CNS Pharmacology

GABA

Synthesis and inactivation

Isoniazid	GABA Synthesis	Inhibits glutamate decarboxylase – originally used for TB
Vigabatrin	GABA Degradation	Inhibits GABA transaminase (GABA → succinate semialdehyde)
Sodium Valproate	GABA Degradation	Inhibits succinate semialdehyde dehydrogenase (succinate semialdehyde → succinate)
Tiagabine	GABA Reuptake	Inhibits the GABA – Na cotransporter

$GABA_A$ receptor (pentameric heteromer, Cl channel – inhibitory)

GABA	Endogenous agonist
Muscimol	Agonist
Bicuculline	Antagonist – competitive
Picrotoxin	Antagonist – ion channel block
Benzodiazepines	Allosteric modulator – binds preferentially between α and γ_2 subunits
Barbiturates	Allosteric modulator
Neurosteroids	Allosteric modulator
β – carbolines	Allosteric modulator
General anaesthetic	Allosteric modulator

$GABA_B$ receptor (GPCR - g_i open K channel,block VGCC, bicuculline insens)

GABA	Endogenous agonist
Baclofen	Agonist – anti spasmodic in spinal cord
Gamma hydroxyl butyrate	Agonist – date rape
Phaclofen	Antagonist
2-hydroxysaclofen	Antagonist

Anxiety and GABA

Buspirone	5 HT_{1A} partial agonist	? feedback inhibitory effect
β – blockers		*Somatic anxiety* by removing peripheral effects
Tricyclics and SSRI	Antidepressants	? overlap between chronic anxiety and depression
Barbiturates	Allosteric activators $GABA_A$	At high [ ] can open channel in absence of GABA. Low TI, tolerance due to hepatic enzyme induction, profound depression and dependence. Largely replaced by BZD but still used as anticonvulsant. Increase channel open time.
Benzodiazepine	Allosteric activators	Safer – higher TI. Only potentiates the action of released GABA. Increases

	$GABA_A$	frequency of opening and increases *affinity* for GABA. BUT – dependence, hypnotic, tolerance (due to subunit change) and synergistic with alcohol and anti histamine. Some have long lived metabolites – e.g. nordiazepam – $t_{1/2}$ = 60hr. – 'Hang over' *(effects: anxiolytic, anticonvulsant, hypnotic, muscle relaxant)*
Diazepam chlordiazepoxide	Benzodiazepine	Anxiolytic – long $t_{1/2}$ metabolised to nordiazepam = hang over.
Nitrazepam	Benzodiazepine	Hypnotic – short $t_{1/2}$ wears off before am.
Zaleplan	Acts at BZD site	short $t_{1/2}$. Shows selectivity for α_1 unit (shown to be involved with hypnotic effect) hence without anxiolytic effects. (thought to be due to $\alpha_2$unit)
Flumazenil		Antagonist at the BZD binding site on $GABA_A$ receptor.
Neurosteroids	Allosteric modulator	Includes progesterone metabolites and dehydroxycorticosterone. Enhance agonist binding and Cl flux by increasing frequency of opening. May be able to open channel in absence of agonist.
β – carboline carboxylate	β – carboline Allosteric modulator	Inverse agonist at BZD site. Decreases frequency of opening and *affinity* for GABA.

Glycine (Spinal cord inhibitory [renshaw cell] pentameric receptor)

Strychnine	Competitive antagonist of glycine receptor. NOT active at glycine site on NMDA receptor.

Glutamate

Reuptake

Dihydrokainate	Inhibits neuronal Na dependent uptake
SITS	Inhibits glial Na dependent uptake.

Ionotropic receptors
AMPA (GluR A,B,C,D pentamer. Flip-flop, Q/R RNA editing GluRB)

AMPA	Selective agonist

Kainate (GluR5-7 KA1-2 pentamer. RNA editing, rapid desensitisation

Kainate	Selective agonist

NMDA (NR1(alternative splice) + $NR2_{A,B,C,D}$. sites: glycine (+), pH (low -), ion channel (Mg), redox (SH ^freq), Zn (-), polyamine (+/-), steroid (+)

N methyl D aspartate	Selective agonist
Dizolcipine	Antagonist
Ketamine	Antagonist (channel block)

Magnesium	Antagonist (channel block)
Phenylcyclidine	Antagonist – angel dust!
Glycine	Co-agonist
Dichlorokynurenate	Antagonist at glycine site

Anticonvulsants

Phenobarbitone	$GABA_A$ modulator (barbiturate)	**Suppress focus**, against all but absence. Sedation and tolerance (hepatic enzyme induction) charged not easy to cross BBB
Diazepam	$GABA_A$ modulator (benzodiazepine)	**Suppress spread** (less on focus) status epilepticus. Sedation and tolerance (subunit change)
Clonazepam	$GABA_A$ modulator (benzodiazepine)	Suppress spread (less on focus) status epilepticus and tonic/clonic.
Tiagabine	$GABA_A$ Reuptake	Inhibits GAT-1 Involved in Na dependent uptake. *Adjunctive* in partials
Vigabatrin	GABA inactivation	Inhibits GABA transaminase (GABA – SSA) *Adjunctive* in partials
Valproate	GABA inactivation	Inhibits SSADH (SSA – succinate) AND Na channels. Hence increasing GABA and decreasing Na (synergistic effects). All types INCLUDING **absence** (other anticonvulsants may be contraindicative of absence. Also no sedation so useful for **children**, because can't afford to sedate children continuously – affect learning…
Carbamazepine	Use dependent Na blockers	**Prevent spread**. Partials and tonic/clonic
Phenytoin	Use dependent Na blockers	Prevent spread. All except absence. *Metabolism saturation* so need to increment dose slowly and titrate plasma to monitor concentration
Lamotrigine	Use dependent Na blockers	Prevent spread. Partials and tonic/clonic
Valproate	Use dependent Na blockers	Prevent spread. All types including absence. Useful for children. see above
Ethosuximide	***T type*** calcium channel blockers	**Absence** – first line treatment
Trimethadione	***T type*** calcium channel blockers	**Absence** – first line treatment
Gabapentin	Calcium channel blockers	Adjunct to partials. Sedation. Role in pain – can overdose
Levetiracetam	**N** type calcium channel blockers	Adjunct to partials. ? effect on AMPA/Kainate
Flebamate	Glutamate receptors	NMDA glycine site.

Levetiracetam	Glutamate receptors	AMPA and Kainate receptors. Partials and tonic/clonic.

Absence seizures

Valproate	Block VG Na channel
Ethosuxamide, trimethadione	Block T type Ca channel
Lamotrigine	Block VG Na channel and neuronal Ca channel
Levetiracetam	N type Ca channel
Carbamazepine, tiagabine, vigabatrin	Contraindicated and enhance absence seizures.

Cerebrovascular accident – ischaemic damage. (save the penumbra!!)

Drugs used	Statins, ACEi, Low dose aspirin, anti inflammatory
Future	NMDA-R block (dizolcipine – side effects) newer tolerated ones like DEXTROMETHORPHAN. Zn chelators, free radical scavengers, anti-inflammatory, adenosine agonists, combined AMPA/NMDA block, ?synergy between NMDA-R block and antiapoptotic drugs.

Alzheimers disease (B amyloid plaques and neurofibrillary tangles due to hyperphosphorylated tau. Role of secretins in misprocessin of APP)

Putative drugs for B amyloid generation	B secretase inhibition (b secretase KO is not harmful) B amyloid vaccination (caused brain inflammation in trials) anti-inflammatory (ibuprofen reduces plaque in a mouse model) plaque solubilisation/inhibition of formation cholesterol lowering agents
Tacrine, dunazepil, rivastigmine	AChE inhibitors, in line with the 'cholinergic hypothesis' But weak effect for 12-24 months maimum.

DOPAMINE

Synthesis and inactivation

Carbidopa and benserazide	DOPA decarboxylase inhibition (note all L aromatic aa are substrates at this enzyme – trypyophan and histidine.)
Clorgyline, Selegiline	MAO A and B inhibitors selectively at low concentration
Reserpine	Blocks synaptic vesicle uptake of DA
Amphetamine	Promotes emptying of vesicles increasing $[DA]_I$ thus decreasing efficiency of uptake process.
Cocaine, nomifensine, benztropine, amphetamine	Block Na DA cotransporter, raising DA $t_{1/2}$ in extracellular space.

Dopamine receptors. D1 = g_s D2 = g_i

Dopamine	$D1_A < D1_B$ $D2_A > D2_B$	Agonist

Quinpirole	$D2_A > D2_B$	Agonist
Flupenthixol	Non selective	Antagonist
Sulpiride	Non selective D2	Antagonist (atypical)
Clozapine	C>A=B	Antagonist (atypical)
Haloperidol	A=C>B	Antagonist (typical)
Spiperone	A=C>B	Antagonist (typical)

Parkinson's Disease

L-DOPA	With carbidopa (save for brain) and Domperidone (antagonise CTZ DA receptors). After 5-10yrs side effects – 80% dyskinesias, choreiform movements, 60% decreased efficacy of drug, rapid on/off, psychosis/hallucinations (^DA in mesolimbic system) Because therapeutic window decreases (supersensitivity and more neurones dying) L-DOPA holidays may help. Now aim is to delay L-DOPA use.
Benztropine	Muscarinic cholinergic antagonist – dry mouth, constipation, blurred vision. 1st line treatment. BUT will exacerbate alzheimers symptoms – 'pro-dementia'
Sellegeline	MAO-B inhibitor – no cheese reaction. Delays requirement for L-DOPA for 1 year and may supplement it to allow a reduced dose.
bromocriptine, lisuride, pergolide	Dopamine agonists. May be used as an adjunct to L-DOPA. Reduces 'off' time but may have more serious side effects than L-DOPA.
Entacapone, tolcopone	COMT inhibitor.
Domperidone	Block peripheral DA receptors in the ChemoTrigger Zone.
Adenosine A2A antagonist	Reduce activity of indirect pathway, decrease ACh activity, decrease cortical striatal input. No rapid on-off, no dyskinesias, synergistic with L-DOPA – allowing reduced dose and prolonging onset of side effects.
Future	Antioxidants, glutamate antagonists, glial derived neurotrophic factor (? Neurones simply dormant not dead), transplants.

Schizophrenia

Chlorpromazine Fluphenazine Haloperidol Flupenthixol	A>B=C Antagonist **TYPICALS**	Typical. Little effect on – symptoms. 90% improve (60% on placebo) BUT side effects – motor disturbance ($D2_A$) and tardive dyskinesia (involuntary face and trunk movements) Reduce aggression – apathy plus loss of emotion. Sedation (H_1 block) Postural hypotension (α_1 block). Breast development and lactation (loss of inhibition by TI DA) and side effects of mACh block – dry mouth, constipation and blurred vision. Shows how 'dirty' drugs are.
Clozapine Sulpiride	A<B=C Antagonist	Fewer motor disturbances. Can reverse negative symptoms. Used if typicals don't

Olanzapine Pimozide	**ATYPICALS**	work. [Clozapine may cause agranulocytosis in ~1% of pt, therefore continuous wbc monitoring must be conducted, making the drug expensive and thus use is limited.
Clozapine, olanzapine Risperidone	5-HT_{2C} inverse agonist; D_2 antagonist	The realisation that inverse agonism had an effect to increase firing of VTA and thus has been found to increase DA in PFC and hence decreasing negative symptoms. Note, typicals are only 5-HT antagonists so the increase in VTA firing is less.
Clozapine [Typical + idazoxan]	D_2 antagonist and α_2 block	Also shown that α_2 block may have and effect. Shown to reduce negative symptoms. Shows how clozapine is 'dirty'!

Serotonin

5-HT_{1A} (g_i Raphe – presynaptic inhibition)

Buspirone	Agonist (anxiolytic) partial
Pindolol	Antagonist

5-HT_{1B} (g_i – presynaptic inhibition)

Methysergide	Agonist
Pindolol	Antagonist

5-HT_{1C} (g_i – alters blood vessel diameter of brain)

Sumatriptan	Agonist (migrane therapy)
Spiperone	Antagonist

5-$HT_{2A\,B\,C}$ (g_q – excitation) (c-thought to excite GABA interneurones - ↓VTA)

A-methyl-5-HT	Agonist
Ketanserin	Antagonist

5-HT_3 (ion channel – depolarisation)

Biguanides	Agonist
Ondansetron	Antagonist (+chemo – antiemetic)

DEPRESSION

Phenelzine tranylcypromine	MAOi	Non selective, irreversible. Thus cheese effect. Also must be careful because MAO ~2-3 weeks to be resynthesised thus if give drugs requiring ^ MAO activity can lead to fatal hypertension.
Moclobemide	MAOAi	Selective. No cheese effect since B still active. Reversible so other drugs can be administered immediately.
Imipramine, amytriptiline	Tricyclics	Inhibit NA and 5-HT uptake. Dirty, having effects at other receptors – α_1, α_2, H_1 (block – sedation), mACh (block – dry mouth…)
Nomifensine	NA SRI	

Citalopram fluoxetine	SSRI	Highly specific, long $t_{1/2}$ 3 weeks to C_{ss}. Nausea side effect (^5-HT in gut) overdose non lethal, efficacy in ~60%.
Mianserin		Not fully understood. No action on monoamine uptake. α_2 block (? ^NA by blocking autoreceptors) H1 block (sedation) 5-HT_{2A} 5-HT_{2C} block.
Iprindole		Evidence against monoamine theory – no effect on MA. Unknown mechanism, no sedation and may not be very efficacious
FUTURE		Substance P antagonist – failed at phase III CRH antagonist - ? implicated in stress induced depression. In phase III

Manic phases of depression *(15% suicide so must be controlled)*

Lithium	Inhibits IMP phosphatase
Valproate	Inositol uptake inhibition. *Anticonvulsant*
Carbamezepine	*Anticonvulsant*
Lamotrigine	*Anticonvulsant*
Anti pshychotics	