamides)
   - Ionophores
   - Others: amprolium, decoquinate, metronidazole, benzimidazoles
     - Many antimalarial drugs used in humans

2. Anthelmintic agents
   - Drugs affecting neurotransmission
   - Drugs affecting metabolic pathways

3. Ectoparasitic agents
   - Drugs affecting neurotransmission
   - Growth regulators
1. Antiprotozoal agents

- Protozoa that cause diseases in animals
  - Flagellates: *Giardia*, *Trichomonas*, *Tritrichomonas*
  - Amoeba: *Entamoeba*, *Acanthamoeba*, *Naegleria*
  - Ciliates: *Balantidium*
  - Coccidia: *Isospora* & *Eimeria*
  - *Toxoplasma*, *Neospora*
  - *Sarcocystis*
  - *Trypanosoma* & *Leishmania*

Giardiasis: Treatment

- All drugs work against the trophozoite stage of *Giardia*, not cysts
  - Metronidazole, febantel & fenbendazole
Metronidazole (Flagyl®)

Plumb 6th Ed p. 610-613

- No vet approved products
- **MOA:**
  - Selective activity for anaerobes; including *Giardia, Entamoeba, Trichomonas, Balantidium*
    - Nitro group serves as electron acceptor, forming reduced cytotoxic compounds that **bind to &/or break DNA** to result in cell death
- **Administration (oral)**
  - Good absorption (50-100% in dogs) from GI tract
    - Given with food, enhances absorption
    - Good systemic distribution

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Metronidazole (Flagyl®)

- **Contraindications:**
  - Prohibited use in food animals (FDA)
  - Potential teratogen, mutagen & carcinogen
    - **Not** recommended for **pregnant animals**
- **Adverse effects & toxicities**
  - Anorexia, vomiting, lethargy
  - High doses & chronic moderate doses cause neurological effects
    - ataxia, tremors & seizures
  - Tablets have metallic taste
    - mix with food or use oral suspension
- **Resistance:** Rare, but beginning to develop
Benzimidazoles

Fenbendazole: Panacur®, Safe-Guard®

- **Labeled for** dogs, cattle, horses, swine for specific helminths
  - ‘Not labeled’, but has been used in cats, sheep, goats, pet birds & llamas

- **MOA (helminths & protozoans)**
  - **Primary:**
    - Prevents tubulin polymerization & inhibits microtubule assembly
      - Necessary for cell mobility (flagella, cilia...), cell division & vesicular transport, therefore leading to cell death
  - **Secondary:** Higher doses
    - Disrupt energy metabolism (ATP)
      - Inhibits fumarate reductase → decreased anaerobic respiration

- **Administration**
  - **Oral:** Only marginally absorbed
    - ~50% in ruminants
    - **Single doses not effective, need to treat for at least 3 days (dogs & cats)**
      - Fenbendazole only partially absorbed
      - Febantel readily absorbed
      - Febantel: pro-drug activated to fenbendazole & oxyfenbendazole in the GI tract & liver

- **Safety:**
  - Safe to use in pregnancy for all species (cats, dogs & lab animals)
Coccidiosis: Treatment

- **Anticoccidial drugs** act on: *Isospora*, *Eimeria*, & *Toxoplasma, Neospora, Sarcocystis*
  - Extracellular stages - prevent penetration of cells
  - Intracellular stages - stop or inhibit development
- Most drugs are **coccidiostats**:
  - Arrest development of coccidia, but do not kill the parasite
- Some drugs are ‘**static**’ or ‘**cidal**’ under therapeutic conditions
  - e.g. sulfonamides & ionophores

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**Coccidian Life Cycle**

**Drugs slow growth:**
- **Intracellular stages** - schizont meronts

**Drugs KILL:**
- **Extracellular stages** - sporozoites, merozoites

**Sanitation:** within 24-48 hours i.e. before oocysts are mature & infective (sporulated oocyst)
Potentiated Sulfonamides

- Only approved in dogs, cats & horses but used in many species
  - Trimethoprim with; sulfadiazine (USA), sulfmethoxazole (Human), sulfadoxine (Canada)
- MOA: inhibit thymidine biosynthesis
  - ↓ Folate synthesis + inhibit reductase, Extracellular stages targeted (kill), but intracellular stages also affected (slow)
- Contraindicated: renal & liver disease, Doberman pinschers

Amprolium (Amprovine®, Corid®)

- MOA:
  - Thiamine (Vitamin B1) structural analog
  - competitively inhibits thiamine uptake in coccidia leading to Vitamin B₁ (thiamine) deficiency
  - Prevents differentiation 1st generation schizonts in cells of the intestinal wall (i.e. acts on asexual intracellular stages)
    - May suppress sexual stages & sporulation of the oocysts
  - coccidiostat
- Administration: oral (food & water) to poultry & cattle
  - Metaphylaxis & treatment
- Concerns:
  - Overdose can lead to thiamine deficiency in host
  - Neurological clinical signs
  - High thiamine in diet can reduce efficacy of amprolium
    - Check thiamine content in feed
Decoquinate (Deccox®)

Plumb 6th Ed., p. 255-256

- Not FDA-approved in lactating dairy animals or laying hens
- **MOA:** Disrupts mitochondria in sporozoites only (coccidiostat)
  → prevents establishment of infection
- **Administer:** in feed to cattle, broilers & dogs
  - Metaphylactic:
    - Not sufficiently efficacious in clinical coccidiosis

Sodium Ionophores:

Monensin (Rumensin®) & Lasalocid (Avatec® & Bovatec®)

- **MOA:**
  - Creates a channel for sodium to enter susceptible cells & potassium to exit
  - ‘cidal’ only to extracellular stages
    - sporozoites, merozoites
- **Administered:** oral but not well absorbed
  - Poultry: in feed
  - Cattle: bolus in rumen (slow release)
  - Therapeutic & metaphylactic
    - Also for ketosis, bloat prevention, growth promotent...
- **TOXIC** to horses, pigs, dogs...fatal cardiomyopathy
Ponazuril (Marquis®) & Diclazuril (Protazil®)

- **Indications:** Equine Protozoal Myeloencephalitis (EPM) - *Sarcocystis neurona*
- Potentially useful in Tx of *Neospora caninum, Toxoplasma, Cryptosporidium, Isospora, Eimeria*…
- **MOA:** triazine class antiprotozoals believed to target the apicoplast (plastid-like organelle) in *Apicomplexans*
- **Administration:** oral - paste or pellets
- **Concerns:** blisters on the nose & mouth, skin rash, loose stool (still considered a new drugs…so report any concerns….)

2. Anthelmintic Drugs

- Control of roundworms (nematodes), tapeworms (cestodes) & flukes (trematodes)
- **Requirements for an effective anthelmintic**
  - Must be able to penetrate the cuticle of the worm or gain access to its alimentary tract so that it can achieve effective concentrations at target sites
Anthelmintics by target

- **Drugs used for nematodes (roundworms)**
  - Benzimidazoles
  - Macro cyclic lactones (Avermectins & Milbemycins)
  - Emodepside
  - Amino-acetonitrile derivatives (AADs): Monepantel
  - Piperazines
  - Tetrahydropyrimidines: Pyrantel, Morantel
  - Arsenicals

- **Drugs used for cestodes (tapeworms)**
  - Praziquantel, Epsiprantel

- **Drugs used for trematodes (flukes)**
  - Clorsulon, praziquantel
  - Some benzimidazoles

Anthelmintics by action

- **Drugs affecting metabolism & cell integrity**
  - Benzimidazoles
  - Praziquantel, Epsiprantel
  - Clorsulon

- **Drugs affecting neurotransmission**
  - Drugs *inhibiting* neurotransmission: *flaccid paralysis*
    - Macro cyclic lactones – open Cl channels
    - Emodepside – latrophilin receptor agonist releases inhibitor neurotransmitters
    - Piperazines – block nicotinic transmission
  - Drugs *stimulating* neurotransmission: *spastic paralysis*
    - Amino-acetonitrile derivatives – stimulate nicotinic receptors
    - Tetrahydropyrimidines – depolarizing nm blocker $\rightarrow$ ↑ ACh
Drugs affecting metabolism & cellular integrity

– Benzimidazoles (nematodes, trematodes & some protozoa)

– Praziquantel, Epsiprantel (cestodes)

– Clorsulon (some trematodes)

Benzimidazoles

• Benzimidazoles & benzimidazole pro-drugs
  – e.g. ‘bendazole family
    – Mebendazole
    – Thiabendazole
    – Fenbendazole
    – Albendazole
    – Oxibendazole
    – etc.
  – Febantel, netobimin, oxfendazole, etc.
    absorbed (Prodrugs), then metabolized to active benzimidazoles

  – Used for removal of parasites in many species
• **MOA:** in helminths (also some protozoans & flukes)
  – **Primary:** Inhibit polymerization of tubulin in cellular microtubules
    • Necessary for cell division, vesicular transport (necessary for glucose uptake) & cell structure/integrity
  – **Secondary:** (High doses) Disrupt energy (ATP) metabolism
    • Inhibit fumarate reductase
      – Decreased respiratory pathway required to generate energy (ATP) in nematodes

• **Administration:**
  – Oral
    • Absorption is dependent on the drug:
      – Mebendazole not absorbed effectively unless administered with high fat meal
      – Thiabendazole readily absorbed
      – Pro-drugs readily absorbed; activated in gut & liver

• **Side effects & concerns:**
  – Usually **very safe & well tolerated**
    • GI discomfort, including nausea & vomiting can occur
      – **OWNER CONCERNS**
    • Hypersensitivity reactions due to antigens from dying parasites (helminths, rare in protozoa)
      – Some benzimidazoles (e.g. Albendazole, Mebendazole) not to be used in pregnant animals; others very safe (e.g. fenbendazole)
      • Teratogenicity risk in some species

**Use the appropriate benzimidazole for the host & parasite to maximize efficacy & minimize side effects & resistance development**
• Resistance:
  – High prevalence world-wide
  – Cross-resistance between all benzimidazoles, especially if dosing required several times per year
    • Solution:
      – alternate with non-benzimidazole
  – Resistance at both uptake (i.e. P-glycoprotein upregulation) & target (i.e. altered β-tubulin)

Treatment of cestodes & trematodes:

• 1) Praziquantel (Droncit®)
  • Taenia, Dipylidium in dogs & cats, Echinococcus in dogs, Alaria in dogs, Spirometra in cats
• 2) Epsiprantel (Cestex®)
  • Taenia, Dipylidium in dogs & cats

• MOA:
  – Stimulates parasite motility by increasing intracellular Ca**→ tetanic contractions of scolex → impairs sucker function
  – Disrupts parasite’s integument → disintegration
• **Administration & Uses:**
  – Oral, topical & parenteral preparations for all species, including fish, birds & reptiles
  
  – **Praziquantel** (pro-drug):
    – Readily absorbed, activated in liver, good systemic distribution
    • used for susceptible trematodes & cestodes
  
  – **Epsiprantel**: 
    – Oral only; not absorbed, stays in intestine
    • cestodes only

• **Side Effects:**
  • Praziquantel safe, even in pregnant or nursing dogs & cats
  • Epsiprantel ?, assumed since not absorbed
  • Epsiprantel – NOT approved in puppies & kittens < 7 weeks.
  • Praziquantel – Contraindicated puppies < 4 weeks, kittens <6 weeks (but **Drontal Plus for puppies @ 3 weeks**)
    • GI discomfort can occur (low incidence)

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3) **Clorsulon (Curatrem®)**
  – Administered orally to ruminants for immature & adult liver flukes (**Fasciola hepatica**)
  
  – **MOA:**
    • Inhibits specific enzymes in glycolytic pathway, depriving fluke of glucose, thus no energy
    • Drug binds to red blood cells; therefore readily available to flukes
  
  – **Safety:** in pregnant animals
  
  – **Contraindications:**
    • Not permitted for milking cows
    • Do not use within 49 days of slaughter for cattle
Drugs affecting neurotransmission

1) Drugs inhibiting neurotransmission
   – Flaccid paralysis
     A. Macro cyclic lactones – open Cl\textsuperscript{–} channels
     B. Emodepside – latrophilin receptor agonist releases inhibitory neurotransmitters
     C. Piperazines – block nicotinic transmission
A. Macrocyclic lactones: Avermectins & Milbemycins

- **Endo/Ecto parasiticides**
  - Nematodes & some ectoparasitic arthropods

- **Uses:**
  
  1. **Heartworm prophylaxis in dogs:**
     - **No adulticide action; only** for larval stages (*Dirofilaria immitis microfilaria*)
     - **Ivermectin** doses in dogs too low to affect GI nematodes
       - Higher doses avoided because of potential host CNS depression
       - Administered in combination with pyrantel to extend range to GI nematodes
     - **Milbemycin** targets both GI & systemic nematodes, but administered with lufenuron to extend range to fleas & other arthropods
     - **Selamectin** used for heartworm, fleas, ear mites & mange...

  2. **GI & systemic nematodes in cattle, swine & horses**
     - Abamectin, Moxidectin, Eprinomectin, Doramectin

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### Macrocylic lactones: Sources

**AVERMECTINS**

- Abamectin (Virbamec®)
- Ivermectin (Ivomec®, Heartgard®)
- Doramectin (Dectomax®)
- Eprinomectin (Ivomec®, Eprinex®)
- Selamectin (Revolution®)
- Emamectin benzoate (SLICE®)

**MILBEMYCINS**

- Moxidectin (Cydectin®)
- Milbemycin (Interceptor®, Sentinel®)
Common features: Avermectins & Milbemycins

- Structural & physicochemical properties
  - Slight structural differences result in changes in lipid solubility & affinity for carriers & targets

- Efficacious & persistent broad-spectrum activity
  - Affects both nematodes & arthropods & most stages
  - Ability to kill parasite depends on administration & distribution

- Same MOA & resistance mechanisms

- No activity against tapeworms & flukes

- Wide safety margin, except for some breeds of dogs & some drugs (esp. Ivermectin)

**Mode of Action**

HIGH AFFINITY BINDING TO GLUTAMATE-GATED CHLORIDE (GluCl) CHANNELS

INCREASES CHLORIDE CONDUCTANCE ACROSS CELL MEMBRANES: hyperpolarization

- PHARYNGEAL PUMP
  - AFFECTS NUTRIENT INGESTION

- Flaccid Paralysis

- SOMATIC MUSCULATURE
  - LIMITS PARASITES ABILITY TO REMAIN AT SITE OF PREDATION

PARALYSIS & DEATH NEMATODES & ARTHROPODS
Selective toxicity

• **GOOD:** Glutamate-gated chloride channels only found in nervous system & neuromuscular junctions of arthropods & nematodes

• **BAD:** Can also interact with GABA-gated chloride channels
  – Located only in CNS in vertebrates
  – Bind with lower affinity (i.e. higher concentration needed)
    • CNS protected by BBB with P-glycoproteins (protein product of the ABCB1 gene) that “pump out” unwanted chemicals
    • Some dogs have **genetic deletion mutation in ABCB1** & toxic levels can be reached with some macrocyclic lactones (esp. **Ivermectin**)
      – **clinical signs:** ataxia, tremors, lethargy, vomiting, mydriasis, disorientation & hypersalivation
    • Can be differences between drugs:
      – Ivermectin > Milbemycin for collies

• **Minor issue:** some dogs itching & allergic reactions reported (due to death of parasites)
Known susceptible breeds:

- **Breeds affected by the ABCB1 mutation**

<table>
<thead>
<tr>
<th>Breed</th>
<th>Approximate Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Shepherd</td>
<td>50%</td>
</tr>
<tr>
<td>Australian Shepherd, Mini</td>
<td>50%</td>
</tr>
<tr>
<td>Border Collie</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Collie</td>
<td>70%</td>
</tr>
<tr>
<td>English Shepherd</td>
<td>15%</td>
</tr>
<tr>
<td>German Shepherd</td>
<td>10%</td>
</tr>
<tr>
<td>Herding Breed Cross</td>
<td>10%</td>
</tr>
<tr>
<td>Long-haired Whippet</td>
<td>65%</td>
</tr>
<tr>
<td>McNab</td>
<td>30%</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>5%</td>
</tr>
<tr>
<td>Old English Sheepdog</td>
<td>5%</td>
</tr>
<tr>
<td>Shetland Sheepdog</td>
<td>15%</td>
</tr>
<tr>
<td>Silken Windhound</td>
<td>30%</td>
</tr>
</tbody>
</table>

- **“White feet…don’t treat”**


FYI…

- **Ivermectin** (antiparasitic agent). While the dose of ivermectin used to prevent heartworm infection is SAFE in dogs with the mutation (6 micrograms per kilogram), higher doses, such as those used for treating mange (300-600 micrograms per kilogram) will cause neurological toxicity in dogs that are homozygous for the ABCB1 mutation (mutant/mutant) & can cause toxicity in dogs that are heterozygous for the mutation (mutant/normal).

- **Selamectin, milbemycin & moxidectin** (antiparasitic agents). Similar to ivermectin, these drugs are safe in dogs with the mutation if used for heartworm prevention at the manufacturer's recommended dose. Higher doses (generally 10-20 times higher than the heartworm prevention dose) have been documented to cause neurological toxicity in dogs with the ABCB1 mutation.

Source: http://www.vetmed.wsu.edu/depts-VCPL/drugs.aspx
Administration & Pharmacokinetics

• Administered:
  – po, sc & spot-on/pour-on
  – for cats, dogs, horses, cattle, swine & fish…

• Absorption:
  – Highly lipid soluble
  – 95% absorbed per os from simple stomach animals
  – 25-40% bioavailability in ruminants if given orally
    • sc or pour-on often used in ruminants
  – Rapidly absorbed into adipose tissue from where it is redistributed to maintain parasiticidal concentrations

• Metabolism & excretion
  • Fairly slow metabolism \( t_{1/2} \) 2-7 days via oxidative pathways
  • Rate & degree of metabolism depends on drug
    • 95% excreted in feces & 5% in urine

• Persistence
  • Much longer than blood \( t_{1/2} \) due to distribution to lipids & adipose tissue & subsequent redistribution
• Environmental concerns
  • Especially for drugs not extensively metabolized & thus excreted in parent form
  • Dog ingested horse poop or spilled dewormer
  • Dung beetles on farms; invertebrates near fish farms…

• Long withdrawal times with some preparations in food animals
  – BUT: Zero withdrawal time for milk with Eprinomectin due to poor distribution to udder
  – Emamectin benzoate: Zero withdrawal time for salmon, but strict minimum residue limits

Resistance

Major concern!
  – Decreased uptake of drug
    • P-glycoprotein upregulation in gut of nematode or arthropod rejecting drug so that insufficient drug reaches target sites
  – Altered receptor sites
    • Glutamate-gated chloride channel mutations

– FYI:
– What to do? Where to start?
  • READ:
    http://www.fda.gov/downloads/AnimalVeterinary/ResourcesforYou/UCM344299.pdf
  • FDA’s Public Meeting on Antiparasitic Drug Use and Resistance in Ruminants and Equines – An Overview
B. Emodepside
(in Profender® with praziquantel)

• **Use**: kills adult & larval roundworms & hookworms in cats (praziquantel for cestodes)

• **MOA**: stimulates *latrophilin receptors* at nematode neuromuscular junctions → causes *release of inhibitory neuropeptides* (Glu, GABA, others) across the synapse → opens *Cl⁻ channels* → *hyperpolarization* → flaccid paralysis (inhibits pharyngeal pump of nematode) & death
  - Use of this drug in dogs with the *ABCB1* mutation has resulted in neurological toxicity

• **Administration**: topical → absorbed through skin via the hair follicles & distributed to the intestine via bloodstream

C. Piperazines

• **Many oral piperazine preparations available OTC**

• **Uses**:
  - Ascarid infections in most species (dogs, cats, horses, swine)
  - Hallucinogen in humans!

• **MOA**:
  - reported to *block nicotinic transmission by hyperpolarizing synapses/neuromuscular (nm) junctions* → Flaccid paralysis

• **Resistance**: prevalent
• **Side effects & concerns**
  – Well tolerated at therapeutic doses
  – GI distress noted at higher doses; better tolerance if administered in feed
  – Safe in pregnant & young animals

  – **Contraindicated:**
    – Chronic liver, kidney disease & GI hypomotility

  – **CAUTION:**
    – Seizure disorders & horses (esp. foals) with heavy infestations of *Parascaris equorum*

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**Drugs affecting neurotransmission**

2) **Drugs stimulating neurotransmission**

  – **Spastic paralysis**
    A. Amino-acetonitrile derivatives – stimulate nicotinic receptors
    B. Tetrahydropyrimidines – depolarizing nm blocker → ↑ ACh
A. Amino Acetonitrile Derivatives

- **Monepantel (Zolvix®)**
  - New class of anthelmintics effective against drug-resistant nematodes
    - currently marketed as a sheep drench
  - MOA:
    - Agonist at unique nicotinic ACh receptor
    - Hypercontraction of body wall muscles → *spastic paralysis*
    - Spastic contractions of helminth pharynx
    - Death
  - Different target than tetrahydropyrimidines
  - Well tolerated & low incidence of host toxicity

B. Tetrahydropyrimidinines

- **Morantel** (ruminants) - Rumatel®
- **Pyrantel** (most species) - Strongid®
  - Morantel slower in onset than pyrantel, but more potent
  - Remove & prevent GI nematode infections
    - Applied orally; *not absorbed* into host
  - Often given to dogs in combination with ivermectin

- MOA:
  - Depolarizing neuromuscular blocking agents and may also have cholinesterase activity →↑ ACh
    - Spastic paralysis & death of roundworms
  - **Inhibits fumarate reductase** in some nematodes
    - Anaerobic respiration reduced: ↓ ATP
• **Side effects & concerns**
  – None noted

• **Drug interactions**: DO NOT administer with drugs which also affect neuromuscular transmission
  – possible interference (e.g. piperazine levamisole, morantel, organophosphates)

• **Resistance**: widespread

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**Other: Heartworm adulticides**

• **Arsenical compounds**
  – Melarsomine (Imicide®),
  – Thiacetarsemide (Caparsolate®)
    • Only for dogs (even more toxic to cats)

• **MOA not known – impacts glycolysis, binds cystine?...**

• Administered IM, rapid distribution & action

• **Toxicity & concerns:**
  – **Narrow safety margin**
    • Respiratory distress, anorexia, vomiting, tremors, lethargy & death
    • Risk of post-treatment pulmonary thromboembolism from dead/broken worms (Possibly FATAL)
3. Ectoparasitic Agents

- Compounds acting against external parasites
  - e.g. mites, ticks, lice, fleas…
  - Drugs affecting neurotransmission
  - Arthropod Growth Regulators

- Modes of application
  - External
    - Dips, sprays, dusts, pour-on/spot-on, shampoos, collars, ear tags, baths (for fish)…
    - Drug will usually be absorbed through the cuticle or taken in through spiracles of arthropods
    - Drug can be absorbed by the host & then taken up by parasite by ingestion
  - Internal
    - Feed additives or coatings, paste feeds, tablets, sc injection
Drugs affecting neurotransmission

1) Acetylcholinesterase inhibitors: ↑ACh → excitatory
   - Organophosphorus compounds & carbamates
2) Sodium channel activators: ↑action potentials→ ↑Ach → excitatory
   - Pyrethroids & organochlorides
3) Nicotinic receptor agonists: ↑ACh activity → excitatory
   - Spinosad
4) Nicotinic receptor antagonists: ↓ ACh activity → flaccid
   - Imidacloprid, nitenpyram
5) Chloride channel openers: hyperpolarization → flaccid
   - Avermectins & milbemycins (see Antiparasitics II)
6) Chloride channel blockers: hypopolarization → excitatory
   - Fipronil
7) Isoxazolines: Blocks GABACl & GluCl channels → spastic paralysis
   - Afoxolaner, Fluralaner, Sarolaner
8) Monoamine oxidase inhibitors: ↑NE → excitatory
   - Amitraz

1) Acetylcholinesterase inhibitors: Organophosphorus (OP) compounds & Carbamates

- **Drugs:** Dichlorvos, azamethiphos, diazinon, malathion, carbaryl etc.
  - For arthropods, as well as susceptible nematodes
  - **Water-soluble:** broken down fairly quickly in environment with minimal absorption into host
  - Administered in powders, sprays, collars & orally

- **MOA:**
  - Acetylcholinesterase inhibitors
    - Increased concentration of ACh at nerve endings ➔ increased cholinergic transmission in parasite
    - ➔ spastic paralysis
      - OP’s: usually irreversible
      - Carbamates: slowly reversible
• **Side effects:**
  – Increased cholinergic activity in host, mainly *muscarinic*, but also increased *nicotinic* activity
    • Contraindicated when increased cholinergic activity undesirable
    • **Avoid in cats:** higher cholinesterase in plasma
    • **Avoid in horses:** fatal colonic impaction

• **Drug interactions:**
  – Any drug that affects the CNS or parasympathetic & somatic nervous systems

• **Antidote:**
  – Atropine to *reverse increased muscarinic effects*
  – Pralidoxime (2-PAM), if early enough, to dissociate OP from ACh esterase

• **Resistance:**
  – Decreased ability of drug to inhibit ACh esterase
    • i.e. change in target
      – ACh levels don’t build up

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### 2) $\text{Na}^+$ channel openers:
Pyrethrins & Pyrethroids

• **Drugs:**
  – Permethrin, cypermethrin, deltamethrin, cyfluthrin...
  – Flea adulticide

• **MOA:**
  – Contact poisons on arthropods
    • Drug absorbed into arthropod respiratory system
    • Affect nerves by *prolonged opening of Na*⁺ *channels* → muscular excitement (repetitive action potentials) & convulsions → **spastic paralysis**
• **Side effects:**
  - Minimal in dogs treated appropriately
    - Slow cutaneous absorption in host & **rapidly metabolized**
      - Decreases side effects to host
    - Piperonyl butoxide incorporated in some products to inhibit pyrethroid metabolism in parasite
      - Prolongs activity in parasite
  - **Problem is accidental or inappropriate application in small dogs & esp. cats!**
  - **Caution:** avoid grooming in **cats**, spasms with oral absorption
    - Lethal dermal exposure in cats of 100 mg/kg
    - Most OTC-Permethrin Spot-On contain
      - 1-8 times the lethal dose for an ~ 4 kg cat.
  - **Resistance:**
    - Alteration in target site: parasite Na+ channel

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3) **Nicotinic receptor agonist:**

**Spinosad (Comfortis®)**

• Flea control in dogs
• **MOA:** activates unique nicotinic ACh receptors
  - different than those blocked by neonicotinoids
    - **Spastic paralysis**
• **Pharmacokinetics**
  - Chewable tablets administered 1/month
    - Rapid action: fleas start to die ~ 30 min, 100% efficacy in 4 hr
• **Side effects:** unlikely if used as directed
  - Some cases of vomiting, diarrhea, lethargy & decreased appetite reported with higher doses
4) Nicotinic receptor antagonists: Neonicotinoids

- **Imidacloprid** (Advantage®)…
- **Nitenpyram** (Capstar®)
  - Control adult & larval fleas in dogs/cats
- **MOA:**
  - **Antagonist of**
    - arthropod nicotinic ACh receptors
  - Flaccid paralysis

- **Side effects:** unlikely if used as directed
  - Some cases of vomiting, diarrhea & hypersalivation reported

**Pharmacokinetics**

- **Topical** administration on back of neck (imidacloprid)
  - Spreads through fur
  - Not absorbed by host
- **Oral** tablets (nitenpyram)
  - Rapid absorption; therapeutic levels in fleas in 30 min

- **Onset of activity** rapid:
  - 0 (imidacloprid) to 30 min (nitenpyram)

- **Persistence**
  - Imidacloprid: Effect persists for about 1 month
  - Nitenpyram: $t_{1/2}$: 24 hrs for dogs, 48 hrs for cats
    - Administered 1/day
6) Chloride channel blocker: Fipronil (Frontline®)

- **Use:**
  - Topical preparation for ticks & fleas (dogs & cats)
    - Collects in oils of skin & hair follicles & then released slowly; spreads over body in 24 hr
      - Long residual activity: ~ 1 month

- **MOA:**
  - Blocks passage of chloride ions through GABA-regulated chloride channels
    - Cells more +ve internally → depolarize easier
      - spastic paralysis

- **Resistance:** reported in cat fleas

7) Isoxazolines

Afoxolaner, Fluralaner, Sarolaner

- **Use:** oral/topical preparations readily absorbed & provide 4–12 wk of insecticide & acaricide activity.

- **MOA:**
  - Blocks passage of chloride ions through GABA-regulated chloride channels (& Glutamate gated chloride channels)
    - Cells more +ve internally → depolarize easier
      - spastic paralysis

- **Side effects:** vomiting, diarrhea…

- **Resistance:** none reported…
8) MAO inhibitor: Formamidines

Amitraz (Preventic®, Mitaban®) - ticks & mites

- **Use:** Lyme disease (Ticks really...), mange
  - For dogs, swine & ruminants
    - Topical solutions & collars

- **MOA:** Monoamine oxidase inhibitor
  - ↑ α₂-adrenergic activity
  - *Increased* norepinephrine concentrations at synapses in arthropod
    - detachment

- **Side effects:**
  - Increased α₂-adrenergic activity in host, especially if collar ingested
    - Lethargy/sedation (reversed by yohimbine)
    - Transient hyperglycemia reported: use with caution in diabetic animals
  - Toxicology reported in cats & rabbits – Do not use

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**Arthropod Growth Regulators**

- 1) Chitin synthesis inhibitors
- 2) Hormone interference

![Arthropod Growth Regulators Diagram]

Lufenuron MOA:
Inhibit chitin synthesis of larvae

Methoprene MOA:
egg & larvae - arrested development
1) Chitin synthesis inhibitors

- **Lufenuron** (Program®, in combo with milbemycin in Sentinel®, with nitenpyram in Capstar®)

- **MOA:**
  - interferes with the incorporation of chitin in the exoskeleton → prevents viable moulting & hatching of eggs
    - Egg tooth too soft to break shell
  - Only effective vs moulting stages of fleas
  - Cutaneous fungal infections in dogs & cats

- **PKs:**
  - Administered: oral suspension, tablets, injectable
  - **Lipophilic:** readily absorbed & redistributed to adipose tissue, but may take 1-3 weeks (cat > dog) to reach therapeutic blood concentrations
    - Administered 1/month
  - Excreted unmetabolized, but undergoes enterohepatic recycling → long acting

- **Toxicology & resistance**
  - None noted; lufenuron safe for pregnant, breeding or lactating animals
2) Hormone interference

- e.g. Methoprene

- **MOA:** juvenile hormone analog that keeps flea eggs or larvae of fleas & ticks at the current state of development (arrested development)
  - Eggs do not hatch & larvae do not pupate
  - No known adulticide effects

- Administered in collars, sprays, shampoos
  - Lasts 8 (dogs) to 12 months (cats)