**Migraine treatment**

Non-pharmacological

- Rest in quiet dark room – avoid movement or any activity and digital screens
- Cognitive behavioural therapy
- Stress management – relaxation, massage, yoga, meditation, acupuncture, chiropractor
- Trigger factors – stress, irregular sleep, skipping meals, food, smoking, perfume/odour
- Headache diary for 4-6 weeks – attack duration, severity, symptoms, triggers, treatments used

First-line therapy

- Aspirin or NSAID – ideally soluble due to gastric stasis, impaired absorption, nausea
    - Avoid aspirin <18yo – refer children to paediatrician if not managed with simple analgesics
    - Take medication as early as possible in the attack
- Anti-emetic drugs – improve absorption of analgesics, relieve nausea
- Avoid opioid analgesics including codeine – worsen nausea, dependence, side effects

| Line | Analgesics | Dosing | Anti-emetics | Dosing |
|---|---|---|---|---|
| 1st | Aspirin *soluble* | 600-900mg q4h | Domperidone | 10-20mg |
| | Diclofenac | 50-100mg q6h | Metoclopramide | 10-20mg |
| | Ibuprofen | 200-400mg q6h | Prochlorperazine | 5-10mg |
| | Naproxen | 550-825mg q6h | | |
| 2nd | Paracetamol *soluble* | 1g q4h | | |

Second-line therapy

- Use if no improvement with NSAIDs after 1-2h, or treatment has failed in previous attacks
    - Initiate at lower dose – if tolerated but ineffective, titrate up in subsequent attacks
    - Work best when taken as soon as possible after headache (not aura) begins
    - Except naratriptan (slower onset), other oral triptans – 30-60 min for relief
- Ergotamine – stimulates $\alpha_1$, $D_2$, 5-$HT_{1B}$, 5-$HT_{1D}$ receptors for vasoconstriction – poor selectivity
- Avoid triptans and ergotamines in vascular or coronary artery disease, or uncontrolled HBP
    - Eletriptan and naratriptan are not substrates of MAO-A – safe for use with MAOIs
- Headache may return within 24h in 30% triptan patients – use additional dose
    - If there is *no response* to initial triptan dose, do *not* repeat
- ADRs – drowsiness, fatigue, tingling/heat/tightness sensations, flushing, dizziness, nausea

| Line | Drug | Dosing | Maximum dose |
|---|---|---|---|
| 3rd | Eletriptan | 40-80mg | 160mg/24h |
| | Naratriptan | 2.5mg | 5mg/24h |
| | Rizatriptan | 10mg wafer dissolved on tongue | 30mg/24h |
| | Sumatriptan | 50-100mg oral; 10-20mg intranasal | 300mg/24h; 40mg/24h |
| | Zolmitriptan | 2.5-5mg | 10mg/24h |
| | Ergotamine | 1-2mg | 6mg/day and 10mg/week |
| 4th | Dihydroergotamine | 0.5-1mg SC or IM | 3mg/day and 6mg/week |
| | Sumatriptan | 6mg SC | 12mg/24h |

Migraine prophylaxis

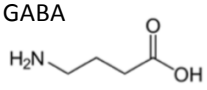
- Suitable if ≥3 attacks per month – unresponsive to acute treatment, severe QoL impairment
- Requires dose titration to minimise ADRs – takes 1-3 months for full benefits
- If well-controlled for 3-6 months, taper dose over 1-2 weeks to assess continuing need

| Drug | Target dose | Common ADRs |
|---|---|---|
| Propranolol (non-selective) | 20mg 2-3xd (max 160mg/day) | Hypotension |
| Metoprolol (selective) | 25-100mg 1-2xd | Hypotension |
| Amitriptyline | 10mg at night (max 75mg/day) | Anticholinergic |
| Sodium valproate | 200mg BD (max 800mg/day) | Weight gain, tremor, hair loss |
| Topiramate | 25mg 1D (max 50mg BD) | Nephrolithiasis, acute glaucoma |
| Pizotifen | 0.5-1.5mg N (max 1.5mg TID) | Sedation, weight gain, anticholinergic |

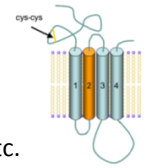
**GABA neurotransmission**

GABA

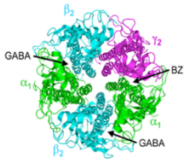
- Major inhibitory neurotransmitter – highly abundant in many interneurons and projection neurons
- Synthesis: α-ketoglutarate → glutamate (excitatory) + decarboxylase (GAD) → GABA
- Applications for increasing GABA neurotransmission:
    - Epilepsy, Huntington's, anxiety, depression, alcoholism, addiction



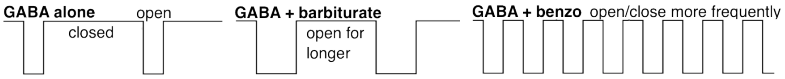

$GABA_A$ receptors




- Cys-loop ligand-gated ion channel (ionotropic)
    - $GABA_A$ activation → $Cl^-$ influx → hyperpolarisation → inhibitory effect
- Each receptor contains 5 subunits from: $\alpha_{1-6}$, $\beta_{1-3}$, $\gamma_{1-3}$, δ, ε, π, θ
    - 30% amino acid sequence identity between α/β/γ… and 70% between $\alpha_{1-6}$, etc.
- Large intracellular loop between TM units 3-4 – anchors receptor to cell membrane surface
    - TM unit 2 lines $Cl^-$ channel pore
- 85% of $GABA_A$ receptors contain $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_{1/2/3}\gamma_2$
    - All receptors include α and β subunits
    - GABA binds at α-β interface
    - Two GABA molecules must bind for channel to open




| Drug | Modulation of $GABA_A$ receptors | Binding location |
|---|---|---|
| Bicuculline | Competitive antagonist of all $GABA_A$ receptors | All $GABA_A$ receptors |
| Benzodiazepines | ↑GABA activity – increases frequency of channel opening | α1/2/3/5 and γ interface |
| Barbiturates | ↑GABA activity or acts alone – prolongs channel open time<br>Slows dissociation of GABA from receptor | All $GABA_A$ receptors |
| Ethanol | ↑GABA activity – prolongs channel open time | Transmembrane domain |
| General anaesthetics | ↑GABA activity<br>May directly stimulate receptors at high concentrations | α and β interface |
| Neurosteroids | E.g. allopregnanolone – promote channel opening | δ subunit most sensitive |

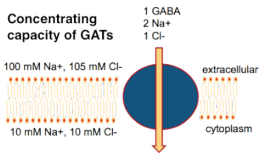



$GABA_B$ receptor

- 7 transmembrane G-protein coupled receptor (metabotropic)
    - Dimer – $GABA_{B1}$ binds GABA, $GABA_{B2}$ binds $G_i$-protein
    - $G_i$ – reduces cAMP, activates $K^+$ channels (efflux) and inhibits $Ca^{2+}$ channels
- Presynaptic $GABA_B$ autoreceptors – inhibit GABA and glutamate release
- $GABA_B$ agonists:
    - Baclofen – muscle relaxant, inhibits glutamate release (phaclofen = antagonist)
    - γ-Hydroxybutyric acid (GHB/fantasy) – treat narcolepsy and alcoholism
        - High concentrations – sedation, ataxia, euphoria, amnesia, hypothermia
        - Agonist at $GABA_{B1}R$ and subset of $GABA_A$ ($\alpha_4\beta_1\delta$: binds GABA binding site)

GABA transporters

- $Na^+$ dependent neurotransmitter transport family – GABA, DA, 5-HT, NAd & glycine transporters
- 4 subtypes of GABA transporters ($GAT_{1-4}$) – expressed throughout CNS neurons and glial cells
- GAT is homologous to LeuT which co-transports leucine with $Na^+$ ions
    - Shot glass shape – 12TM domains
    - GAT: GABA is co-transported with $2Na^+$ and $1Cl^-$
- $GAT_1$-selective inhibitors – increase GABA transmission
    - Nipecotic acid, tiagabine (anticonvulsant)




| Activity | Influx | Effect | Receptors |
|---|---|---|---|
| Excitation | $Na^+$ influx | Depolarisation (more positive mV) | Glutamate |
| Inhibitory | $Cl^-$ influx | Hyperpolarisation (more negative mV) | GABA |

Treatment

- Based on severity – clinical impression, Hamilton scale (HAM-D), Beck scale, questionnaires
- Mild (psychotherapy), moderate to severe (pharmacotherapy), severe (electroconvulsive therapy)
    - St John's wort – superior to placebo, as effective as (but fewer ADRs than) antidepressants
- Generally continue drugs for 6-9 months after remission of depressive episode, then review
    - Greatly reduces risk of relapse, antidepressants not associated with addiction
- All antidepressants are approximately equi-effective and have similar tolerability

| **Drugs** | **Mechanism of action** | **Examples** |
|---|---|---|
| SSRI | Inhibit serotonin reuptake | Citalopram, sertraline, fluoxetine, paroxetine |
| SNRI | Inhibit serotonin and NAd reuptake | Duloxetine, venlafaxine, desvenlafaxine |
| TCA | Inhibit serotonin and NAd reuptake | Amitriptyline, nortriptyline, imipramine, doxepin |
| MAOI | Inhibit MAO (5-HT, NAd and DA) | Tranylcypromine, phenelzine |
| RIMA | Reversibly inhibits MAO-A | Moclobemide |
| Agomelatine | Melatonin ($MT_1$ and $MT_2$) receptor agonist and 5-$HT_{2C}$ antagonist | |
| Mirtazapine | Presynaptic blockade of central $\alpha_2$-adrenergic inhibitory receptors<br>Postsynaptic blockade of 5-$HT_2$ and 5-$HT_3$ receptors | |
| Reboxetine | Inhibits noradrenalin reuptake, weakly inhibits serotonin reuptake | |

Serotonin toxicity

- Overstimulation of 5-$HT_{1A}$/$_{2A}$ receptors
    - Restlessness, diaphoresis (sweating), tachycardia, tremor, myoclonus/rigidity, confusion, convulsions, coma, death
- Contributors – antidepressants, St John's wort, stimulant and illicit drugs, lithium, linezolid
    - Opioids – tramadol, pethidine, dextromethorphan, fentanyl

Selective serotonin reuptake inhibitors (SSRIs)

- Citalopram, escitalopram, dapoxetine, fluoxetine, fluvoxamine, paroxetine, sertraline
- Indications – depression, anxiety disorders (OCD), bulimia nervosa, premenstrual dysphoric disorder, PTSD (paroxetine), insomnia (except fluovoxamine/paroxetine)
    - First-line for depression in adults
    - Not approved for use in children in depression – increased risk of suicidal ideation (2-4%)
- Review after 2 weeks (1 week if risk of suicide)
    - If response is absent or minimal after 3-4 weeks of treatment, increase dose or switch drug
- ADRs – nausea, diarrhoea, agitation, tremor, dry mouth, dizziness, headache, sweating, anxiety
    - Lethargy, myalgia, weight changes, sexual dysfunction, rhinitis, rash, bleeding risk (>80yo)
    - Insomnia – take in morning
    - Drowsiness – fluvoxamine, paroxetine
    - Suicidal thoughts on initiation, manic episodes, may reduce seizure threshold

| | |
|---|---|
| **CYP1A2/3A4 inhibitors** | Fluvoxamine (strong) |
| **CYP2D6 inhibitors** | Clomipramine, fluoxetine (strong), paroxetine (strong), sertraline (weak) |

Monoamine oxidase inhibitors (MAOIs)

- Second line – depression, anxiety disorders (panic disorder, phobias)
- Tyramine can induce hypertensive crisis
    - Tyramine ↑NAd release, MAO-A inhibition blocks NAd degradation
- Avoid tyramine-containing foods – during therapy and for 2 weeks after ceasing
    - Cheese, fermented/cured meats (salami), yeast extracts (Vegemite), avocado, pineapple, sauerkraut, soy bean extracts (tofu, miso)

Serotonin-noradrenalin reuptake inhibitors (SNRIs)

- Venlafaxine, desvenlafaxine, duloxetine
    - Lower doses (SRI) vs. higher doses (SNRI)
- ADRs – suicidal thoughts on initiation, seizures, manic episodes, bleeding risk in >80yo