Pharmacological management of anxiety disorders

Overview

- Problem statement
- Anxiety disorders and neurobiological targets
- Principles of management
- Modes of treatment
- Classes of drugs
- Treatment guidelines for individual disorders
- Children and adolescents
- Future possibilities
- Summary: key points
- References

Problem statement

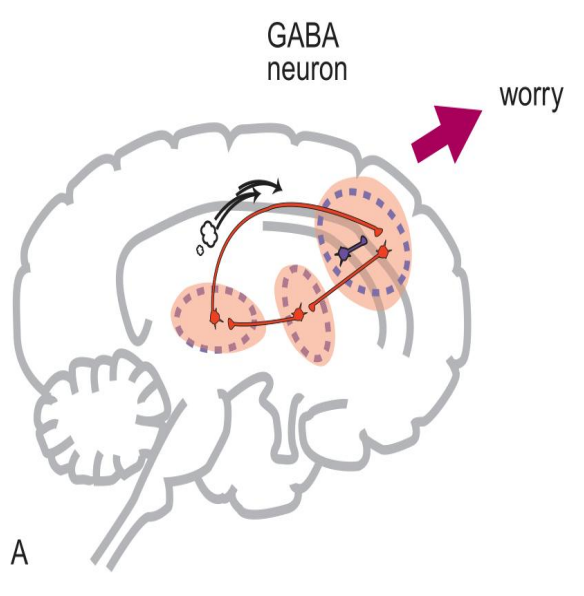
- Most widely diagnosed
- Long-term, fluctuating
- Societal and personal burden
- Global Burden of Anxiety- 10% DALY
- Under-diagnosed and under-treated
- ‘medicalization’ concern

Anxiety disorders

- GAD
- Panic disorder
- Agoraphobia
- Social phobia/ social anxiety disorder
- Specific phobia
- OCD
- PTSD

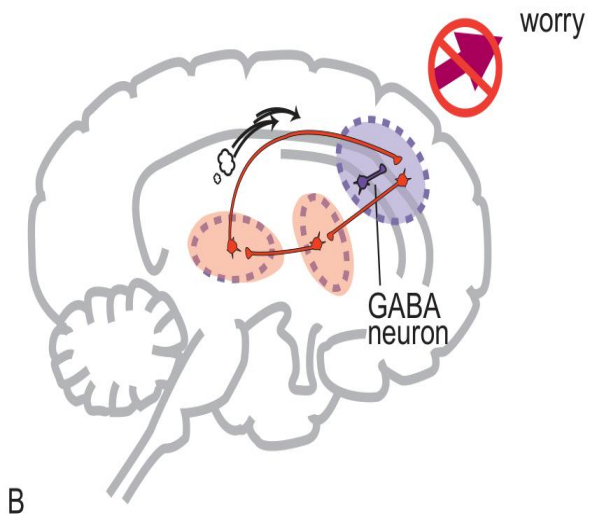
Removed in DSM-5 and ICD- 10

Neurobiology of anxiety



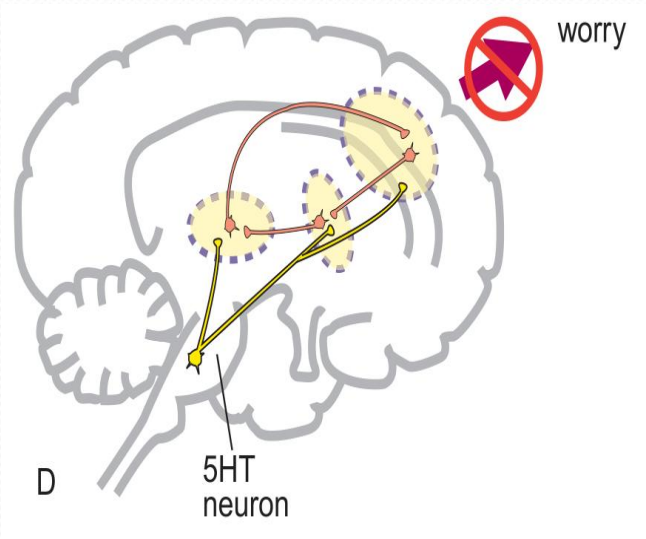
- Pathological worry - overactivation of cortico-striato-thalamo-cortical (CSTC) circuits.

Neurobiology of anxiety



- GABAergic agents such as benzodiazepines may alleviate worry by enhancing the actions of inhibitory GABA interneurons within the prefrontal cortex

Neurobiology of anxiety



- The prefrontal cortex, striatum, and thalamus receive input from serotonergic neurons, which can have an inhibitory effect on output. Thus, serotonergic agents may alleviate worry by enhancing serotonin input within CSTC circuits.

Neurobiology of anxiety

Neurochemical	Association with Anxiety Disorders	Treatment Approaches
Serotonergic system	Low activity of post synaptic 5-HT1A receptors in PD & SAD	SSRIs & SNRIs – 1st line therapy for anxiety disorders
Noradrenergic system	Unrestrained, excessive system activation	SNRIs – 1st line therapy for anxiety disorders Ppnl – performance anxiety
Dopaminergic system	Excessive mesocortical dopamine release, persistently high levels of dopamine in prefrontal cortex	NDRI (buproprion) – adjunct for anxiety disorders
Hypothalamic-pituitary-adrenal axis	Dysregulated HPA axis function (excessive cortisol release, abnormal feedback)	Cortisol – under study for SAD & spider phobia Mifepristone – under study for GAD & PD

Neurobiology of anxiety

Neurochemical	Association with Anxiety Disorders	Treatment Approaches
Corticotropin-releasing hormone	Persistently increased CRH concentration	CRH-1 receptor antagonists - no efficacy demonstrated in trials
Ɣ-amino butyric acid (GABA)	Reduced GABA-A & BZD binding in PD; Reduced GABA levels in PD, possible imbalance between tonic GABAergic inhibition and glutamate-mediated excitation	SGRI (Tiagabine) & GABA transaminase inhibitor (Vigabatrin) – potential treatment Tiagabine – equivocal findings in GAD Topiramate (blocks voltage-gated sodium channel and potentiates GABA) – mixed findings pregabalin

Neurobiology of anxiety

Neurochemical	Association with Anxiety Disorders	Treatment Approaches
Glutamate	Possible imbalance between tonic GABAergic inhibition and glutamate-mediated excitation in PD	Efficacy of DCS – adjunct to exposure therapy for acrophobia, SAD and PD NMDA receptor antagonist (Riluzole) – potential anxiolytic for GAD Glycine transporter and Metabotropic transporter under study
Endocannabinoid system	Dysregulation of endocannabinoid signalling	Cannabidiol – reduces anxiety in SAD during public speaking

When to treat anxiety?

	Normal anxiety	Pathological anxiety
Apprehension	Proportional to trigger	Out of proportion, irrational, illogical
Attention	External trigger > body response	Body response > external trigger
Features	Adaptive, improves functioning	Significant distress, impaired functioning

Principles of management

- Diagnostic assessment

1. Medical and psychiatric comorbidities
2. Life stressors
3. Genetic vulnerability.

- Physical examination
- Laboratory assessments
- Psycho-education -adherence and self-management techniques.
- Systematic monitoring-structured instruments and scales.

Patient-Related Factors Influencing Choice of Treatment

- Severity and chronicity of illness
- Presence of medical and/or psychiatric comorbidity
- Personal or family history of response to a proposed intervention
- Concomitant medications and possibility of drug interactions
- Situation-specific versus generalized nature of symptoms (eg: performance anxiety-related panic attacks)
- Patient preference

Patient-Related Factors Influencing Choice of Treatment

- Insight and likelihood of adherence
- Psychological-mindedness and motivation to change thoughts and behaviour
- Accessibility and cost of treatments

Modes of treatment

PHARMACOTHERAPY

- SSRI
- SNRI
- TCA
- MAOI, RIMA
- NOVEL ANTIDEPRESSANTS
- BZD
- ANTI-EPILEPTICS
- SGA
- OTHERS

PSYCHOTHERAPY

- CBT- exposure, relaxation
- Family therapy
- Insight-oriented therapy
- Supportive therapy

SSRI

- Effective in broad spectrum of anxiety disorders
- First-line by most guidelines
- Start at half the initial anti-depressant dose for GAD & PD- initial anxiogenic effect, std dose in SAD
- Reach to antidepressant dose
- Citalopram, sertraline- bottom range
- Paroxetine- higher dose

SSRI

- Onset of response- 3 to 4 weeks
- Trial- 8-12 weeks at therapeutic doses

- ADRs

1. Nervousness, insomnia, drowsiness, git s/e, sexual dysfunction
2. serotonin syndrome, NMS, hyponatremia, agranulocytosis, osteoporosis, increased risk of GI bleeding

SNRI

- Venlafaxine, desvenlafaxine, duloxetine
- First-line- similar efficacy and s/e profile
- Initiation same as SSRI
- ADR-

1. sweating, dry mouth, constipation
2. dose-related hypertension

- Desvenlafaxine- dual uptake inhibition at lower dose and better tolerability

TCA

- Equally efficacious
- Replaced by SSRI and SNRI
- ADR (cholinergic, histaminic and alpha-1 blockade)

1. Hypotension, dry mouth, blurred vision, and constipation
2. Jitteriness
3. Cardiac s/e
4. Seizures
5. Potential fatal overdose

Antidepressant use concern

- **Suicidality-**

1. Black box warning in children and young adults.
2. Low absolute risk versus impairment caused by anxiety
3. Least- citalopram and fluoxetine

Antidepressant use concern

- **Discontinuation syndrome**

1. Abrupt stop- 2-4 days post cessation
2. increased anxiety, irritability, tearfulness, dizziness or lightheadedness, malaise, sleep disturbance, and concentration difficulties.
3. shorter half-lives- more risk
4. Gradual taper

MAOI & RIMA

PHENELZINE, TRANYLCYPROMINE

- Irreversible
- Phenelzine- PD & SAD
- Hypertensive crisis

MOCLOBEMIDE

- reversible
- RCT- effective
- Not as efficacious
- Tolerance
- Alternative to SSRI and SNRI in generalized SAD

Novel anti-depressants

- **Mirtazapine**
  1. anxiety symptoms in elderly
  2. Increased sleep and appetite, sexual s/e low
- **Bupropion**- adjunctive in residual symptoms
- **Vortioxetine**
  1. Mixed results in GAD
  2. Effective in anxiety symptoms in MDD
- **Agomelatine-** GAD
- **Milnacipran-** GAD and PD

Benzodiazepines

- Enhance GABAnergic action- anxiolytic effect
- Efficacious, rapid onset and well-tolerated
- Short and intermediate acting- alprazolam and lorazepam

Benzodiazepines

- Use-

1. Brief 3-4 week adjunct to anti-depressant : improve response and counter initial jitteriness and insomnia
2. PRN- acute exacerbation, performance anxiety, PD(not by NICE)
3. Monotherapy- failure/intolerance of other agents, disabling severe anxiety
4. Those who have stabilized on BZD for years with no dependence

Benzodiazepines

- ADR

1. Dizziness and sedation
2. Alcohol comorbid use
3. Tolerance and abuse potential
4. Dementia

- Not recommended- comorbid depression or substance use disorder

Anticonvulsants

- **Pregabalin**

1. RCT- monotherapy/ adjunctive
2. Acute treatment and prophylaxis
3. Several anxiety disorders
4. Improve sleep and depressive symptoms
5. Dose- initial 150 mg, therapeutic- 600 mg
6. ADR- sedation and dizziness, avoid in renal impairment

- Gabapentin, levetiracetam, topiramate, tiagabine and lamotrigine- adjunctive

Anti-psychotics

- SGA- SDA and decreased ADR
- Lacking/ equivocal evidence
- **Quetiapine-**

1. RCT
2. monotherapy / augmentation agent
3. acute and maintenance treatment of GAD

Other medications

- **Beta-blockers**

1. Physical symptoms
2. PRN basis- performance anxiety
3. Fixed regimen
4. Propranolol-20 to 40 mg per dose
5. Atenolol- 25-50 mg per dose
6. Dose titration- 10 bpm reduction
7. C/I- cardia, pulmonary, angle closure glaucoma, DM
8. Alternative – PNR BZD

Other medications

- **Buspirone**

1. Partial agonist- 5-HT1A
2. 30-60 mg/day in 3 divided doses
3. Effective in GAD
4. Anecdotal evidence as adjunctive in others

- **Hydroxyzine**

1. GAD
2. Short-term alternative to BZD

Novel agents

- **rTMS-**

1. Comorbid anxiety and depression
2. Case reports- SAD and PD
3. Trial- fMRI guided- GAD

- **Kava**

1. Mild-moderate anxiety
2. Hepatotoxicity

Novel agents

- **Yoga-** performance anxiety

- **Lysine**
- **Mg-Ca combination**

} Mild anxiety

Pros and cons of various classes

Class	Advantages	Disadvantages
SSRIs	Well-tolerated Safe in overdose Little weight gain Once-daily dosing	Initial activation Nausea, headache Insomnia initially Sexual side effects
SNRIs	Similar to SSRIs	Hypertension
BZDs	Rapid efficacy Reduce anticipatory anxiety Well tolerated No initial activation Safe in overdose	Sedation Memory problems Withdrawal Abuse potential Rare sexual dysfunction

Pros and cons of various classes

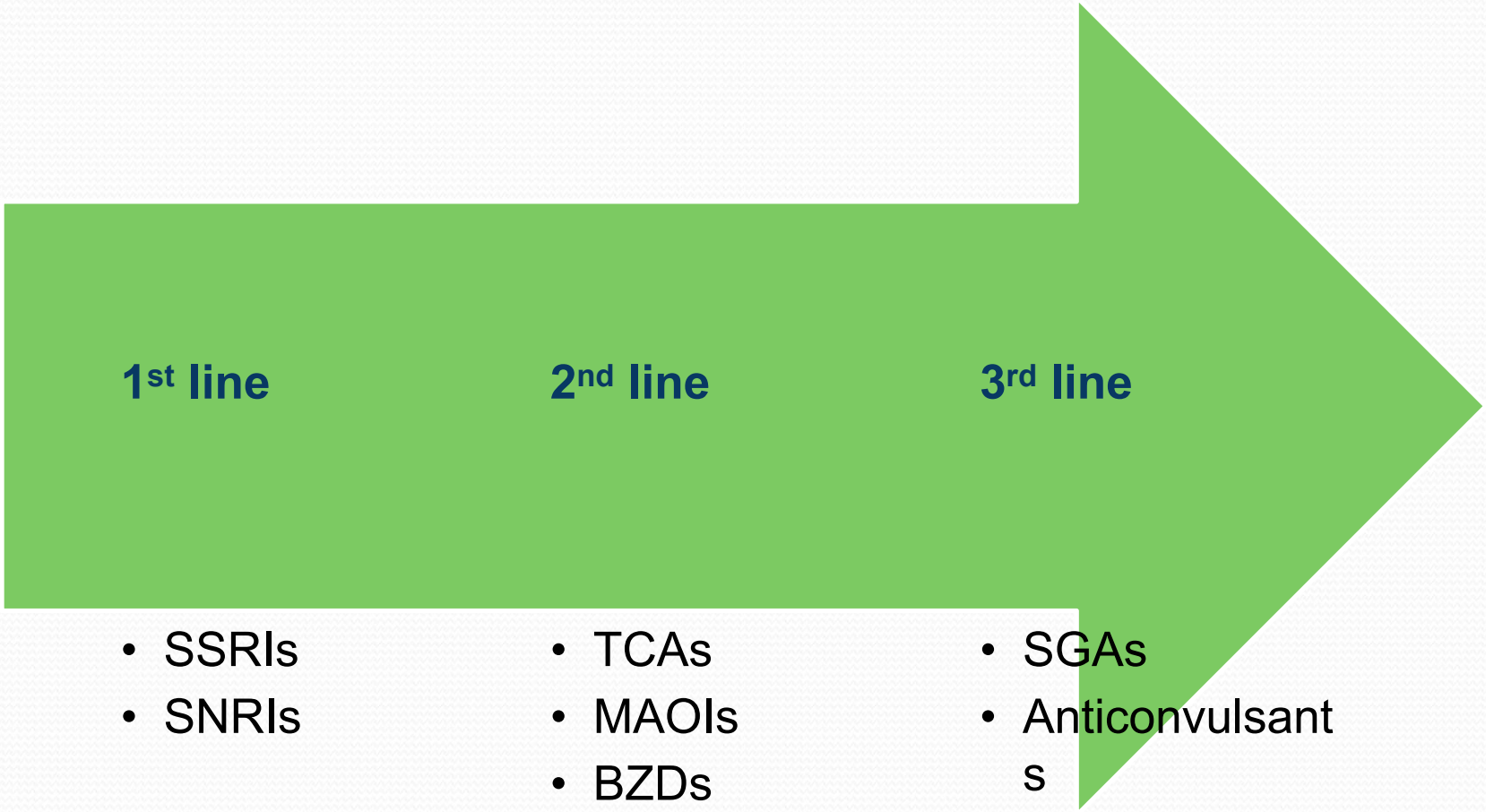
Class	Advantages	Disadvantages
TCAs	Single daily dose Less expensive Long experience Antidepressant	Initial activation Anticholinergic A/E Weight gain Orthostatic hypotension Dangerous in overdose Sexual dysfunction
MAOIs	More effective against comorbid depression Antidepressant	Dietary restrictions Hypertensive crisis (rare) Initial activation Insomnia Onset delayed Anticholinergic A/E Orthostatic hypotension Dangerous in overdose

Classes & Agents	GAD	PD	SAD
SSRIs	1st line	1st line	1st line
SNRIs	1st line	1st line	1st line
TCAs	2nd line	2nd line	Not recommended
MAOIs	Insufficient evidence	2nd line	2nd line
RIMA	Insufficient evidence	Insufficient evidence	2nd line
Agomelatine, Buspirone, Mirtazapine	2nd line	2nd line	2nd line
Benzodiazepines	2nd line	2nd line	2nd line
SGA - Quetiapine	2nd line	Insufficient evidence	Not recommended
Anticonvulsant - Pregabalin	2nd line	Insufficient evidence	2nd line

class	drug	FDA indications	Dose range(mg/day)
SSRI	Escitalopram	GAD	10-20
	Fluoxetine	OCD, PD	20-60
	Fluvoxamine	OCD, SAD	100-300
	Paroxetine	GAD, OCD, PD, PTSD, SAD	20-50
	Sertraline	OCD, PD, PTSD, SAD	50-200
SNRI	Duloxetine	GAD	60-120
	Venlafaxine	GAD, PD, SAD	75-225
BZD	Alprazolam	PD, anxiety(non-specific)	1-4
	Chlordiazepoxide	anxiety(non-specific)	15-40
	Clonazepam	PD	1-4
	Diazepam	anxiety(non-specific)	2-10

class	drug	FDA indications	Dose range(mg/day)
	Lorazepam	anxiety(non-specific)	1-6
	Oxazepam	anxiety(non-specific)	30-120
TCA	Clomipramine	OCD, PD	25-250
	Imipramine	PD	100-200
MAOI	Phenelzine	PD	45-90
antihistamine	Hydroxyzine	anxiety(non-specific)	200-400
Asapirone	Buspirone	anxiety(non-specific)	20--60

Panic disorder



Panic disorder

Class	Drug	Starting dose (mg/day)	Therapeutic range (mg/day)
SSRIs			
	Paroxetine	10-12.5 CR	10-40
	Fluoxetine	2.5-10	10-20
	Sertraline	25	50-200
	Citalopram	10	20-30
	Escitalopram	5	5-10
	Fluvoxamine	50	100-300
SNRIs			
	Venlafaxine	37.5	75-225

Panic disorder

Class	Drug	Starting dose (mg/day)	Therapeutic range (mg/day)
TCAs			
	TID or QID		**Acute total daily dose**
	Clomipramine	25	25-150
	Imipramine	10	50-200
MAOIs			
	Phenelzine	15	15-45
	Tranylcypromine	10	10-40

Panic disorder

Class	Drug	Starting dose (mg/day)	Therapeutic range (mg/day)
BZDs			
	BID		
	Alprazolam	0.25-0.5	2-10
	Clonazepam	0.25-0.5	1-4
	Lorazepam	0.5	1-7
	Diazepam	5	5-40

Panic disorder

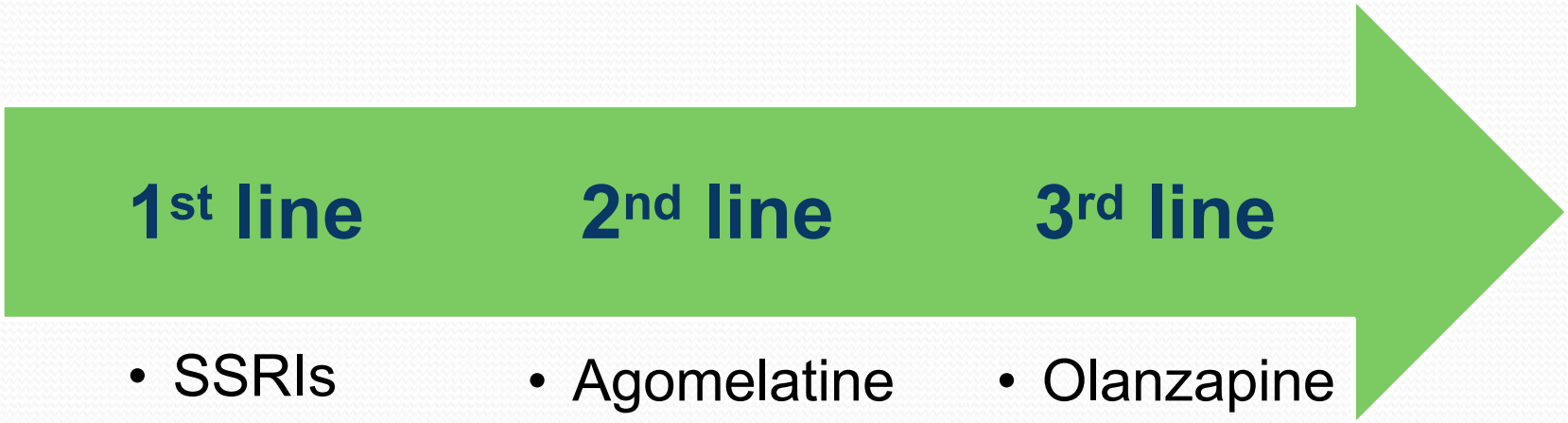
- Paroxetine
1. Sedative effects, immediate calm
2. Better compliance
3. Less discontinuation

- PD + depression- fluoxetine, venlafaxine
- Alprazolam- rapid control
- Anticipatory anxiety- clonazepam
- BZD- not recommended by NICE

Agoraphobia

- Mostly comorbid with PD > social phobia, GAD, avoidant personality disorder
- Treat comorbid condition
- No effective pharamacotherapy evaluated so far for pure agoraphobia- negative finding- TCA, BZD, MAOI

GAD



- SSRIs
- SNRI

- Agomelatine
- Pregabalin
- Buspirone
- Quetiapine
- Imipramine

- Olanzapine
- Risperidone
- Aripiprazole
- Bupropion

DOSE

SSRI s	Recommended initial dose	Daily dose mg/day
Fluoxetine	5 mg / day	20 - 80
Fluvoxamine	50 mg/day	100 - 300
Paroxetine	10 mg/day CR : 12.5 mg/day	20 – 50 25 - 75
Sertraline	25 – 50 mg/day	50 - 200
Citalopram	10 mg/day	20 -60
Escitalopram	5 mg/day	10 – 30
Venlafaxine er	37.5 mg/day	75-225

GAD

- Not recommended-propranolol,tiagabine,ziprasidone
- Maintainence-

1. SSRI, SNRI, pregabalin,quetiapine
2. 6 months

SAD

- ‘Generalized’ and ‘performance’
- First line initiate
- Refractory

1. Switch
2. Phenelzine
3. Augmentation- pregabalin and clonazepam
4. Combine with CBT
5. Subgroups- high doses

- Performance- beta blockers

SAD

- SSRIs
- Venlafaxine
- Pregabalin
- Clonazepam

- Mirtazapine
- Moclobemide
- Gabapentin
- Bromazepam
- Alprazolam

- SGAs
- Anticonvulsants

SAD

- Incremental continued response
- Maintainence - 6 months

Specific phobia

- First line- psychotherapy
- Second line- SSRI
- Treat comorbid depression and anxiety symptoms

Children and adolescents

- SSRI- effective in GAD, SAD and seperation anxiety, selective mutism
- Black box- suicidality
- Second line if psychotherapy fails/ symptoms severe

Future possibilities

- Corticotrophin-releasing factor type 1 (CRF-1)–receptor antagonists
- Metabotropic glutamate receptor agonists
- Agents promoting neurogenesis
- Cannabidiol

Pharmacotherapy: Key Pointers

- SSRIs/SNRIs – 1st line
- Start low and go slow
- Routine increase to higher doses not recommended
- Short-term concomitant benzodiazepine helpful in initial treatment
- Assess after optimum doses given for 8-12 weeks
- Maintenance treatment for at least up to 6 months, preferably up to 1-2 years

Pharmacotherapy: Key Pointers

- Dose reduction/ discontinuation- 10 to 25% gradual decrements in about 1 month
- Response rates

1. PD- 60-70 %
2. GAD and SAD- 50-60 %

Pharmacotherapy: Key Pointers

- partial or non- responders:
- Switch- another 1st line
- Augment- BZD
- Combine- psychological treatment
- Sequential CBT

References

- Sadock, Benjamin J.; Sadock, Virginia A.; Ruiz, Pedro Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 10th Edition 2017 Wolters Kluwer

- David M. Taylor, Thomas R. E. Barnes, Allan H. Young. The Maudsley prescribing guidelines in psychiatry. 13th edition 2018 John Wiley & Sons

References

- Sadock BJ, Sadock VA. Kaplan and Sadock's synopsis of psychiatry: Behavioral sciences/clinical psychiatry. Lippincott Williams & Wilkins; 2011 Dec 26.

- Gelder MG, Juan J, Nancy A. New Oxford textbook of psychiatry, Vol 1 & 2. Oxford: Oxford university press; 2004.

References

- Murrough JW, Yaqubi S, Sayed S, Charney DS. Emerging drugs for the treatment of anxiety. Expert opinion on emerging drugs. 2015 Jul 3;20(3):393-406.

Thank you