

Migraine Comorbidities and Their Impact on Management

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Specialist Registrar Teaching Weekend on Headache Disorders

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Migraine Comorbidities

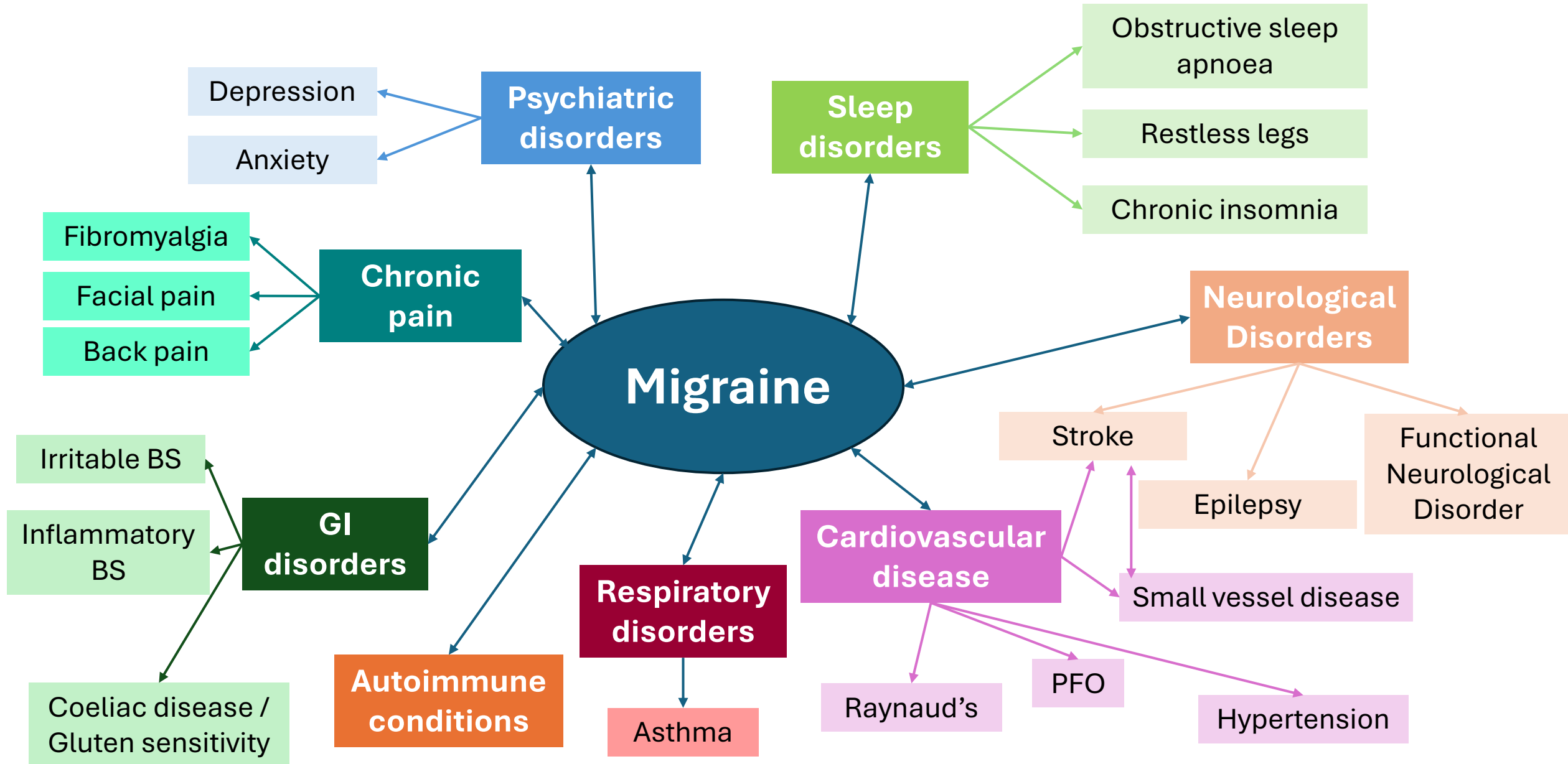
- Prior studies have found that migraine occurs together with other illnesses at a greater coincidental rate than is seen in the general population = comorbidities
- Why detecting them?
 - Co-occurrence may complicate diagnosis
 - It can help improving treatment strategies
 - Further understanding of the possible pathophysiology of migraine
- How many/How important? → depends on review paper

Comorbidities as a risk factor from migraine

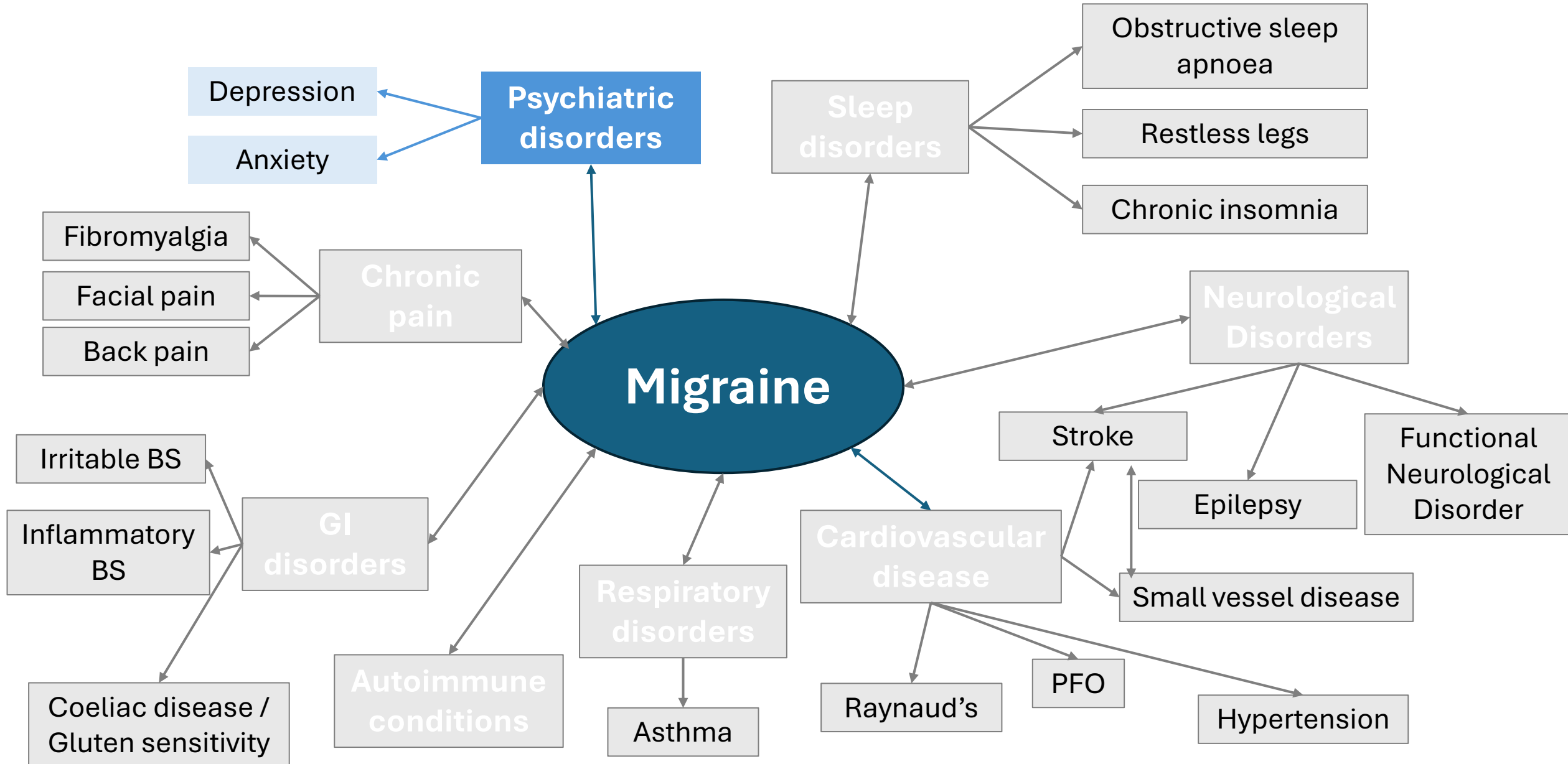
- A systematic search → 17,330 records → 38 studies identified → 124 effect sizes from 58 exposures
- Pre-existing conditions significantly associated with new migraine onset:
 - Atopic conditions
 - Psychiatric disorders
 - Sleep disorders
 - Cardiovascular diseases
- Likely due to :
 - shared genetic predisposition
 - mediating factors like stress and inflammation

Atopic conditions/ disorders	Allergic conjunctivitis	Autoimmune and inflammatory conditions/ disorders	Chronic osteomyelitis
	Allergic rhinitis		Autoimmune disease
	Atopic dermatitis		Rosacea
	Asthma		Chronic periodontitis
Psychiatric and psychological conditions/ disorders	Food allergy	Metabolic conditions/ disorders	Psoriasis
	Depression		Fibromyalgia
	Anxiety		High C-Reactive Protein (CRP) ^a
	Anxiety and depression		Recurrent gastrointestinal disturbance
	ADHD		Gallbladder stone disease
	Autism spectrum disorder		Chronic kidney disease
	Low sense of coherence		Diabetes mellitus
Sleep conditions/ disorders	Pavor nocturnus	Other conditions/ disorders	Hyperlipidemia
	Sleepwalking		Abdominal migraine
	Sleep-related breathing disorders		Benign paroxysmal vertigo
	Insomnia		Bruxism
	Sleep disorder		Cyclic vomiting
	Sleep duration <3.5h or 3-5h		Chronic obstructive pulmonary disease
	Incomplete circle of Willis: any/anterior/ posterior		Neck/back/head injury
Cardiovascular conditions/ disorders	Fetal configuration circle of Willis		Osteoporosis
	Coronary artery disease		Marfan syndrome
	Hypertension		Nasal septum deviation
	Stroke		Back pain
	Diastolic blood pressure (increments)		Infantile colic
	Systolic blood pressure (increments)		Asphyxia, retinopathy of prematurity or bronchopulmonary dysplasia
			Neurological problems

Common comorbid disorders of migraine



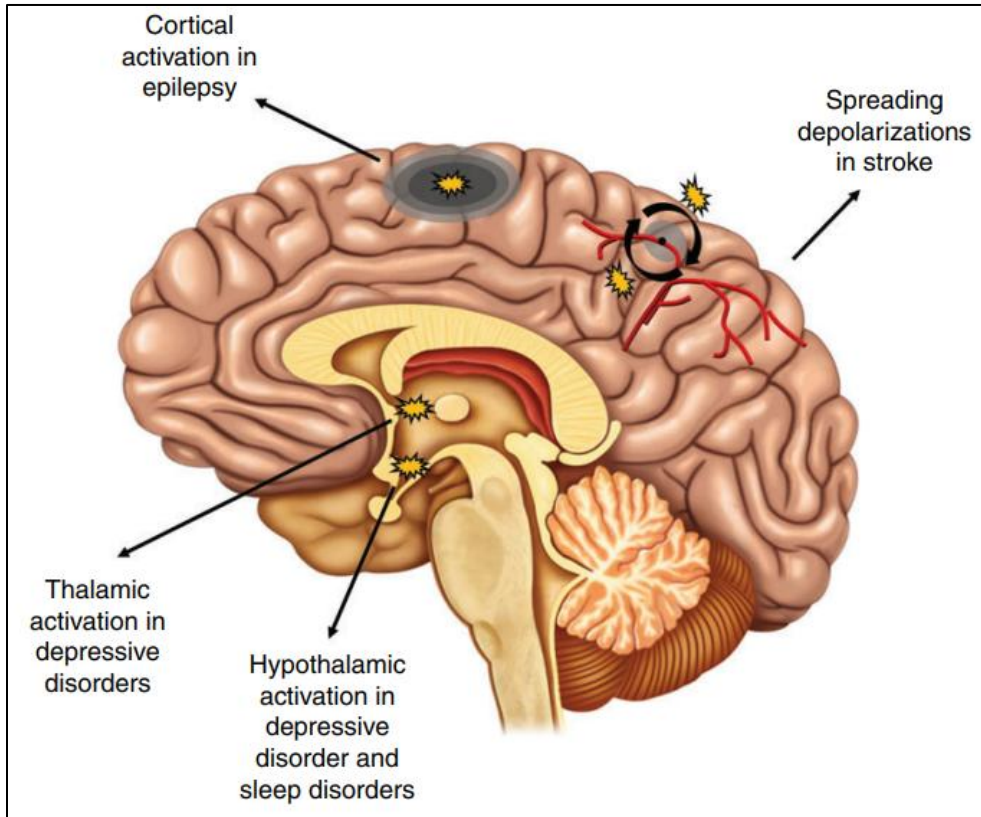
Common comorbid disorders of migraine



Migraine and psychiatric disorders

- **Depression:** bidirectional association
 - risk of new onset migraine in people with depression: 2.8 - 3.5
 - risk of new onset of depression in people with migraine: 2.4 - 5.8
- Psychological distress was related to a poorer health-related quality of life in patients with migraine
- Disabling chronic headache → ↑ fq of somatic complaints (OR 8.6) and major depressive disorder (OR 25.1) and panic disorders
- Patients with chronic migraine and depression, ↑fq of medication overuse
- Presence of major depression was a poor outcome predictor in patients with chronic daily headache (RR = 1.8)

Migraine and psychiatric disorders



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- Shared pathophysiological pathways:
 - Decreased thalamic activity in chronic migraine and depression
 - Altered neurotransmitters balance: serotonin, dopamine, others
- Shared genetic susceptibility:
 - Cross-disorder genetic correlation → ion channel dysregulation
- Shared environmental factors:
 - Exposure to stress → CRF release → depression

Migraine and psychiatric disorders

Consequences in clinical practice:

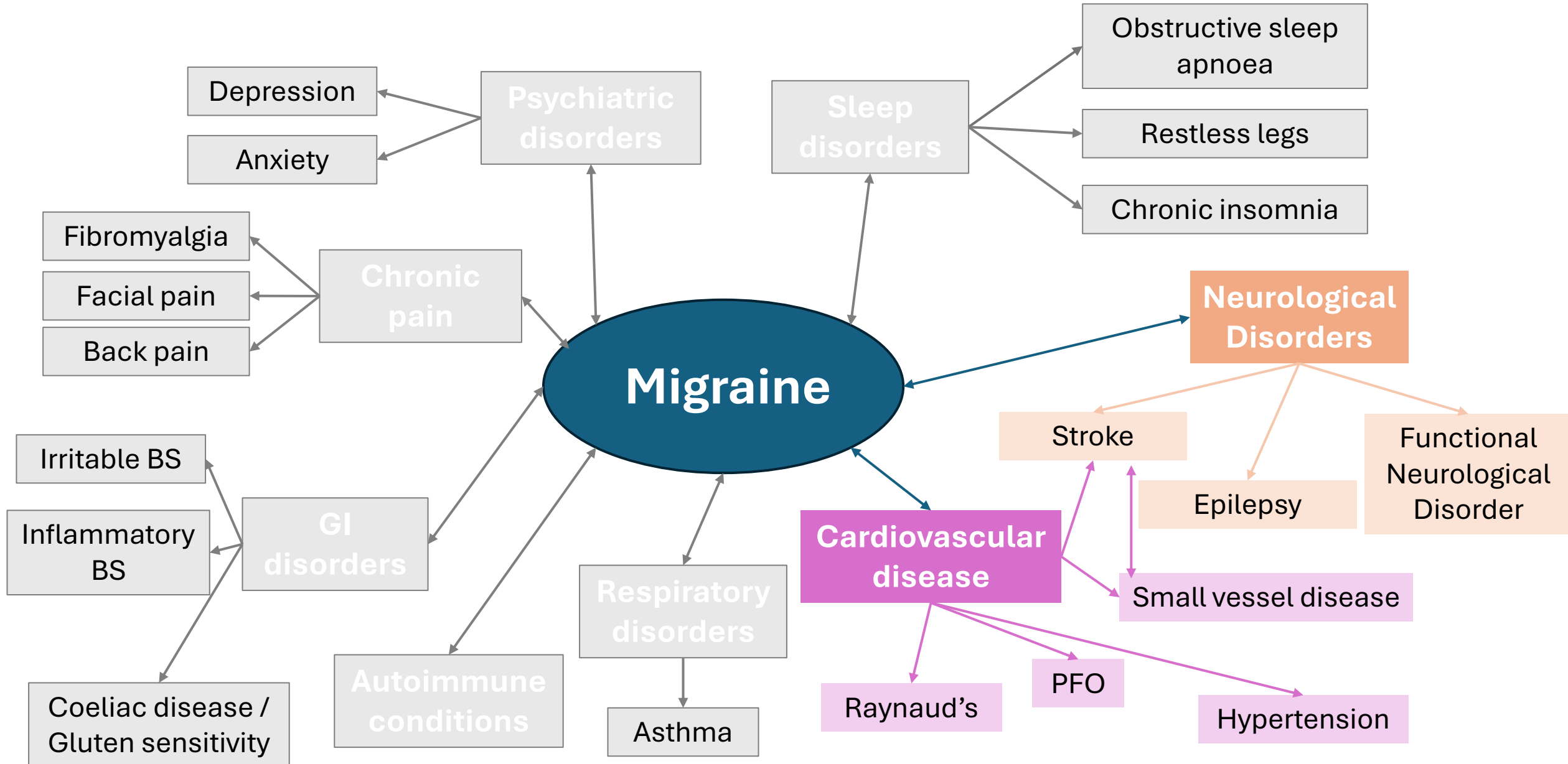
Condition	Acute treatment	Prophylactic treatment	Safety concerns
Depression	• Be aware of medication overuse (especially in high-frequent migraine) • If medication overuse is present, withdrawal of acute medication should be considered as first-choice treatment	• Valproate (mood stabilizer) • Amitriptyline (especially if tension type headache is also present)	• Risk of serotonin syndrome in patients taking SSRI/SNRI and triptans is low • Flunarizine, topiramate and beta-blockers may provoke depressive symptoms

- Onabotulinumtoxin A → poorer response was associated with depressive symptoms
- CGRP- monoclonal antibodies → presence of depression or depressive symptoms was associated with a poorer response
- Post-hoc analysis: fremanezumab → effective in chronic migraine in patients with comorbid depression compared with placebo (Headache 2021; 61)

Migraine and psychiatric disorders

- **Generalised anxiety disorder:** bidirectional association
 - 9.1% of migraine patient have anxiety (OR = 3.9)
 - Triad of Migraine-Anxiety-Depression (anxiety in early childhood, early onset migraine and depression episodes in adulthood)
- **Panic disorder:** ↑ fq in migraine and severe headaches
- **Bipolar disorder:** fewer studies, young adults
- **Suicidal ideation and attempt:** young adults, migraine with aura and high frequency of headache

Common comorbid disorders of migraine

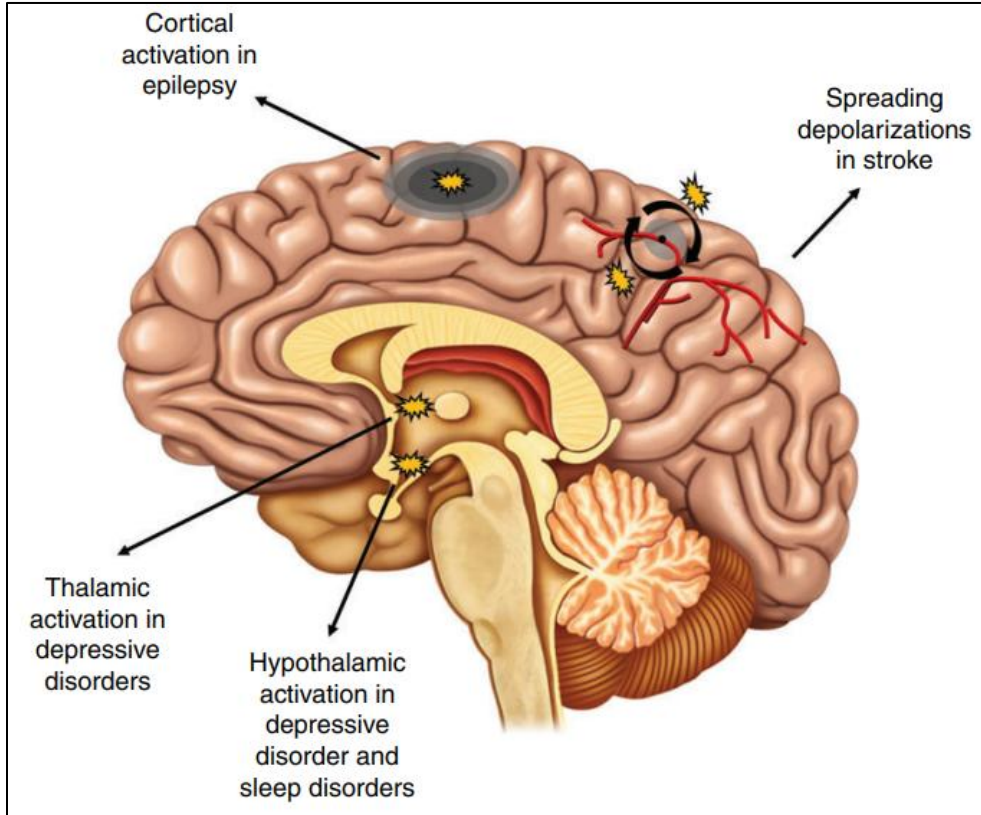


Migraine and cardiovascular disease

- **Stroke and Migraine with Aura**

Migraine and risk of Stroke	RR
Migraine with aura	2
Migraine without aura	Uncertain
Men Vs Women	1.4 Vs 2
Women > 45yo	3.6
Oestrogen oral contraception (MwA)	7
Oestrogen oral contraction + Smoking (MwA)	10

Migraine and Stroke



- Shared pathophysiological pathways:
 - Cortical spreading depolarization → a wave of neuronal and glial cell depolarization, followed by a prolonged phase of nerve cell depression + hypoperfusion
 - Endothelial dysfunction
 - CTP in migraine is normal but prolonged (motor) aura: ↓ perfusion (CTP)
 - Animal studies: Mice with Hemiplegic migraine had larger ischaemic strokes
- Shared genetic susceptibility:
 - Several cerebral hereditary angiopathies are associated with migraine and cerebrovascular disease: CADASIL, RVCL-S, CAA, MELAS
- Shared environmental factors:
 - Smoking, Oestrogen containing oral contraception

Shared genetic factors (monogenic syndromes)

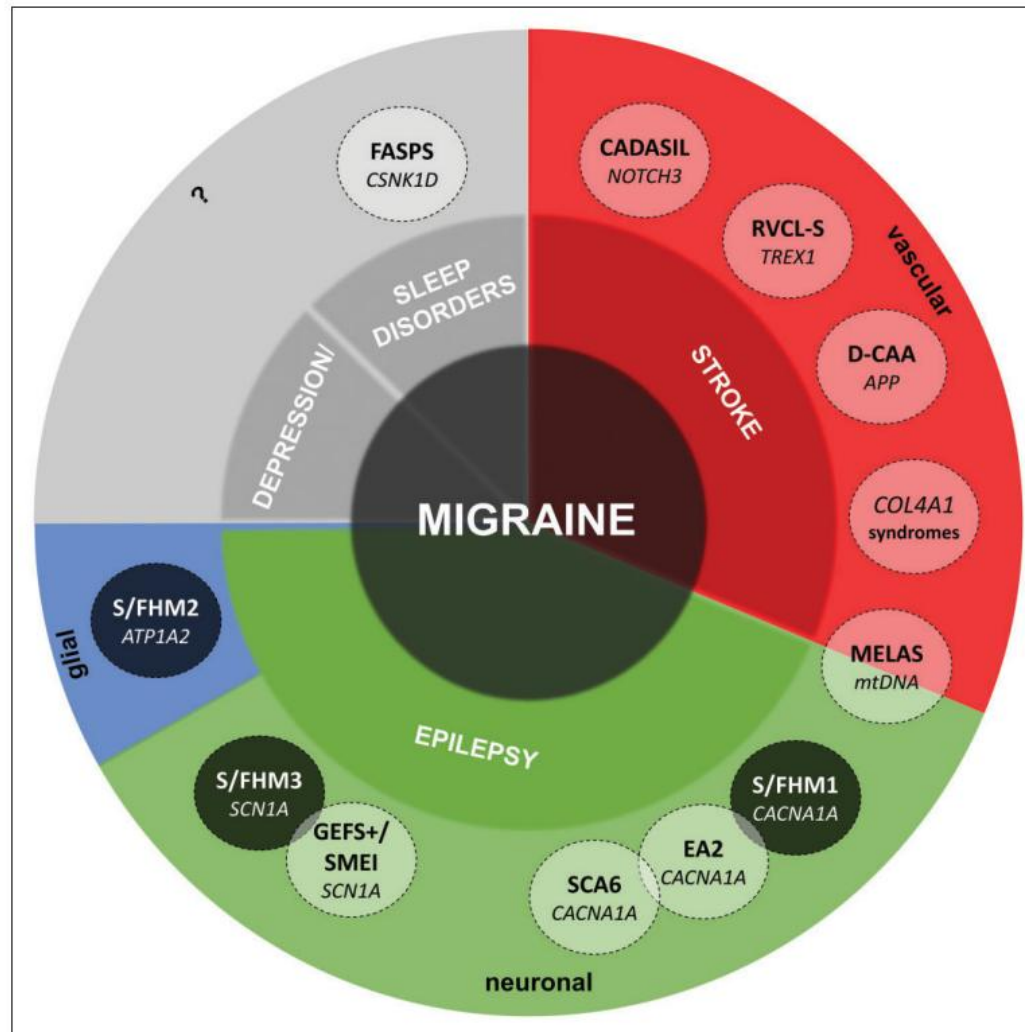


Figure 2. Monogenic syndromes associated with migraine and comorbidity with stroke, epilepsy, depression and sleep disorders.

Migraine and stroke

Consequences in clinical practice:

- Triptans are contraindicated in patients with ischaemic heart disease and stroke and uncontrolled hypertension due to VC effects
 - Increasing evidence that the risk is lower than initially thought
- CGRP has a vasodilation effect and most studies excluded patients with CV disease → further safety evidence needed
- Ditans do not carry VC effect
- Migraine is a stroke mimic, IV Thrombolysis seems safe in patients with migraine → use IVT if in doubt

Migraine and cardiovascular disease

- **Small vessel disease:**

- White matter hyperintensities and posterior lesions more common in MwA (CAMERA study)
- Infratentorial lesions in border zone cerebellar areas
- Hypoperfusion and emboli as main mechanisms

- **Hypertension:** controversial

- Multiple studies showing positive and negative association
- Ample studies showing hypotensive medication improving headache frequency
- CGRP monoclonal antibodies (Erenumab, Fremanezumab) may increase BP

- **Patent foramen ovale:** shunt right-to-left associated to MwA and Stroke

- Paradoxical emboli = ischaemic stroke
- Small bubbles/debris in blood may trigger MA and ischaemia
- PFO closure indicated in cryptogenic cortical strokes but not migraine

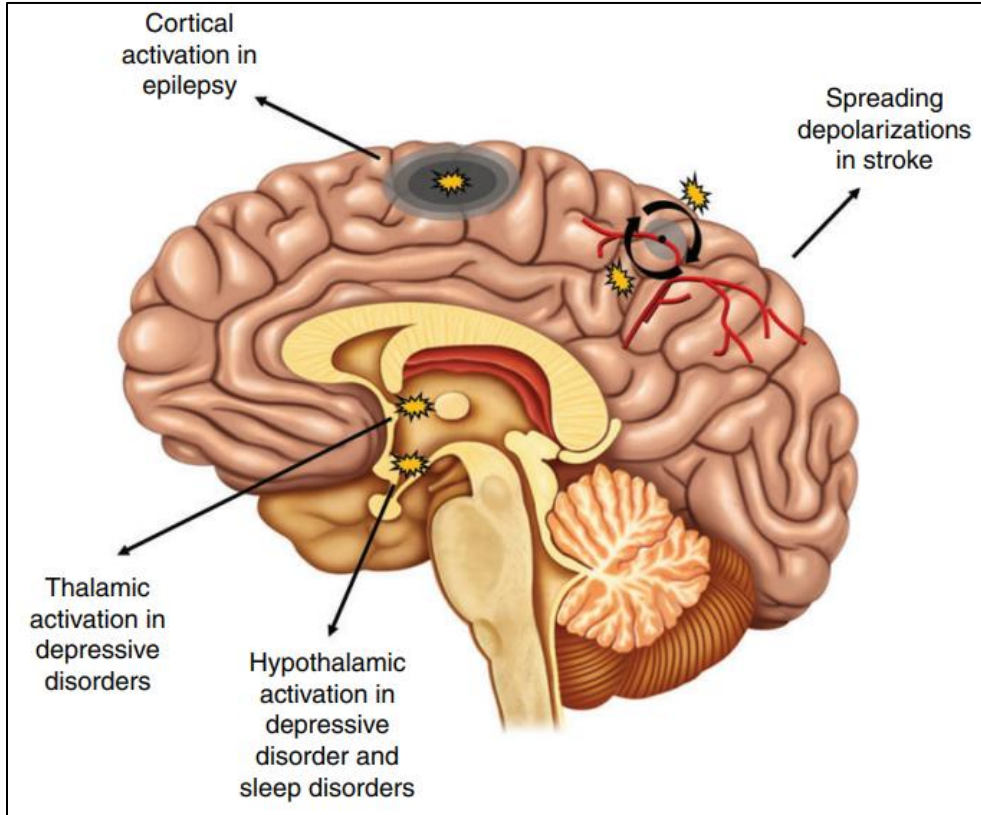
- **Raynaud's:** positive association

- Caution with betablockers and CGRP therapies

Migraine and epilepsy

- Lifetime prevalence of migraine is increased in epilepsy patients (OR 1.5)
- Lifetime prevalence of epilepsy is increased in migraine patients (OR 1.8)
- Familial hemiplegic migraine: 40% epilepsy (genetic commonalities)
- Clinical situations:
 - Migraine with aura triggering a seizure
 - Ictal headache in focal seizures is rare (tension type phenotype)
 - Post ictal headache more frequent (migraine phenotype)
- Patients with epilepsy and migraine: ↑ treatment resistance

Migraine and epilepsy



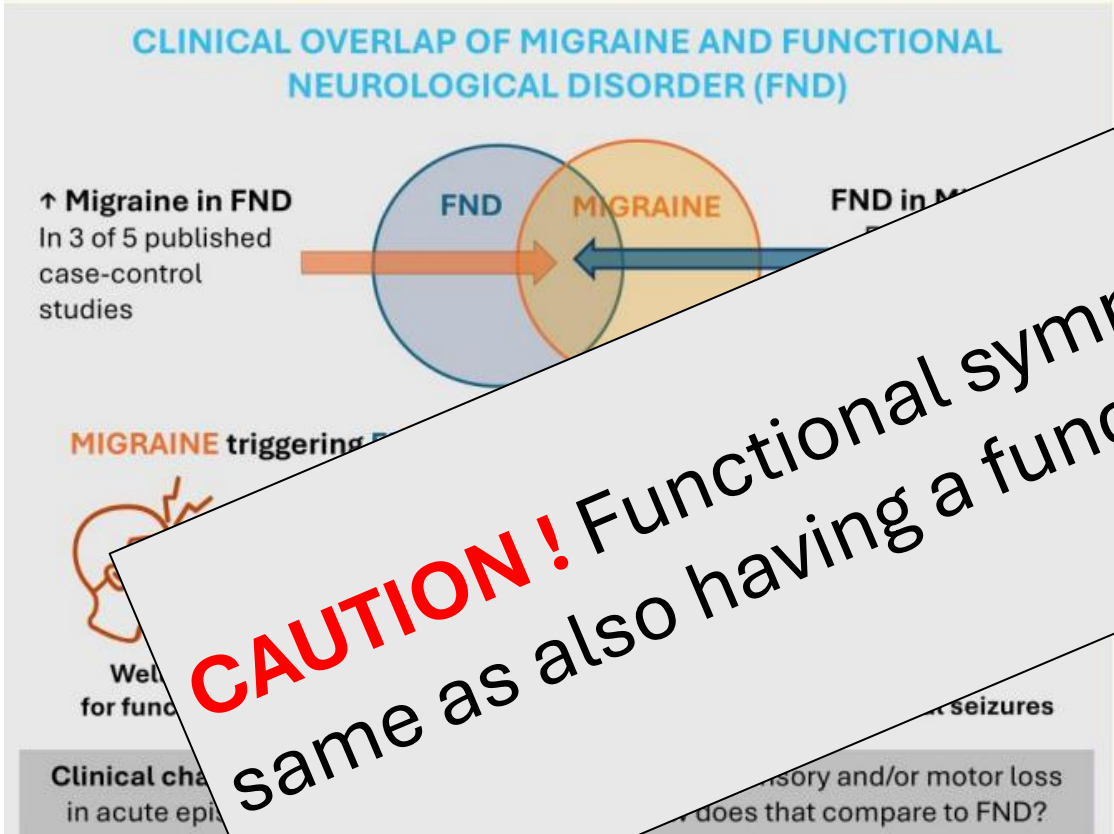
- Shared pathophysiological pathways:
 - Neuronal hyperexcitability causing:
 - Cortical spreading depression in migraine
 - Synchronous firing of cortical neurons
 - Repolarization phase after a seizure of CSD lowers the threshold for one another → co-occurrence
- Shared genetic susceptibility:
 - Overlapping involvement of genes encoding ion transporters → CACNA1A, ATP1A2, SCN1A, and PRRT2
- Shared environmental factors:
 - Brain damage due to traumatic head injury or stroke may cause post-traumatic headache resembling migraine and increases the risk of epilepsy
 - Shared triggers: stress, sleep deprivation, fatigue, alcohol, hormonal changes

Migraine and epilepsy

Consequences in clinical practice:

- Migraine with aura and focal seizure: clinical similarities/differences
 - Visual and Sensory aura may be similar
 - Post ictal headache has migraine phenotype
 - Aura tends to develop over a longer period and last longer
- Valproate, Topiramate and Lamotrigine preferred medications for patients with epilepsy and migraine *
 - *HMRA regulation for use of VPA and TPM in < 55
- SCN1A mutation should not be treated with sodium channel blockers

Migraine and functional neurological disorders



CAUTION! Functional symptoms during migraine is not the same as also having a functional neurological disorder

Disorder	Trigger
Limb injury/Migraine	
Syncope/Panic attack	
Brain injury	
Vestibular insult/ Mig	

Migraine and functional neurological disorders

- Shared demographics:

- Females
- Childhood maltreatment
- Life stress
- Comorbidities

	FND	Migraine	MS	Epilepsy
Female sex	~75%	~75%	~75%	~50%
Onset < 11 yrs	-	+	-	++
11-18 yrs	++	++	+	+
18-65 yrs	+++	++	++++	+
> 65 yrs	+	+	+	++
Childhood maltreatment	+++	+	+	+
Life stress	+++	++	+	+
Psychiatric Disorder comorbidity	+++	++	++	++
Functional Disorder comorbidity	+++	+	+	+

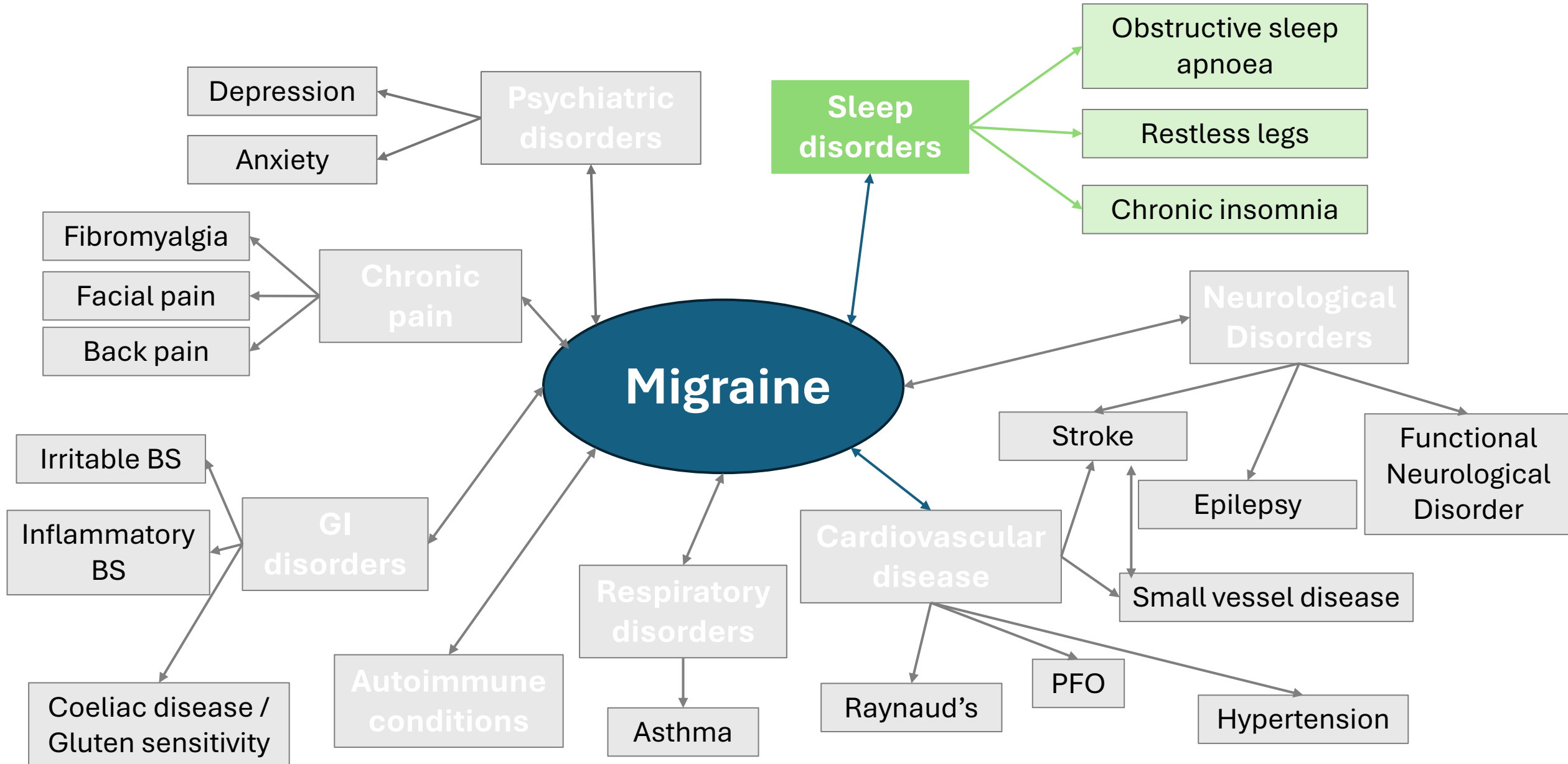
- Shared genetic susceptibility:

- Migraine is moderately heritable
- Genetic research in FND is in its infancy, reported family clustering

- Shared comorbidities:

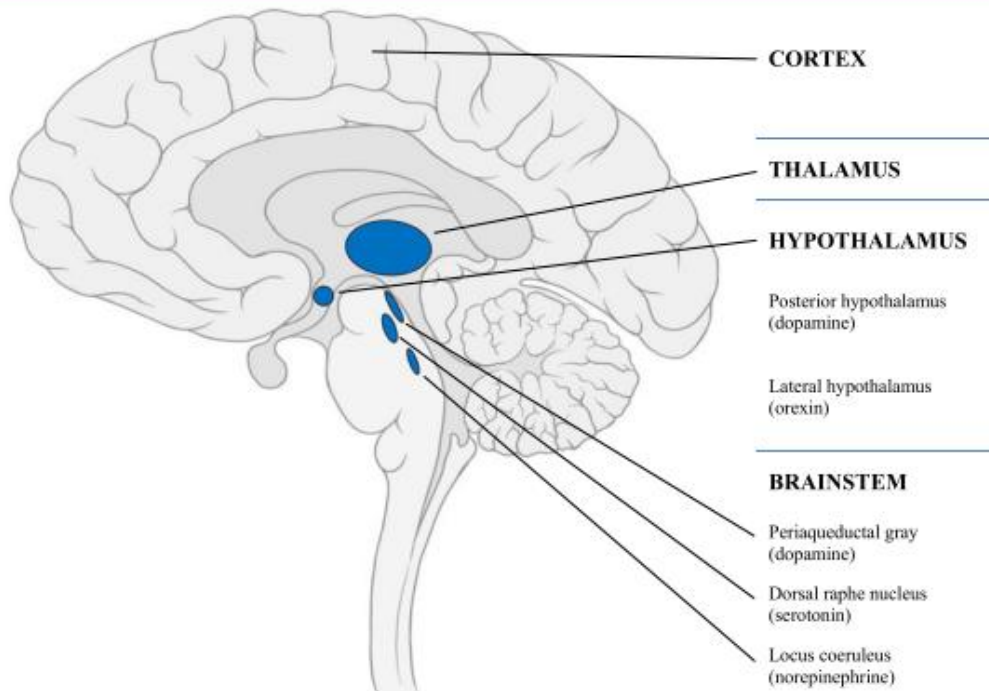
- Psychiatric: depression, anxiety, PTSD
- FND: chronic pain, irritable bowel syndrome, chronic fatigue syndrome

Common comorbid disorders of migraine



Migraine and sleep disorders

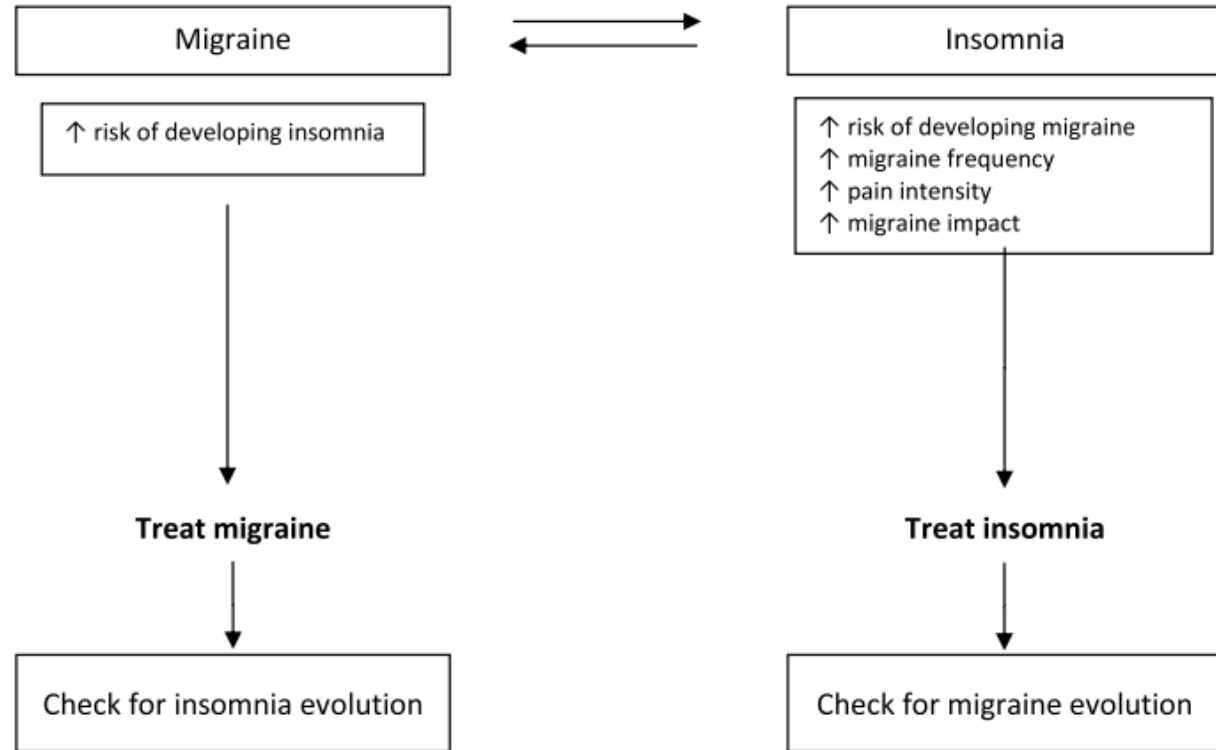
SHARED ANATOMICAL STRUCTURES



- Common neurobiological mechanisms:
 - Transition from wakefulness to sleep →
 ↑ Deafferentation (thalamus/brainstem/cord)
 - When sleep is reduced → ↓ in pain threshold
- Shared neurotransmitters:
 - Orexinergic system (orexin A, B) → wakefulness + pain sensitivity modulation
 - Melatonin (pineal gland) → circadian rhythms/sleep maintenance + analgesic effect
 - Adenosine (A1, A2 rec) → sleep stimulator, increased in migraine attacks
 - Serotonin → wakefulness stimulator, anti-nociceptive
- Shared environmental factors:
 - Common emotional background: anxiety, vulnerability to stress, low self esteem, maladaptive behaviours in relation to the disease
 - Coexistence of anxiety and depression

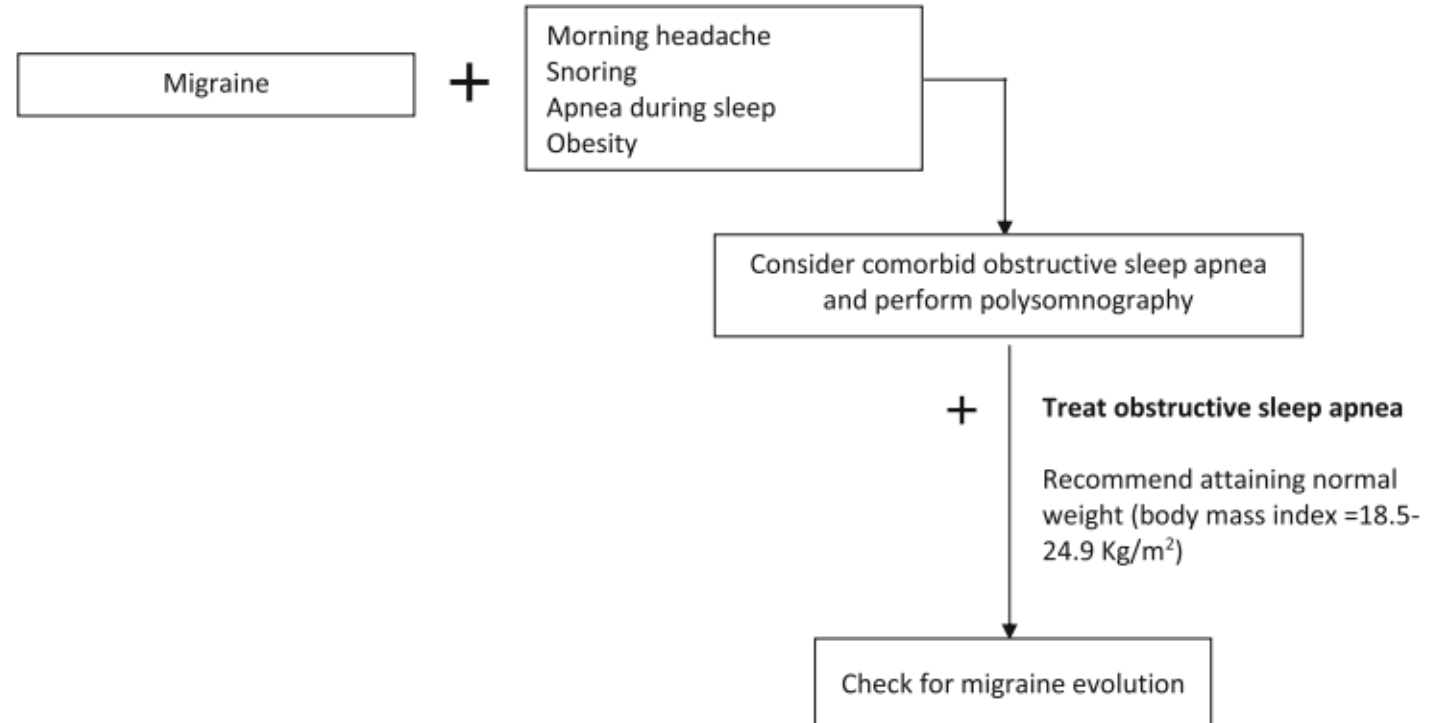
Migraine and insomnia

The Journal of Headache
and Pain (2020) 21:126



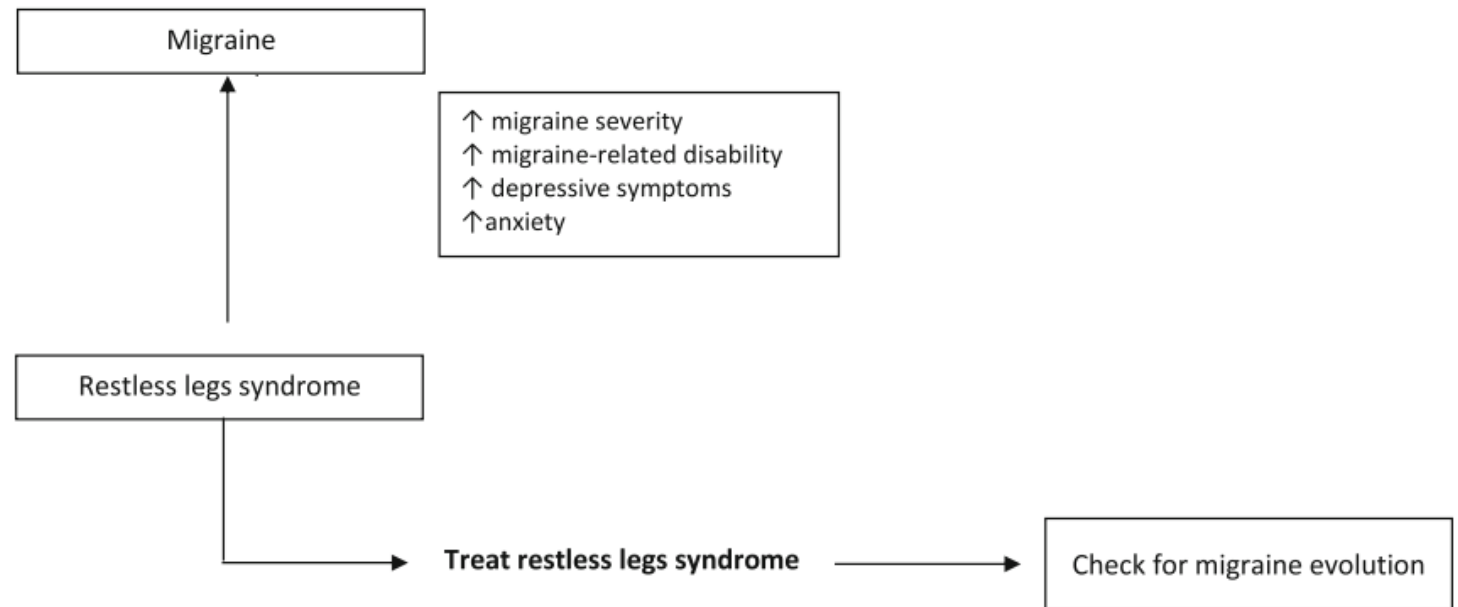
Migraine and sleep apnoea

The Journal of Headache
and Pain (2020) 21:126



Migraine and restless legs

The Journal of Headache and Pain (2020) 21:126

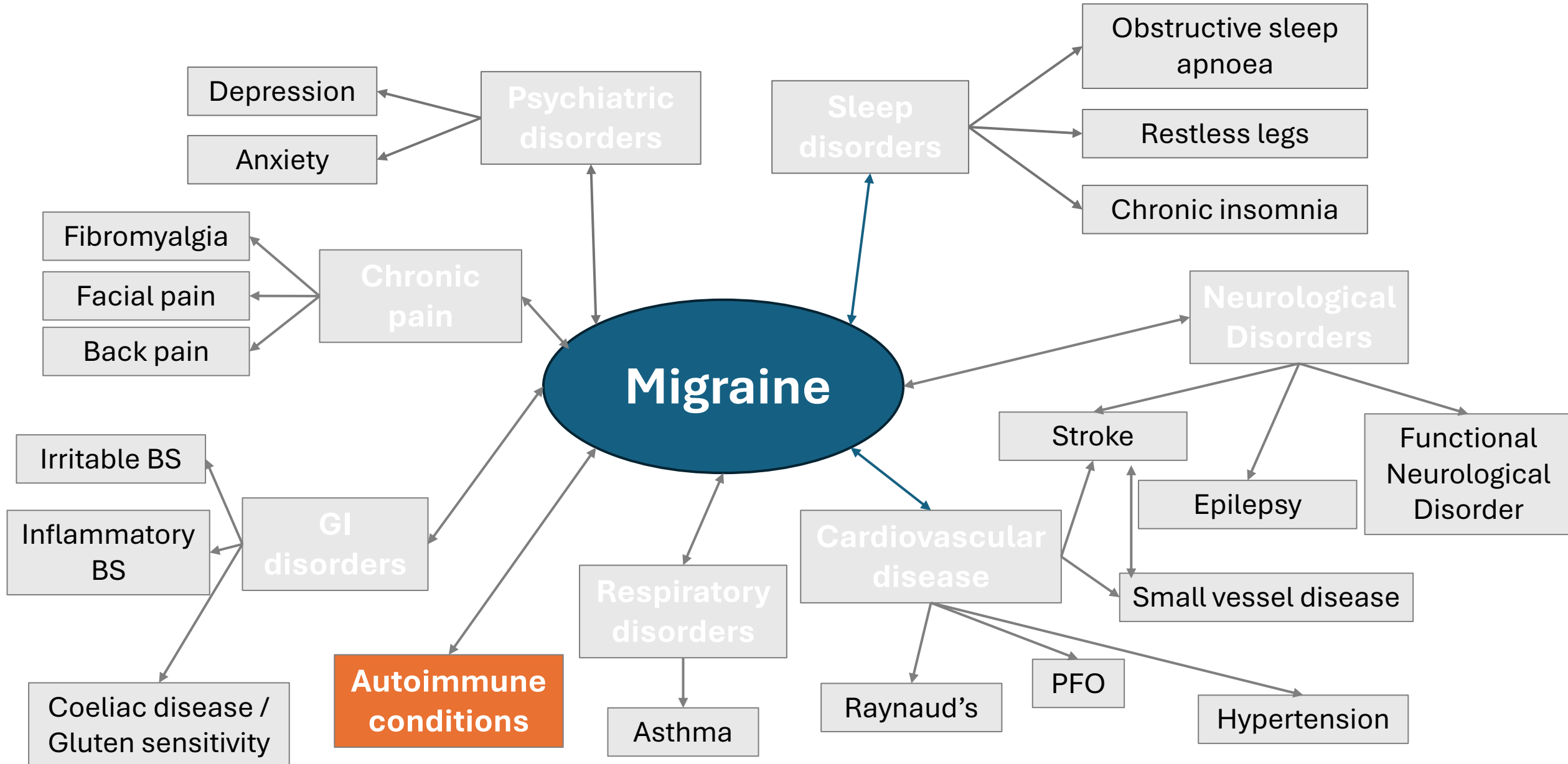


Migraine and sleep disorders

Consequences in clinical practice

- Relationship between headaches and sleep disorders should be considered when choosing therapeutic options
- Lifestyle recommendations should always be considered first
- Importance of sleep improvement in migraine and vice versa
- Possible strategies:
 - **Melatonin**: treatment for primary headaches (cluster, hypnic HA, migraine), and sleep regulation
 - **Serotonin**: role in migraine prevention and comorbid anxiety and depression for both conditions
 - **Psychotherapy**: CBTi reduced migraine days in patients with coexistent insomnia
- Cautions:
 - **Betablockers**: worsening insomnia
 - **Tricyclic antidepressants**: reduce total sleep time, increase nightmares and diurnal somnolence
 - **SSRIs**: may cause bruxism and jaw pain

Common comorbid disorders of migraine



Headache in Autoimmune disorders

- Can be associated to most central nervous system (CNS) vasculitides
- Most common neurological symptom
- Usually the first sign of CNS involvement in systemic autoimmune (AI) diseases and vasculitis
- AI disorders: reported higher prevalence of primary headaches
- Mechanisms
 - Inflammation of pain sensitive structures (subs P, CGRP, other cytokines)
 - Aseptic meningitis
 - Intracranial hypertension
 - Cortical sinus thrombosis
 - Intracranial haemorrhage / infarction

Headache in Autoimmune disorders

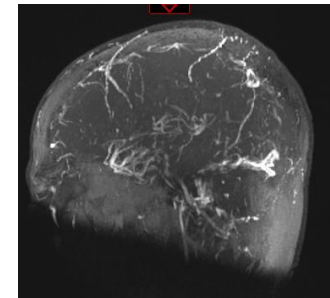
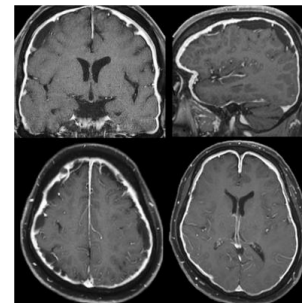
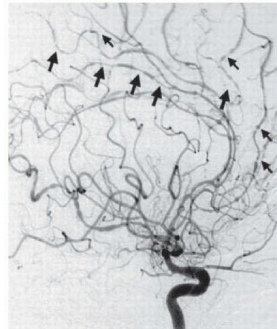
- Headache characteristics are not specific
- Some AI disorders more associated to headache than others
- Vigilance for red flags is imperative to detect association to underlying AI disorder:
 - Extracephalic symptoms
 - Laboratory abnormalities
 - Neuroimaging



Skin rash
Arthritis
Eye abnormalities
Jaw claudication
Fever
Night sweats



FBC, U&E, LFT
ESR, CRP
ANA, ENA, ANCA,
APL

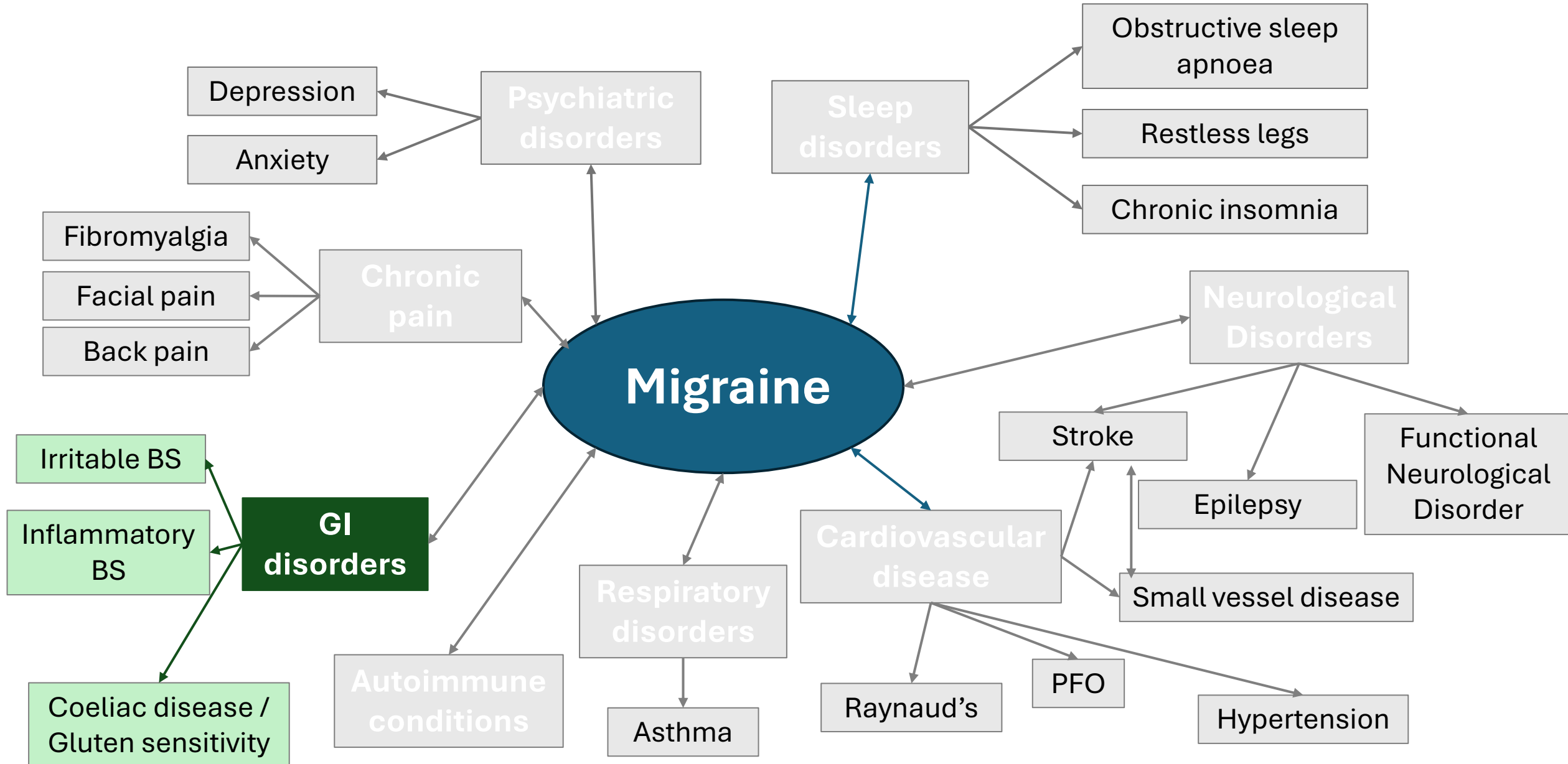




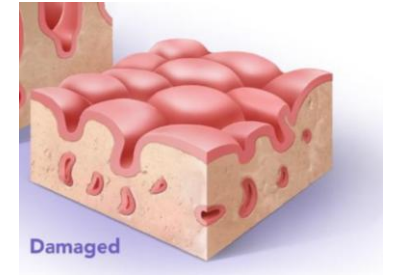
Antiphospholipid syndrome

- Migraine: most common type of headache in APLS
- Forms:
 - Migraine without aura
 - Migraine with aura
 - Unremitting debilitating headache
- TIA/Stroke associated to APLS with Migraine
- Some authors recommend to screen for APLS in patients with migraine as there may be a link between migraine/APLS/Stroke
- Patent foramen ovale also linked to migraine with aura and stroke
- Refractory headache seems to improve with APLS treatment (warfarin)

Common comorbid disorders of migraine



Headache and Coeliac Disease



- Increased frequency of migraine and headache has been associated with untreated CD, regardless the presence of histological changes in the bowel biopsy (1.5-2)
- At diagnosis of CD, headache is the most common neurological symptom reported
- Gluten free diet reduces migraine frequency in patients with both disorders
- No evidence that gluten free diet in non-coeliac patients benefit migraine
- Current evidence does not support to routinely screen for CD in patients with migraine other than in the paediatric population*

*Negative
biopsy

Thank you!