Te Whatu Ora
Health New Zealand

From CGRP to CMO via PML

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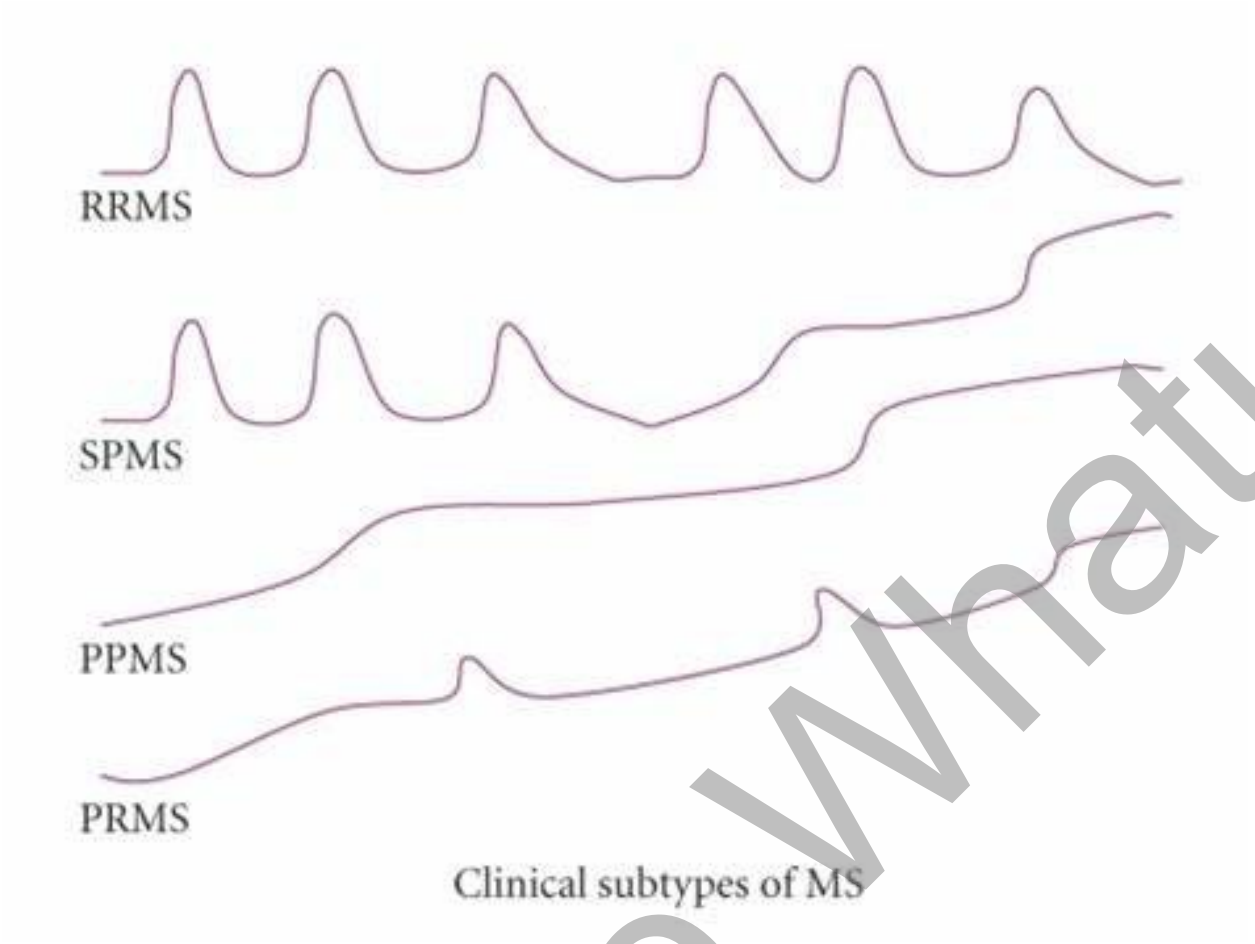
Plan

- New MS treatments:- when can we give them? What are the up and downsides?
- What is a CMO? What does it mean in the current dynamic system?
- What is new in Migraine therapeutics and why do we inject heads?



Clinical subtypes of MS

Zhang et al. Clinical & developmental immunology 2010

Old Pharmac funding criteria

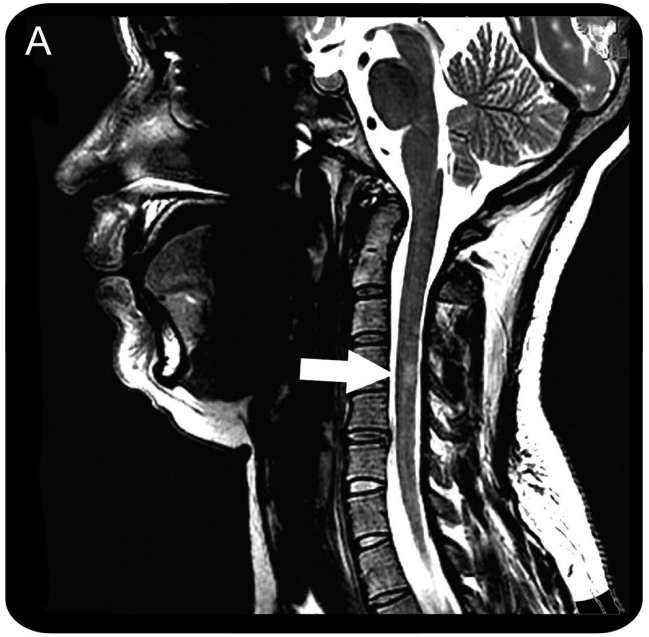
- CDMS - at least 2 relapses
- Relapsing MS
- EDSS 0 - 4.0 ie able to walk at least 500m without assistance/aid
- 1 relapse in last 12/12 or 2 in last 24/12
- Active MRI within last 2 years - enhancing lesion/new lesion/lesion causing relapse in last 2y/T2 halo lesion
- Stop if EDSS > 4.0

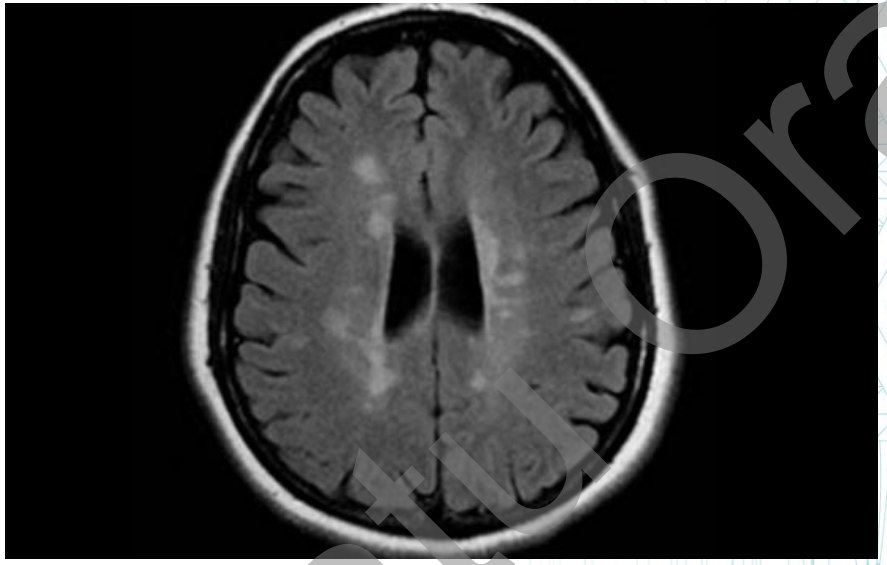
New (since 1/3/21)

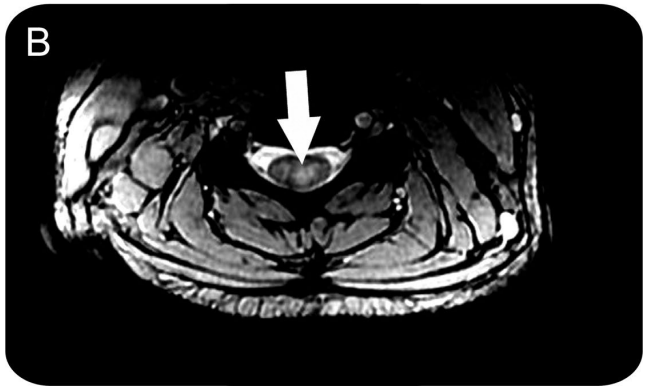
- As old criteria, but EDSS 0 - 6.0 (able to walk 100m with or without unilateral or bilateral aid/assistance).
- Apply via SA site.
- Anyone who has ever been approved can resume treatment if EDSS <=6.0 (via waiver process).
- Switching does not require you to contact Pharmac or MOH - same SA number
- People who already had approval numbers before 1/3/21 will have a bridging number too - you can look this up - this is the number you need if switching Rx.

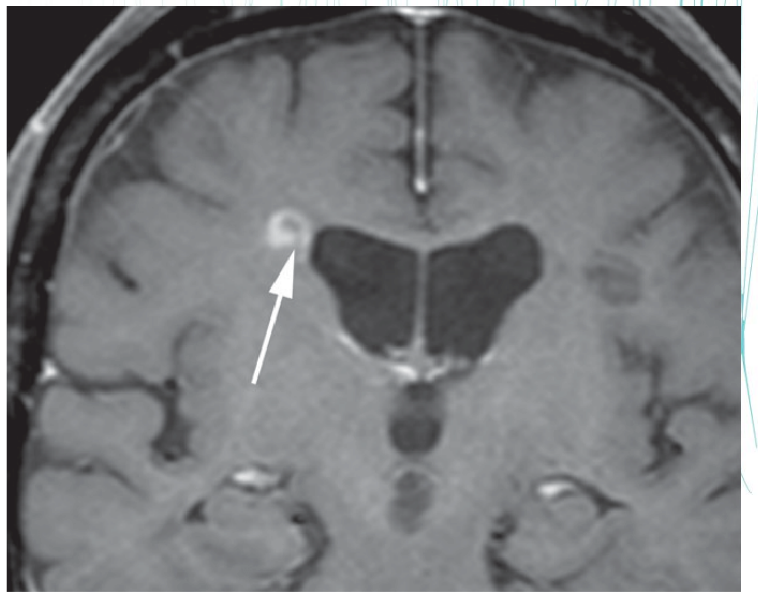
New – since 1/7/22

- Patients with a single clinical episode who fulfill McDonald 2017 diagnostic criteria* are eligible for funding of DMT.
- Must be within 12/12 of the clinical episode, so not historic cases.
- *To be eligible must have mixture of enhancing/not enhancing MRI lesions, or new lesion on repeat scan, or typical MRI lesions + OCB+ve.









Renard D et al. Neurology 2010;75:e74-e74

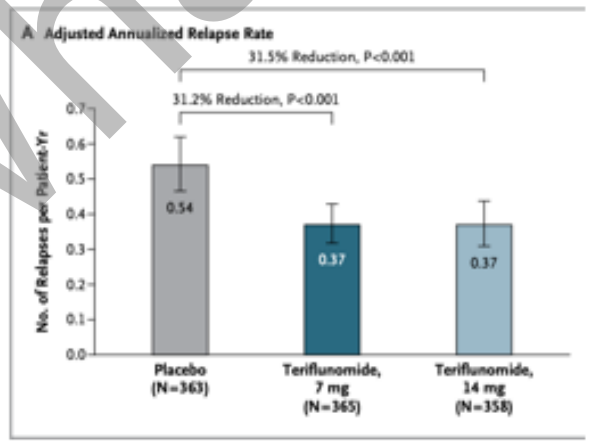
Relapsing Remitting

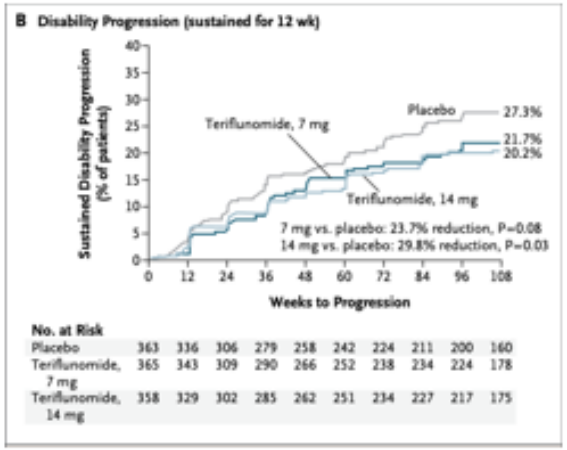
The drugs

- Teriflunomide
- Fingolimod
- Dimethyl Fumarate (DMF)
- Natalizumab
- Ocrelizumab
- ABC

TOWER trial 2011 Teriflunomide vs Placebo

TOWER trial 2011 Teriflunomide vs Placebo





Infection Screening dictates choice

- JCV - also monitor every 6/12+ on Natalizumab
- Hep B - consider vaccination if not immune
- VZV - vaccinate if not immune (esp Gilenya and Natalizumab)
- Hep C and HIV
- ? Quantiferon Gold (TB)
- MMR - consider vaccination if not immune

If JCV negative:- Natalizumab

Sentinel trial

- Patients with at least one relapse in 12/12 on avonex randomised to have avonex plus natalizumab or avonex plus placebo (Rudick et al 2006).
- 54% reduction in ARR
- 24% reduction in EDSS progression
- 83% and 89% reduction in T2 and Gad MRI activity.

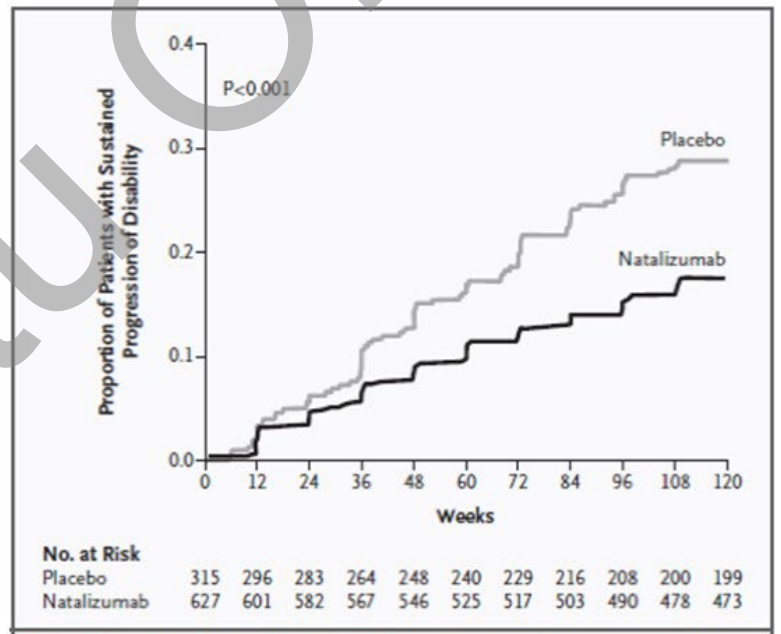


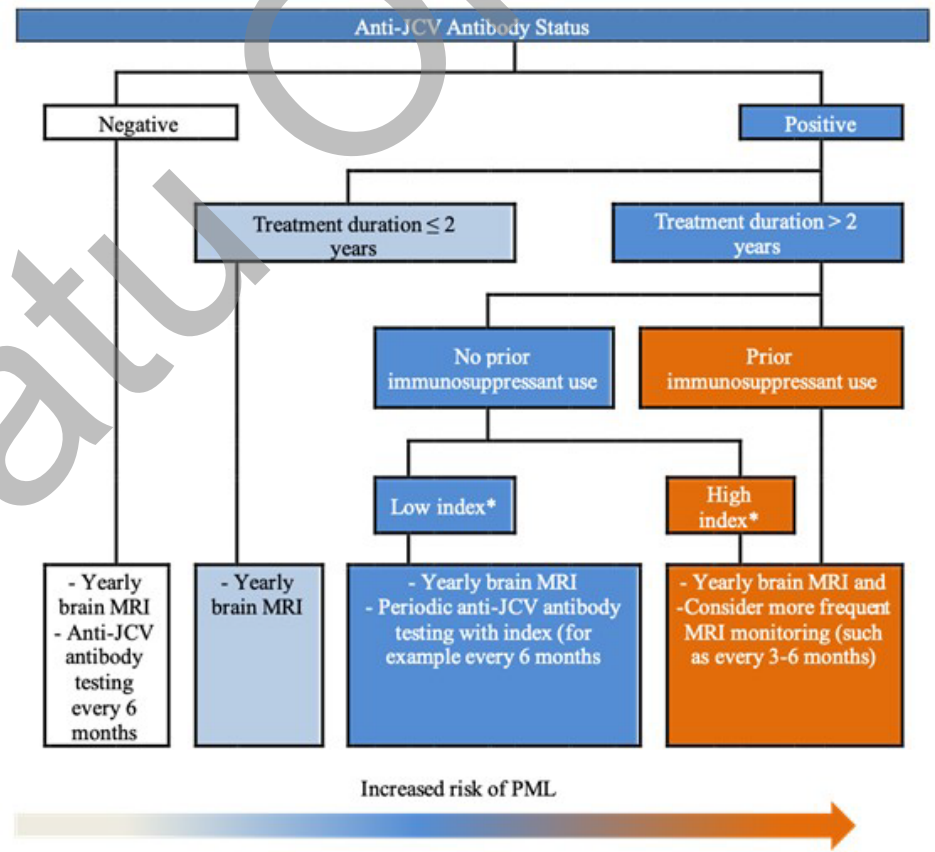
Figure 2. Kaplan–Meier Plots of the Time to Sustained Progression of Disability among Patients Receiving Natalizumab, as Compared with Placebo.
Natalizumab reduced the risk of sustained progression of disability by 42 percent over two years (hazard ratio, 0.58; 95 percent confidence interval, 0.43 to 0.77). The cumulative probability of progression was 17 percent in the natalizumab group and 29 percent in the placebo group.

N ENGL J MED 354;9 WWW.NEJM.ORG MARCH 2, 2006

But…

- PML risk
- Overall risk 3 per 1000 patients
- Risk higher with >24 months treat prior immunosuppressive use anc virus positive.
- All 3 risk factors: 1/100 risk

In practice - MedSafe algorithm

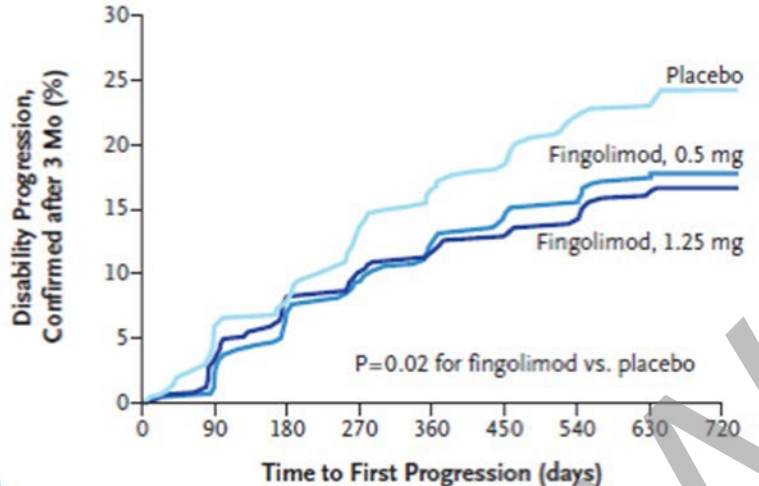


*Index values ≤0.9 are associated with a PML incidence <1/1,000. PML risk increases substantially at index values above 1.5. Refer to Figure 2 of the DS for more comprehensive information.

If JCV positive:- Medium efficacy 40-50% RR

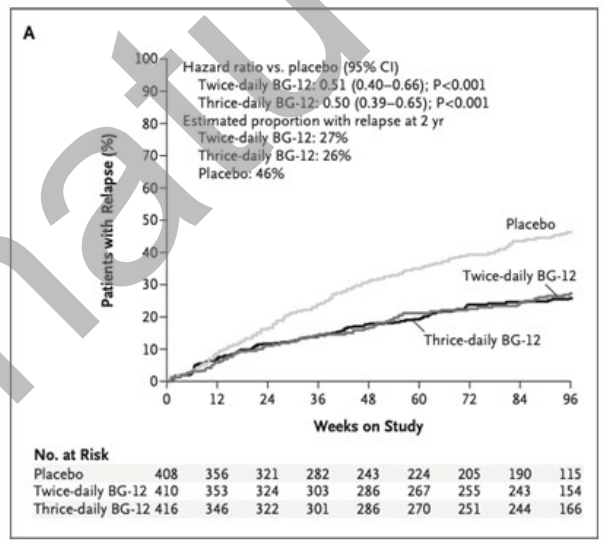
DMF vs Placebo; Gold et al 2010

B

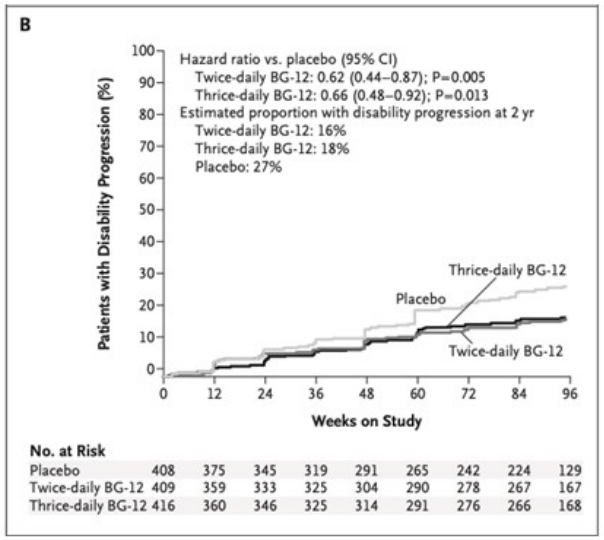


No. at Risk									
Fingolimod, 1.25 mg	429	401	373	356	344	332	322	305	165
Fingolimod, 0.5 mg	425	416	388	370	354	340	332	321	152
Placebo	418	391	371	341	320	308	290	279	143

N ENGL J MED 362;5 NEJM.ORG FEBRUARY 4, 2010



No. at Risk									
Placebo	408	356	321	282	243	224	205	190	115
Twice-daily BG-12	410	353	324	303	286	267	255	243	154
Thrice-daily BG-12	416	346	322	301	286	270	251	244	166



No. at Risk									
Placebo	408	375	345	319	291	265	242	224	129
Twice-daily BG-12	409	359	333	325	304	290	278	267	167
Thrice-daily BG-12	416	360	346	325	314	291	276	266	168

If JCV positive:- High efficacy 50-70% RR

Ocrelizumab

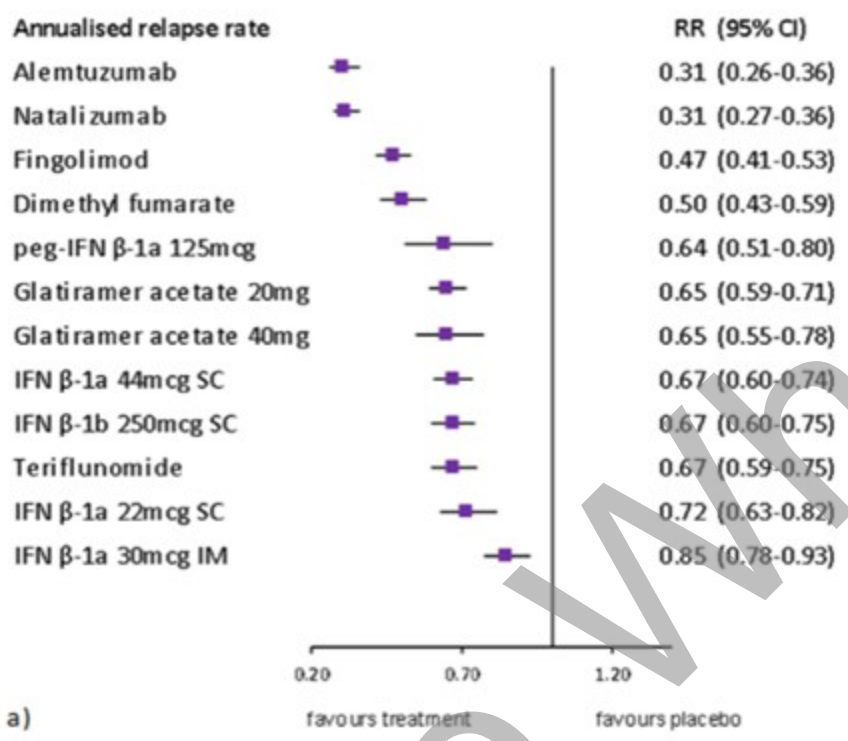
- Anti-CD20 monoclonal antibody
- Reduces B-cell populations and hence antibody production
- May be higher infection risks with longer treatment and in older more disabled patients
- Reduces vaccine efficacy
- May reactivate Hep B

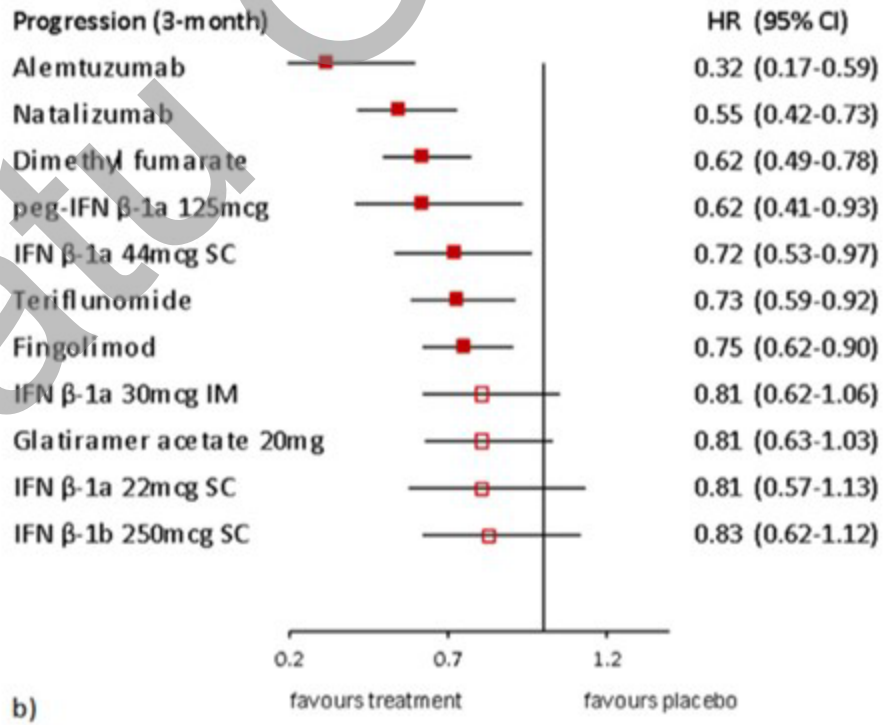
OPERA 2017 Relapse data

Table 2. Clinical and MRI End Points during the 96-Week Trials.*

End Point	OPERA I Trial			OPERA II Trial		
	Ocrelizumab (N=410)	Interferon Beta-1a (N=411)	P Value	Ocrelizumab (N=417)	Interferon Beta-1a (N=418)	P Value
Primary end point						
Annualized relapse rate at 96 wk (95% CI)	0.16 (0.12 to 0.20)	0.29 (0.24 to 0.36)		0.16 (0.12 to 0.20)	0.29 (0.23 to 0.36)	
Rate ratio (95% CI)	0.54 (0.40 to 0.72)		<0.001	0.53 (0.40 to 0.71)		<0.001

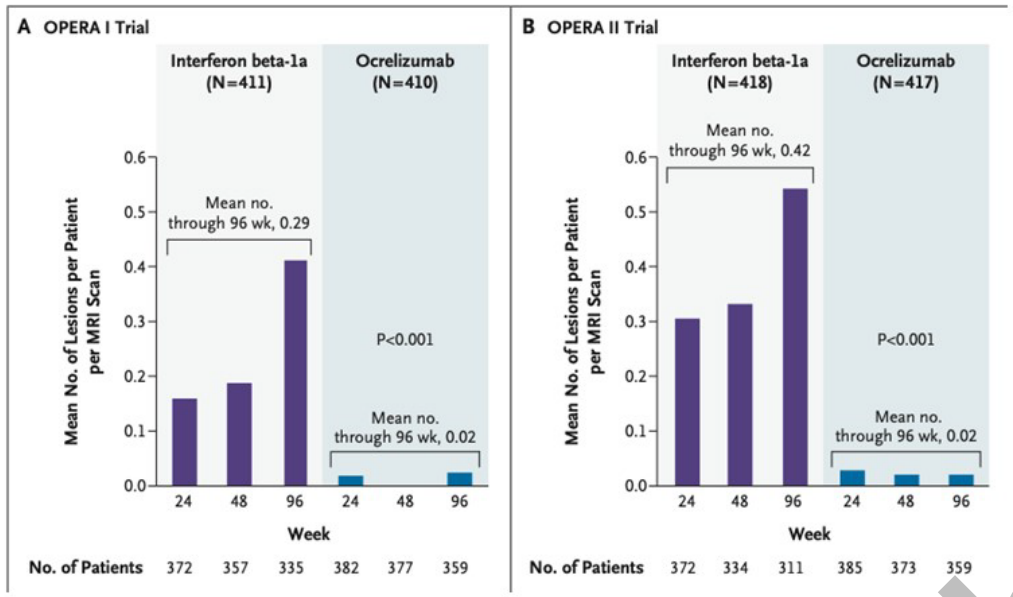
Significant efficacy differences





Fogarty et al. MS & Related Disorders 2016(9):23-30

Ocrelizumab vs Rebif; Opera 2017



MRI data

OPERA disability data

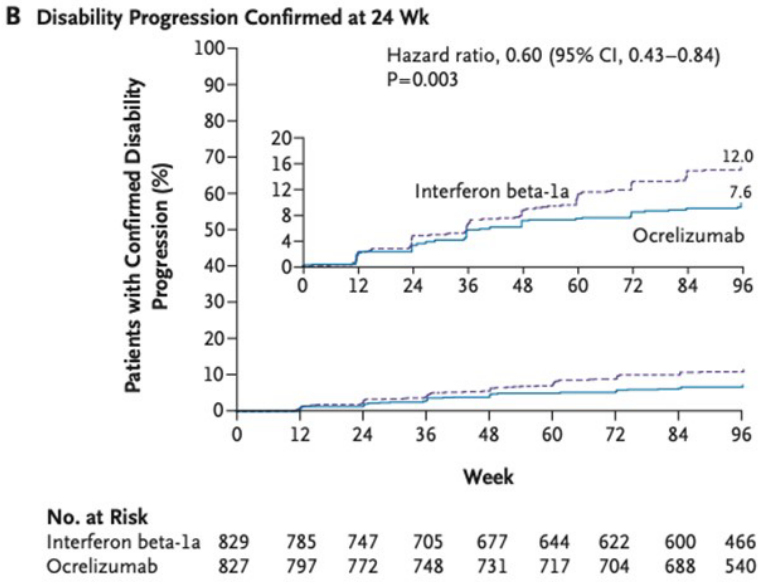
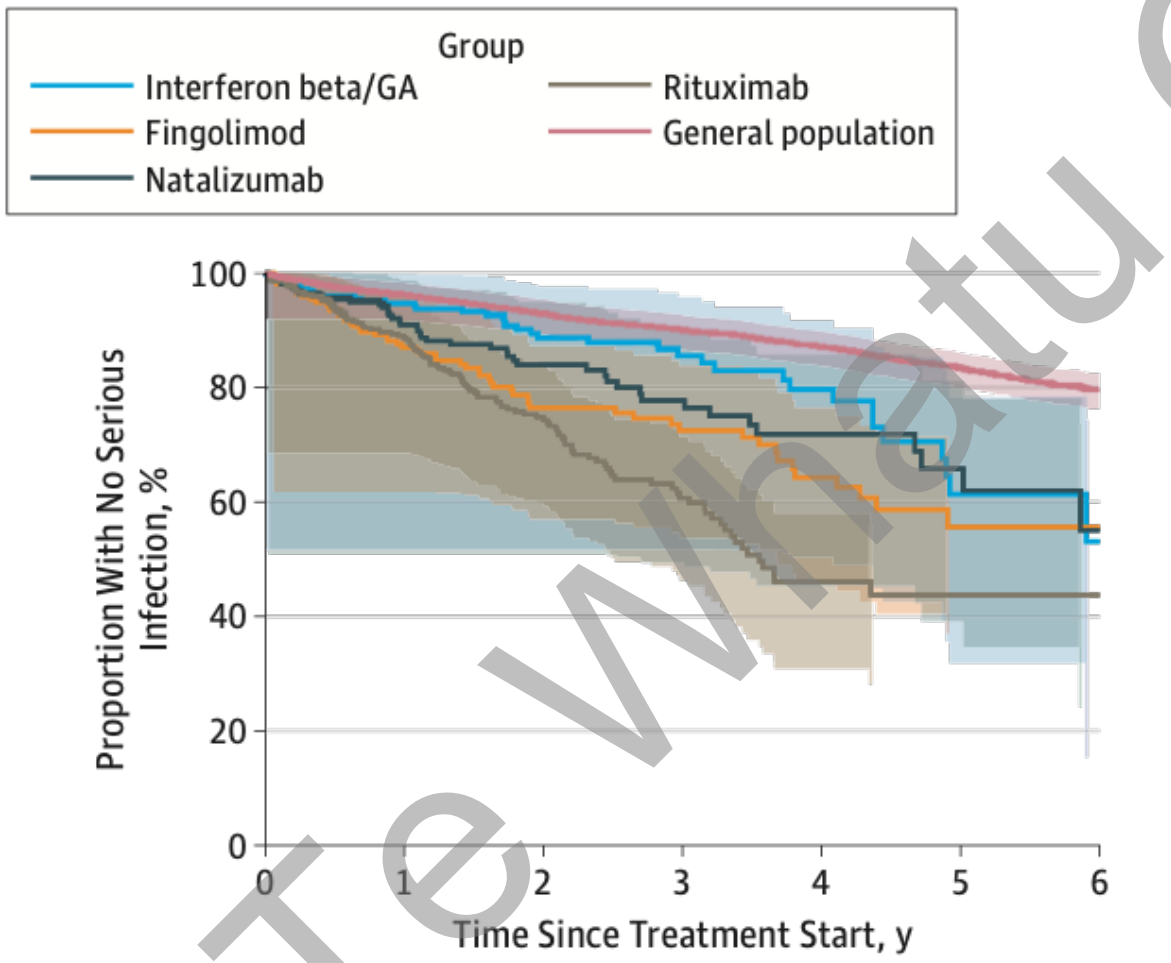


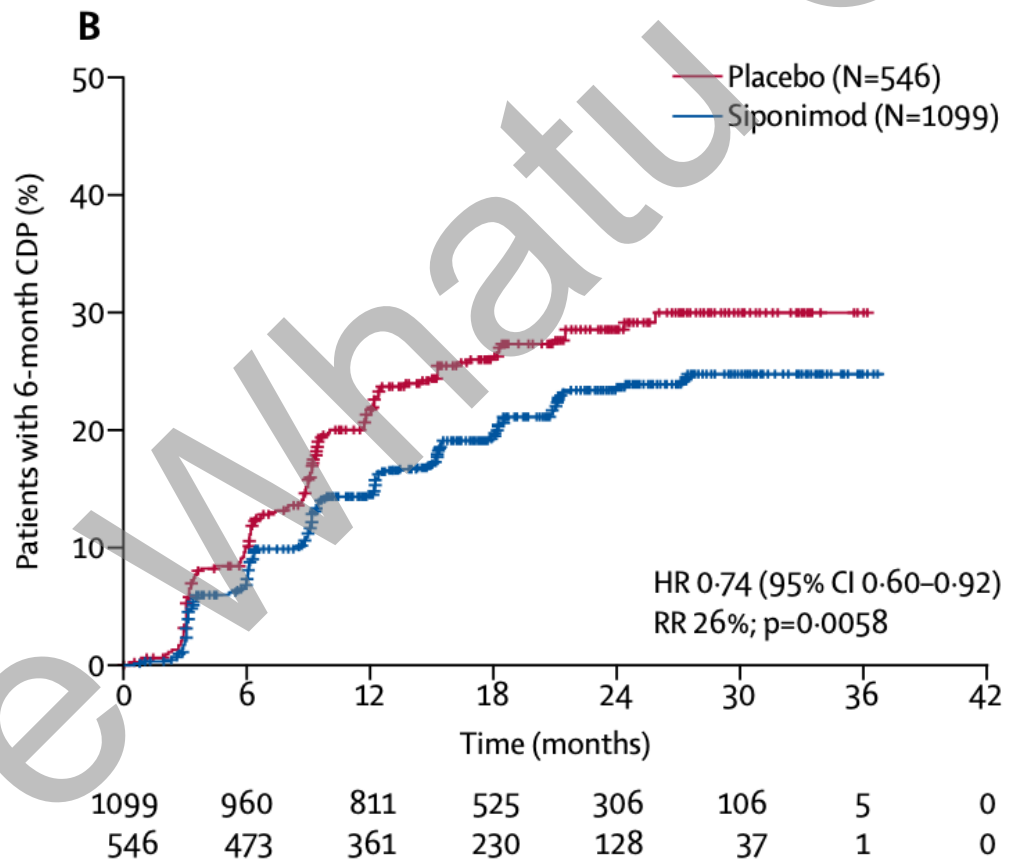
Figure. Survival Plot for the Time to the First Serious Infection



COVID-19

- Risks of serious outcome with COVID-19 higher in non-ambulant MS patients.
- Ocrelizumab and Fingolimod associated with slightly worse outcomes from COVID-19
- Vaccine responses reduced with Ocrelizumab (B-cell response) and Gilenya (B and T-cell responses).
- Patients on Ocrelizumab or Fingolimod are eligible for evusheld protective treatment and should also be offered Paxlovid/molnupiravir/remdesivir if they contract COVID-19.

Siponimod vs Placebo in SPMS; EXPAND trial 2018



Te Whatu Ora
Health New Zealand

The Medical Leadership Team

What is the national picture?

National/Regional Structure.

National Medical Dir
Peter Watson

Dr Rawhiri McKree Jansen
Te Aka Whai Ora

National CMO group

Northern

Te Manawa Taki

Central

Te Waipounamu

South island CMO Group

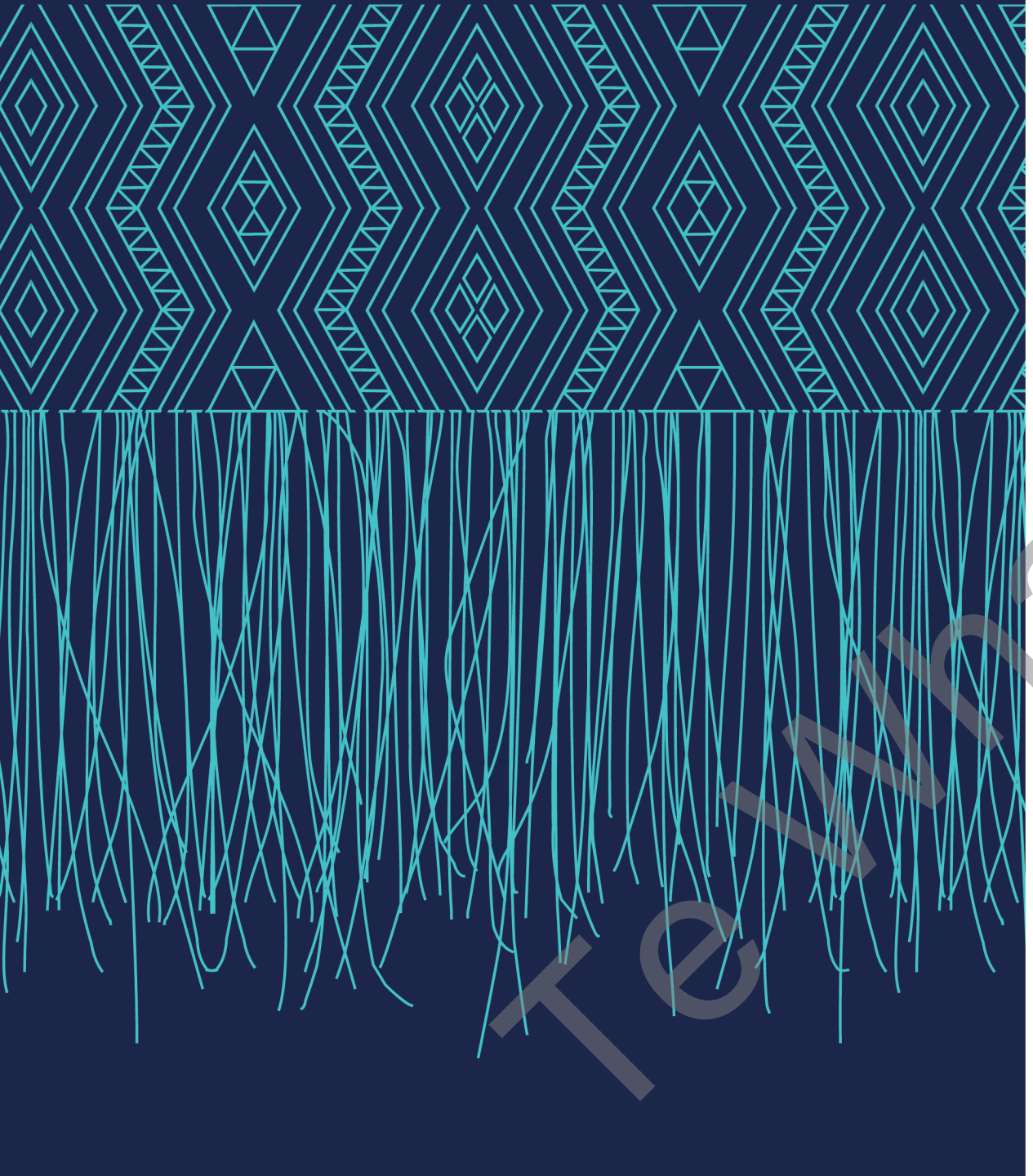
Canterbury
Richard French

West Coast
Graeme Roper

South Canterbury
Ben Pearson

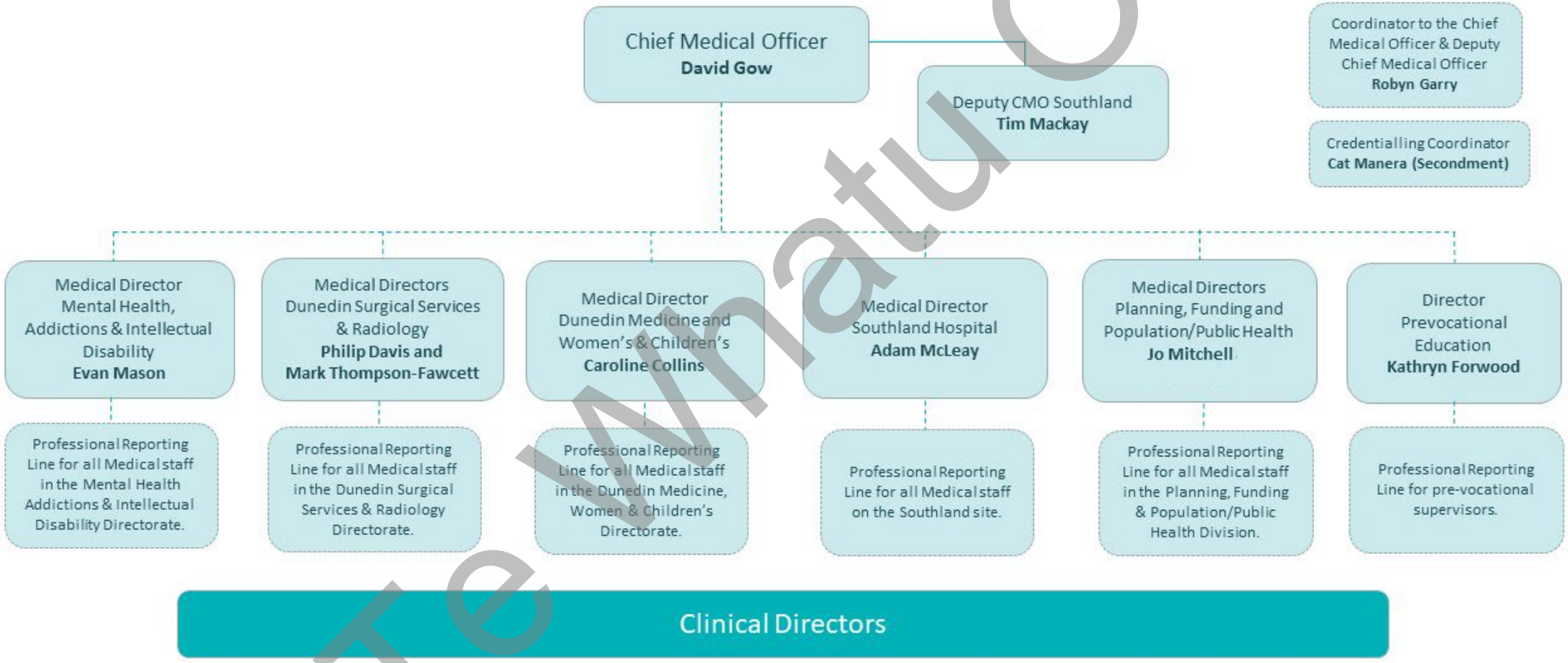
Nelson Marlborough
Nick Baker

Southern
David Gow

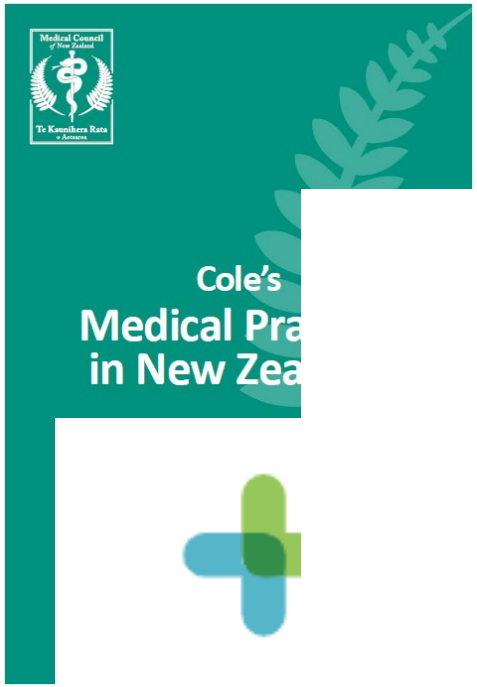


How are we organized locally?

Local structure



What statutory areas do the CMO and MLT work in?



NEW ZEALAND DISTRICT HEALTH BOARDS

SENIOR MEDICAL AND DENTAL

ialty Trainees of New Zealand (STONZ)

and

20 District Health Boards Employer Collective Agreement

District Health Boards

ember 2021 – 13 December 2023

Health and Disability Commissioner

Te Toihau Hauora, Hauātanga

Te Kaunihera Rata o Aotearoa
Medical Council of New Zealand

raining
al Supervisors Guide

Te Kāika

ARAI TE URU WHARE HAUORA

Prevocational Medical Training
Clinical Supervisors' Guide

Te Tiriti o Waitangi

Migraine preventers

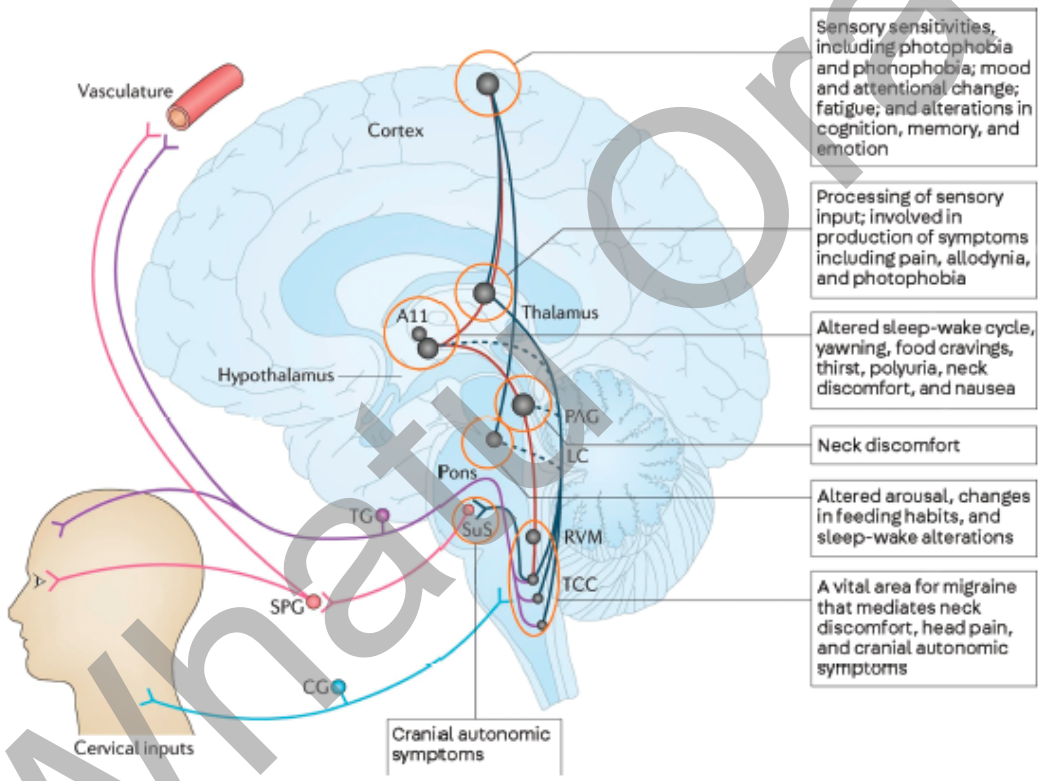


FIGURE 2-1
Pathophysiology of migraine in relation to its clinical manifestations. Trigeminal afferents arise from the trigeminal ganglion (TG) and innervate cranial structures, vasculature, and the dura. These sensory afferents converge with cervical afferents from the upper cervical dorsal root ganglion (CG) in the trigeminocervical complex (TCC) in the brainstem and upper cervical spine. Second-order neurons from the TCC project to the thalamus, from which thalamocortical neurons relay sensory information to multiple cortical areas. Several structures, such as the rostroventral medulla (RVM), locus coeruleus (LC), periaqueductal gray (PAG), and hypothalamic nuclei, have been implicated in trigeminovascular sensory modulation. The parasympathetic pathway mediates cranial autonomic symptoms through the superior salivatory nucleus (SuS) and the sphenopalatine ganglion (SPG). The boxes summarize the clinical manifestations of migraine attributed to each relevant anatomic area.
A11 = diencephalic A11 area.

KEY POINTS

- **It is widely accepted that migraine is an inherited disorder of sensory processing, but many aspects of the underlying basis of this disorder still remain unknown.**
- **Migraine attacks are often preceded by alterations in homeostasis, supporting the role of the hypothalamus in the prodromal phase.**
- **Neuroimaging studies have found hypothalamic activation and altered connectivity with other brain and brainstem regions that could explain the polyuria, yawning, food cravings, and changes in appetite reported in the prodromal phase.**

When?

- Two severe or disabling or four less disabling migraine attacks per month
- Acute migraine treatment is ineffective or contraindicated
- Medication-overuse headache is present
- Highly disabling migraine attacks (eg, hemiplegic migraine or migraine with brainstem aura)
- Patient preference[8,9]

What?

Pregabalin

TABLE 4-1 Classes of Treatments Used for Preventive Treatment of Migraine

Class	Drugs
Antiepileptic drugs	Divalproex sodium,[a] topiramate, gabapentin
Antidepressant drugs	Amitriptyline and other tricyclic antidepressants, venlafaxine and other serotonin norepinephrine reuptake inhibitors (SNRIs)
Beta-blockers	Propranolol,[a] metoprolol, timolol[a]
Other antihypertensive drugs	Verapamil, lisinopril, candesartan
Neurotoxins	OnabotulinumtoxinA[a]
Calcitonin gene-related peptide monoclonal antibodies	Erenumab,[a] fremanezumab,[a] galcanezumab,[a] eptinezumab[a]
Other	Memantine, cyproheptadine
Herbal and nutritional supplements	Magnesium, vitamin B_2 (riboflavin), feverfew, coenzyme Q10, melatonin

[a] US Food and Drug Administration (FDA)–approved for prevention of either episodic or chronic migraine.

Which?

TABLE 4-3 **Preventive Medication Choices Based on Side Effects, Contraindications, and Comorbidities**

Area of concern	Consider	Avoid
Side effects[a]		
General	Verapamil and memantine well tolerated; lisinopril and candesartan if normal blood pressure	Valproate, topiramate, amitriptyline
Weight gain	Topiramate, venlafaxine	Valproate, amitriptyline, cyproheptadine
Fatigue/exercise intolerance	Topiramate, venlafaxine	Beta-blockers, amitriptyline, verapamil
Cognitive symptoms	Verapamil, lisinopril, candesartan, venlafaxine, memantine	Antiepileptic drugs
Contraindications		
Hypotension		Antihypertensive drugs
Nephrolithiasis		Topiramate, zonisamide
Possibility of pregnancy	Propranolol first line; amitriptyline, verapamil, coenzyme Q10 second line	Valproate, topiramate, lisinopril, candesartan, feverfew
Glaucoma		Topiramate (narrow-angle glaucoma), amitriptyline
Comorbidities		
Insomnia	Amitriptyline, melatonin	Memantine
Anxiety	Beta-blockers	Topiramate
Depression	Venlafaxine	Beta-blockers
Hypertension	Antihypertensive drugs	Erenumab, venlafaxine, duloxetine
Obesity	Topiramate	Valproate, amitriptyline
Frequent migraine aura	Verapamil, valproate, magnesium, topiramate	None identified

[a] Herbal and nutritional supplements and behavioral treatments are good choices for patients with side effect concerns.

New stuff

Emgality

Antibodies to Calcitonin Gene-Related Peptide or Its Receptor[a]

TABLE 4-4

Targ				
Subc				
Prod				
Dose				
Time maxi (T_{max})				
Half-				
Notes	leads to fastest onset of efficacy	suggests higher risk of constipation than with other monoclonal antibodies	reactions than for erenumab; quarterly dosing may be convenient for some patients	site reactions than for erenumab

IV = intravenous.

[a] Data from Do TP, et al, J Headache Pain.[21]

Very effective in real world setting

Other stuff

Procedure	Treatment type	Injection frequency	Evidence highlights
OnabotulinumtoxinA	Preventive	12-week intervals	Randomized controlled trials for chronic migraine[2,3] Randomized controlled trial for sleep-related bruxism[12] Observational studies for new daily persistent headache,[13] chronic posttraumatic headache,[14] nummular headache,[15] trigeminal neuralgia[16]
Peripheral nerve blocks	Acute, short-term preventive	Single or repeated at 2-week or longer intervals as needed	Randomized controlled trials for migraine (short-term prevention)[6–9,17] Randomized controlled trials for migraine in emergency department[18,19] Randomized controlled trials for cluster headache (short-term prevention)[4,5] Observational studies in pediatric,[20] pregnant,[21] and geriatric[22] populations
Trigger point injections	Acute, short-term preventive	Single or repeated at 2-week or longer intervals as needed	Randomized controlled trials for tension-type headache[10,11]
Sphenopalatine ganglion blocks	Acute, short-term preventive	Single or repeated twice weekly or longer intervals as needed	Randomized controlled trial for acute and preventive treatment of chronic migraine[23,24] Randomized controlled trial for acute headache in emergency department[25]

Botox:- not Public!

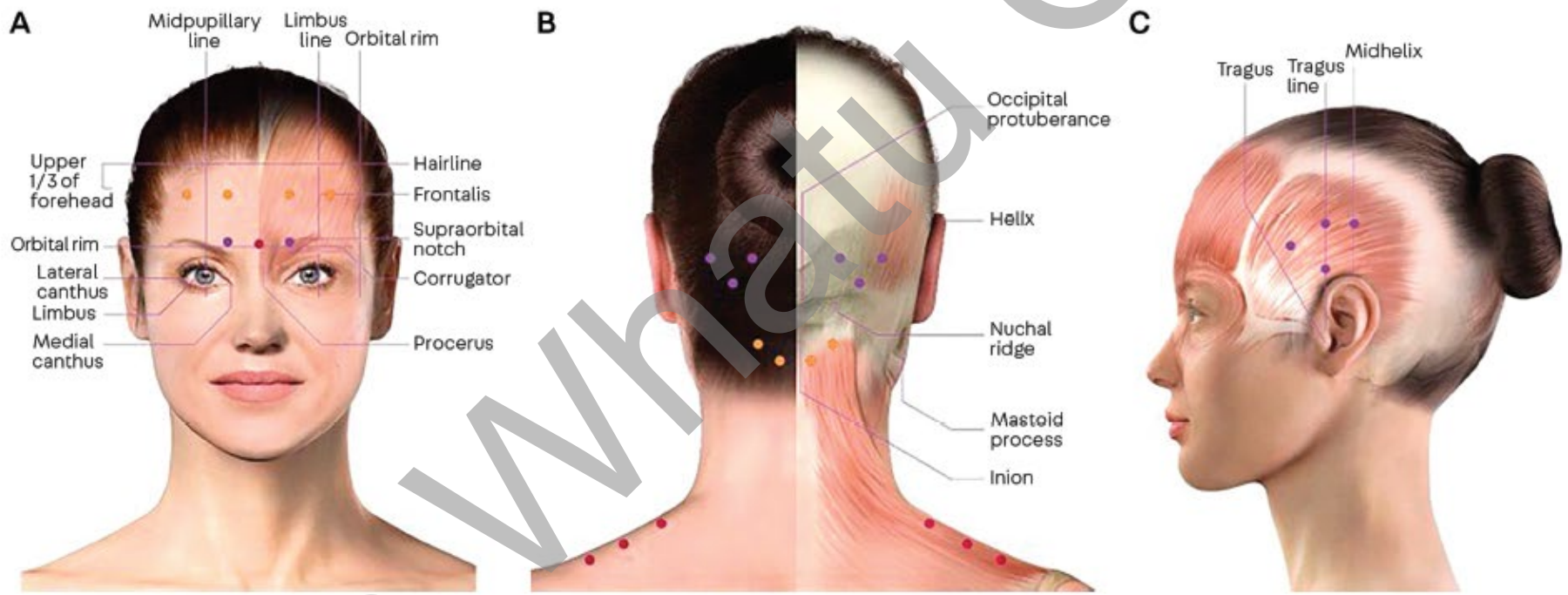
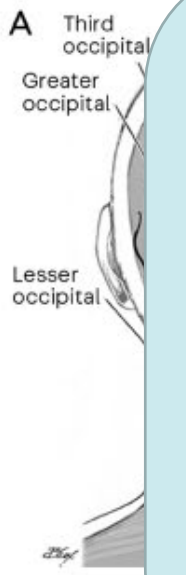


FIGURE 10-1
Injection paradigm for onabotulinumtoxinA in the treatment of chronic migraine. Injection site locations for onabotulinumtoxinA in the treatment of migraine include the following muscles: corrugator (*A, purple dots*), procerus (*A, red dot*), frontalis (*A, orange dots*), occipitalis (*B, purple dots*), cervical paraspinal muscles (*B, orange dots*), trapezius (*B, red dots*), and temporalis (*C, purple dots*).
Modified with permission from Blumenfeld A, et al, Headache.[33] © 2017 Allergan plc.

Nerve blocks



Very effective in well selected patients

headache disorders. Common peripheral nerve block injection site locations include the greater and lesser occipital nerves (*A*), the supraorbital and supratrochlear nerves (*B*, *C*), and the auriculotemporal nerves (*B*, *C*).

Reprinted with permission from Blumenfeld A, et al, Headache.[41] © 2013 American Headache Society.

Acute therapies

TABLE 3-2 Select Summary of American and Canadian Headache Societies Guidelines for Acute Migraine Treatment

Medication	American Headache Society[8]	Canadian Headache Society[7]
Acetaminophen 1000 mg for nonincapacitating attacks	Strong evidence (Level A)	Strong evidence
Aspirin 500 mg, diclofenac 50 mg or 100 mg, ibuprofen 200 mg or 400 mg, naproxen 500 mg or 550 mg	Strong evidence (Level A)	Strong evidence
Triptans	Strong evidence (Level A)	Strong evidence
Dihydroergotamine nasal spray	Strong evidence (Level A)	Weak evidence but may be first line in some cases
Dihydroergotamine IV/IM/subcutaneous	Medium evidence (Level B)	Weak evidence but may be first line in some cases
Acetaminophen/aspirin/caffeine	Strong evidence (Level A)	Not addressed
Butorphanol nasal spray	Strong evidence (Level A)	Weak evidence, should not use
Codeine	Medium to weak evidence (Level B/C)	Weak evidence, should not use
Tramadol	Medium evidence (Level B)	Weak evidence, should not use

IM = intramuscular; IV = intravenous.

TABLE 3-3 **Side Effects of Acute Migraine Medications**[a]

Medication	Most common adverse events and warnings
Acetaminophen	Nausea, vomiting, headache, and insomnia
Nonsteroidal anti-inflammatory drugs (NSAIDs)	NSAIDs have a US Food and Drug Administration (FDA) boxed warning regarding cardiovascular and gastrointestinal risk; discuss medication-overuse headache with patients
	Common side effects of NSAIDs include nausea, vomiting, constipation, diarrhea, reduced appetite, headache, dizziness, rash, and drowsiness
	Other possible adverse events include edema, renal failure, liver failure, allergic reaction causing anaphylaxis, and bleeding
	NSAIDs (except aspirin) may increase the risk of myocardial infarction or stroke with increased duration of use and when used in those with underlying risk factors for cardiovascular disease
Triptans	Triptans have an FDA boxed warning regarding cerebrovascular or cardiovascular disease and risk of serotonin syndrome when used with other serotonin drugs; discuss medication-overuse headache with patients
	Triptans are contraindicated in patients with a history of cardiovascular or cerebrovascular disease, including those with uncontrolled hypertension, peripheral vascular disease, or cardiac arrhythmias; patients with ischemic bowel disease; and those with hemiplegic migraine.
	Common side effects can include nausea, dizziness, somnolence, paresthesia, dry mouth, dyspepsia, feeling hot or cold, chest pain/tightness, flushing, throat/neck symptoms, heaviness sensation
Ergotamines	FDA boxed warnings for ergotamines include risk of life-threatening peripheral ischemia with coadministration with potent cytochrome P450 3A4 isozyme (CYP3A4) inhibitors
	Common side effects of dihydroergotamine include rhinitis, nausea, altered sense of taste, dizziness, vomiting, flushing
Ditans	Warning for medication-overuse headache and driving restriction for 8 hours after use; Schedule V controlled substance
	Common side effects include dizziness, fatigue, paresthesia, and sedation
Gepants	Use with caution in medications that use the CYP3A4 system and breast cancer resistance protein or P-glycoprotein–only inhibitors
	Common side effects include nausea and somnolence

[a] Data from Cooper W, et al, Postgrad Med.[12]

Acute neuro-modulation treatments

Neuromodulation Dosing and Side Effects TABLE 3-4

Device	Dosing	Side effects
External trigeminal stimulation	1 hour during migraine attack	Paresthesia
Single-pulse transcranial magnetic stimulation	Three pulses up to 3 times per attack as needed	Lightheaded, tingling, tinnitus
Noninvasive vagus nerve stimulation	Bilateral 120 seconds to right and left of neck within 20 minutes of onset of attack; repeat once after 15 minutes	Application site discomfort, nasopharyngitis
Remote electrical neuromodulation	To upper arm for 45 minutes within 1 hour of onset; increase stimulation until perceptible but nonpainful	Transient warmth, redness, or tingling sensation into the arm

Questions?