Anthelmintic drugs

Nicotinic Agonists

Induce muscle contraction and spastic paralysis. Note open channel block (especially at negative potentials) – self antagonism

Imidazothiazoles	**Levamisole**	Lowest open channel block characteristics
Tetrahydropyrimidines	**Pyrantel**	Insoluble so reduced toxic effect
Quaternary ammonium salts	Bephenium	

Anticholinesterases

Induce increased [ACh] causing contraction and then paralysis. Either carbamylate or phosphorylate AChE serine. Multiple helminth isoforms. ? A most important. Also helminths secrete AChE to surroundings (? Decrease glandular secretions). Host AChE sensitive so reduced use now.

Organophosphates	**Dichlorus**
Carbamates	**Aldicarb**

Nicotinic Antagonists

Flacid paralysis by inhibiting $nACh_n$ selectively. Inhibit motility etc.

Paraherquamide
Macfortines

GABA Agonists

Ligand gated Cl channels. Lacks carboxyl group so ^ $[CO_2]$ may be required to mimic. Hence selectivity towards GI worms (anaerobic conditions, c.f. free living worms) $GABA_n$ isotype – insensitive to vertebrate antagonist BICUCULINE.

Piperazine

Glutamate gated Cl channels

Flacid paralysis due to hyperpolarisation. (pharynx, egg laying and motile musculature. At low [ ] potentiate endogenous glutamate. At high [ ] directly opens channels (selective toxicity on helminths depends on presence of P-gp (Mdr-1 product) protecting mammalian CNS) Helminth resistance by expressing different receptor isoforms.

Avermactins	**Ivermectin,** moxidectin
Milbemycins	**Milbemycin**

Calcium permeability

Increase calcium permeability by unknown mechanism. Causes rapid contraction and spastic paralysis. ? also damaging tegument revealing antigens (immune response) or functional proteins (proteolytic disassembly) VG β unit appears to decrease permeability but also confer sensitivity to drug. ? also action on calcium induced calcium release

Praziquantel

Microtubule formation inhibitor

Responsible for vesicle trafficking (inc GLUT), structural integrity and cell division.. Drugs bind to β tubulin preventing elongation/polymerisation. Dynamic instability leads to breaking down of microtubules. Results in slow starvation – so require slow release boluses. Resistance by mutation in tubulin genes.

Benzimidazoles	Fenbendazole, **thiabendazole**
Colchines	
Vincristine, Vinblastine	

Proton Ionophores

Dissociatable proton, lipophilic – able to cross membrane. Uncouple oxidative phosphorylation. ? also action on dissipating H gradient across body wall – causing decreased motility BEFORE decrease in ATP (hence helmith selectivity) ? also bind to plasma proteins and hence selectively accumulated in blood sucking helmiths.

Salicyclanides	**Closantel**
Substituted phenols	**Nitroxynil**

Others

Diamphenithide	Inhibits malate concentration (hence glucose metabolism)
Clorsulon	Inhibits phosphoglycerate kinase and mutase (glucose metabolism)
Diethylcarbamazine	Inhibits arachidonic acid metabolism (may require host vasoconstriction for effect)

The drugs in **BOLD** are a selection that I think is representative and were the ones that I learnt.