TrEatment, utiLisation and safEty of medicines for MUltiple Sclerosis (TELEMUS)

***Telemus* is *Eurymus'* son, a prophet and a master at reading signs**

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Multiple Sclerosis

- Multiple Sclerosis (MS) is an immune mediated demyelinating and degenerative central nervous system disease, which results in multifocal disability that can include limb weakness, visual impairment, sensory loss, gait ataxia, incontinence and cognitive dysfunction
  - >2.8 million people worldwide are estimated to be living with MS
  - Age at diagnosis is commonly between 20 and 40 years
  - MS affects three times more women than men
- The majority of people living with MS will have disease free periods punctuated with periods of relapse (relapsing-remitting multiple sclerosis, RRMS), which often leads to residual deficits after each relapse
- RRMS is managed by using disease modifying treatments (DMTs) to induce apparent remission (i.e., no evidence of disease activity or a state of clinical and MRI stability) and delay progression of disease

1. What is the prevalence of multiple sclerosis across the APAC region?

frontiers in Neurology

SYSTEMATIC REVIEW
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Multiple Sclerosis in the Asia Pacific Region: A Systematic Review of a Neglected Neurological Disease

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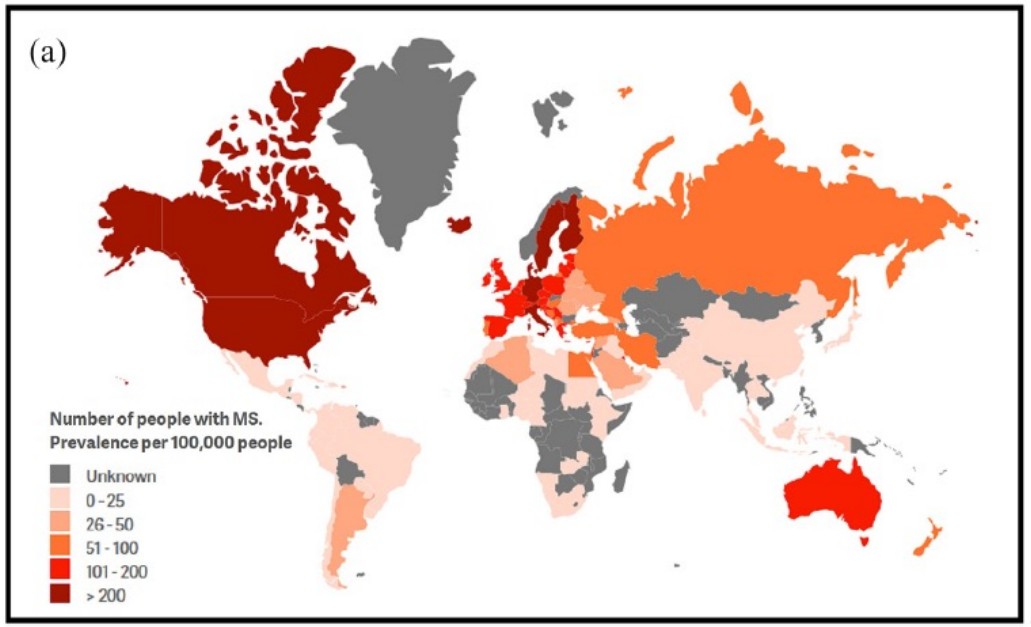
Background: Multiple sclerosis is thought to be relatively uncommon in the Asia Pacific region with prevalence estimated between 0 and 20 per 100,000. There is reason to doubt these estimates due to the lack of data from many countries and the growing evidence of variability in prevalence across small geographic areas. This study was conducted to systematically review the population prevalence, incidence, mortality and disability progression estimates of MS within the Asia Pacific region.



Conclusions

The global prevalence of MS has risen since 2013, but good surveillance data is not universal. Action is needed by multiple stakeholders to close knowledge gaps.

Phenotype Phebruary!

- https://forums.ohdsi.org/t/phenotype-phebruary-day-18-multiple-sclerosis/15978

1. There is no specific test for MS. Doctors use a medical history, physical exam, neurological exam, MRI, and other tests to diagnose
2. Given that MS is a disease with a natural tendency to remit spontaneously it is important to define what kind of MS patients we want to model?
    a. Patients with a new and first ever onset of MS
    b. Patients with relapsing MS
    c. **Patients with evidence of MS regardless of the stage or the status of their disease**

Cohort	Logic (entry event, inclusion criteria)	Exit criteria	Cohort in atlas
Earliest occurrence of Multiple sclerosis	Earliest occurrence of MS diagnosis,	End of observation period	ATLAS 2
Widdifield	Earliest occurrence of MS diagnosis, requiring 1 hospitalization with MS or 5+ occurrence of MS diagnosis in 2 year	End of observation period	ATLAS 1
Culpepper 3x	Earliest occurrence of MS diagnosis, requiring ≥3 MS-related occurrences of any combination of inpatient or outpatient diagnosis, or S-specific disease-modifying therapies (DMT) within a 1-year time period;	End of observation period	ATLAS 6

Show 100 entries Search:

Cohort	cprd		jmdc		optum_ehr		optum_extended_dod		truven_ccae		truven_mdcd		truven_mdcr	
	Entries	Subjects	Entries	Subjects	Entries	Subjects	Entries	Subjects	Entries	Subjects	Entries	Subjects	Entries	Subjects
C7	34,035	20,700	3,337	3,127	346,267	226,311	295,146	230,638	434,403	350,573	96,070	77,304	50,006	38,294
C11	2,117	2,117	2,542	2,542	138,913	138,913	146,486	146,486	220,696	220,696	44,645	44,645	20,601	20,601
C13	722	722	2,423	2,423	95,370	95,370	124,908	124,908	173,829	173,829	43,078	43,078	20,016	20,016

Showing 1 to 3 of 3 entries Previous 1 Next

CDM	Phenotype algorithm	sensitivity	ppv	specificity	npv
CCAE	[Phenotype Phebruary][MS] Earliest occurrence of Multiple sclerosis	0.905 (0.896 - 0.913)	0.761 (0.750 - 0.771)	0.999 (0.999 - 0.999)	1.000 (1.000 - 1.000)
	[Phenotype Phebruary][MS] by Widdifield NSJ 2015	0.542 (0.529 - 0.555)	0.943 (0.934 - 0.951)	1.000 (1.000 - 1.000)	0.999 (0.999 - 0.999)
	[Phenotype Phebruary][MS] Culpepper 3x	0.685 (0.672 - 0.698)	0.938 (0.930 - 0.946)	1.000 (1.000 - 1.000)	0.999 (0.999 - 0.999)
Medicaid	[Phenotype Phebruary][MS] Earliest occurrence of Multiple sclerosis	0.846 (0.836 - 0.855)	0.722 (0.711 - 0.733)	0.999 (0.999 - 0.999)	1.000 (1.000 - 1.000)
	[Phenotype Phebruary][MS] by Widdifield NSJ 2015	0.585 (0.572 - 0.598)	0.885 (0.874 - 0.895)	1.000 (1.000 - 1.000)	0.999 (0.999 - 0.999)
	[Phenotype Phebruary][MS] Culpepper 3x	0.624 (0.611 - 0.637)	0.926 (0.917 - 0.934)	1.000 (1.000 - 1.000)	0.999 (0.999 - 0.999)
Medicare	[Phenotype Phebruary][MS] Earliest occurrence of Multiple sclerosis	0.684 (0.675 - 0.692)	0.754 (0.746 - 0.762)	0.999 (0.998 - 0.999)	0.998 (0.998 - 0.998)
	[Phenotype Phebruary][MS] by Widdifield NSJ 2015	0.442 (0.434 - 0.451)	0.869 (0.861 - 0.877)	1.000 (0.999 - 1.000)	0.996 (0.996 - 0.996)
	[Phenotype Phebruary][MS] Culpepper 3x	0.443 (0.434 - 0.451)	0.926 (0.919 - 0.932)	1.000 (1.000 - 1.000)	0.996 (0.996 - 0.996)

The more specific algorithms (Widdifield and Culpepper) showed higher PPV than the sensitive 1X code algorithm. The interesting thing that I saw was that if there was a choice between Widdifield and Culpepper it seems that Culpepper wins. In 2 of the 3 databases it had higher PPV as well as higher sensitivity in 2 of the 3. It had both higher PPV and sensitivity in Medicaid. That said, the performance on sensitivity and PPV were actually quite similar with the exception of a large sensitivity gain with Culpepper in CCAE, people of working age and their dependents. Widdifield requires a hospitalization (early in the disease possibly so may not need hospitalization) or 5 codes (early in the disease so may not need clinical care as frequently as those farther along with the condition) which may be less likely in younger subjects.

2. What is the utilisation of multiple sclerosis treatments across the APAC region?

Early aggressive/highly effective

Medicine	Concept_ID
natalizumab	735843
alemtuzumab	1312706
Ocrelizumab	1593457
rituximab	1314273
ofatumumab	40167582
cladribine	19054825

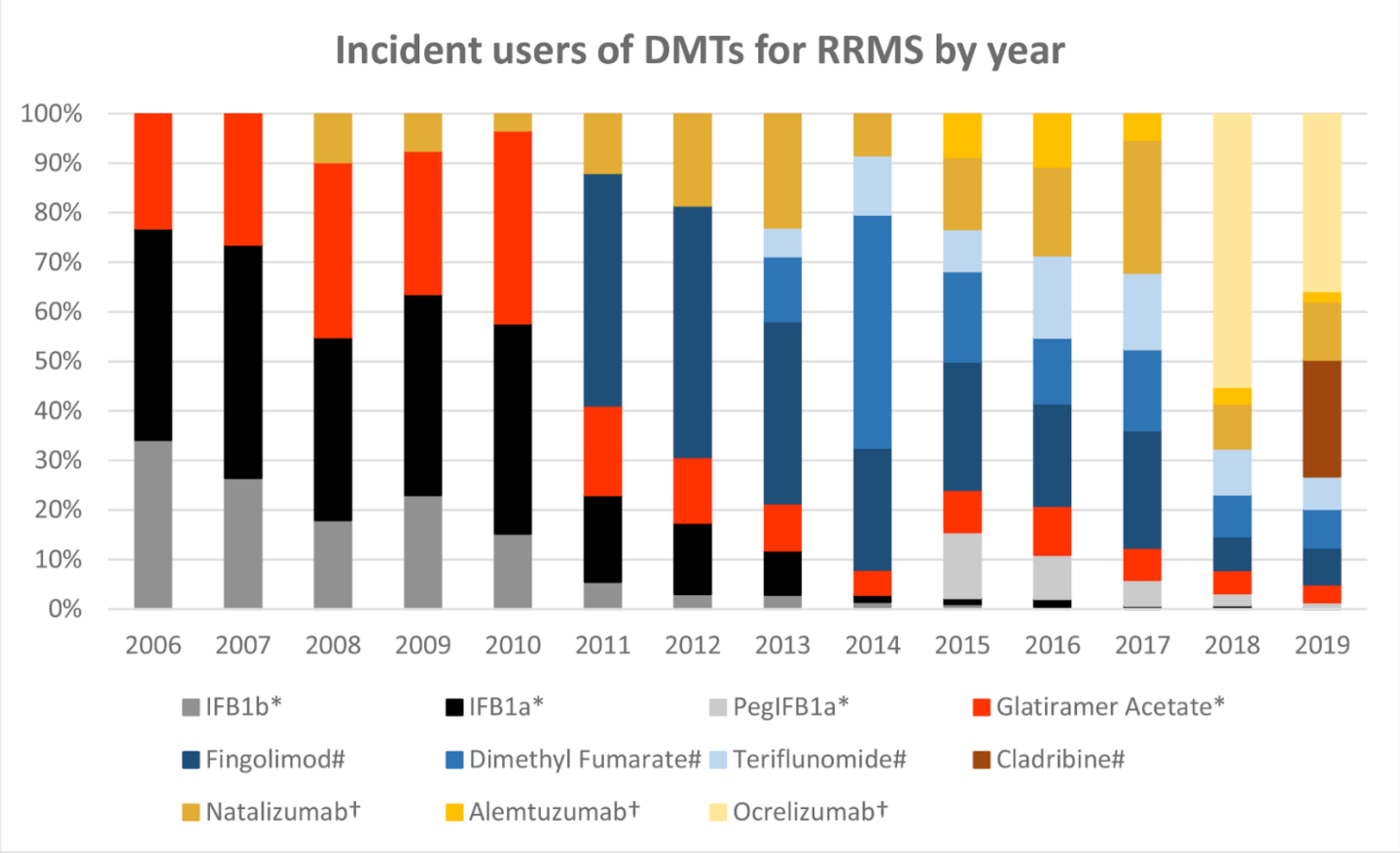
Traditional/escalation

Medicine	Concept_ID
peginterferon beta-1a	45775146
Glatiramer	751889
teriflunomide	42900584
diroximel fumarate	37497593
dimethyl fumarate	43526424
fingolimod	40226579
siponimod	1510913
ozanimod	37499437
Interferon beta-1a	722424
interferon beta-1b	713196

Other FDA approved

Medicine	Concept_ID
Daclizumab	19036892
Mitoxantrone	1309188

2. What is the utilisation of multiple sclerosis treatments across the APAC region?



Multiple Sclerosis and Related Disorders 57 (2022) 103412

Early aggressive/highly effective

It's a dynamic market!

2. What are the treatment pathways of multiple sclerosis medicines across the APAC region?

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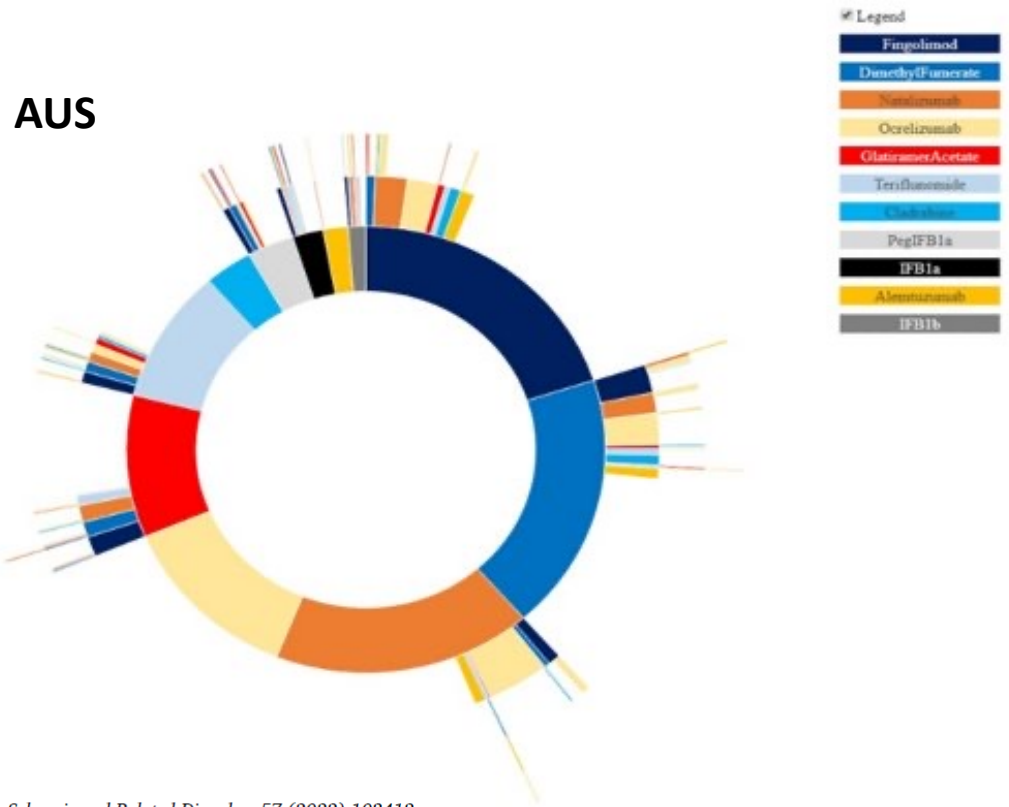

Multiple Sclerosis and Related Disorders 57 (2022) 103412

US

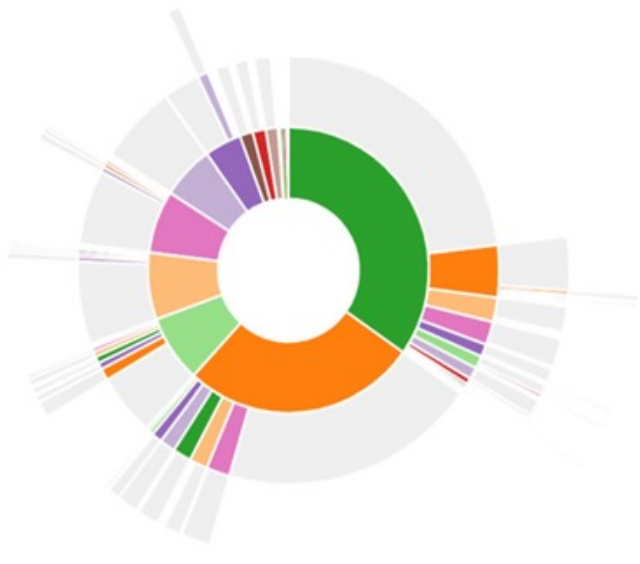

Fig. 1 Sunburst of treatment patterns starting with first line (inner-most donut) to fourth line (outer slices). Each color represents a distinct medication, and each layer represents a new treatment line and illustrates the sequence in which patients received different therapies; for example the large green piece in the middle indicates first-line glatiramer use, and the dark orange slice on the next outer ring adjacent to the green indicates a switch from glatiramer to dimethyl fumarate. Slices that have multiple colors indicate combination therapy with more than one medication. Slices in grey indicate no additional medication was taken

Kern and Cepeda *BMC Neurology* (2020) 20:296
https://doi.org/10.1186/s12883-020-01882-2

Has there been a change overtime in the use of High Efficacy treatments earlier in the treatment pathway?

3. Real world safety and effectiveness of treatments for MS?

Curr Treat Options Neurol (2021) 23:19
DOI 10.1007/s11940-021-00677-1

Multiple Sclerosis and Related Disorders (J Graves, Section Editor)

Early Aggressive Treatment Approaches for Multiple Sclerosis

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Recent findings

- **Natalizumab** promising efficacy in RCTs and observational studies when compared with placebo, the injectable DMTs, and fingolimod.
- The anti-CD20 B cell depleting therapies (**rituximab, ocrelizumab, and ofatumumab**) demonstrated superiority in RCTs compared to their comparator group (placebo, interferon, and teriflunomide, respectively) and
- **Rituximab** has shown in observational studies to be more effective than older injectable therapies and some of the oral therapies.
- **Alemtuzumab** has shown good efficacy in RCTs and observational studies yet has several potentially severe side effects limiting its use.

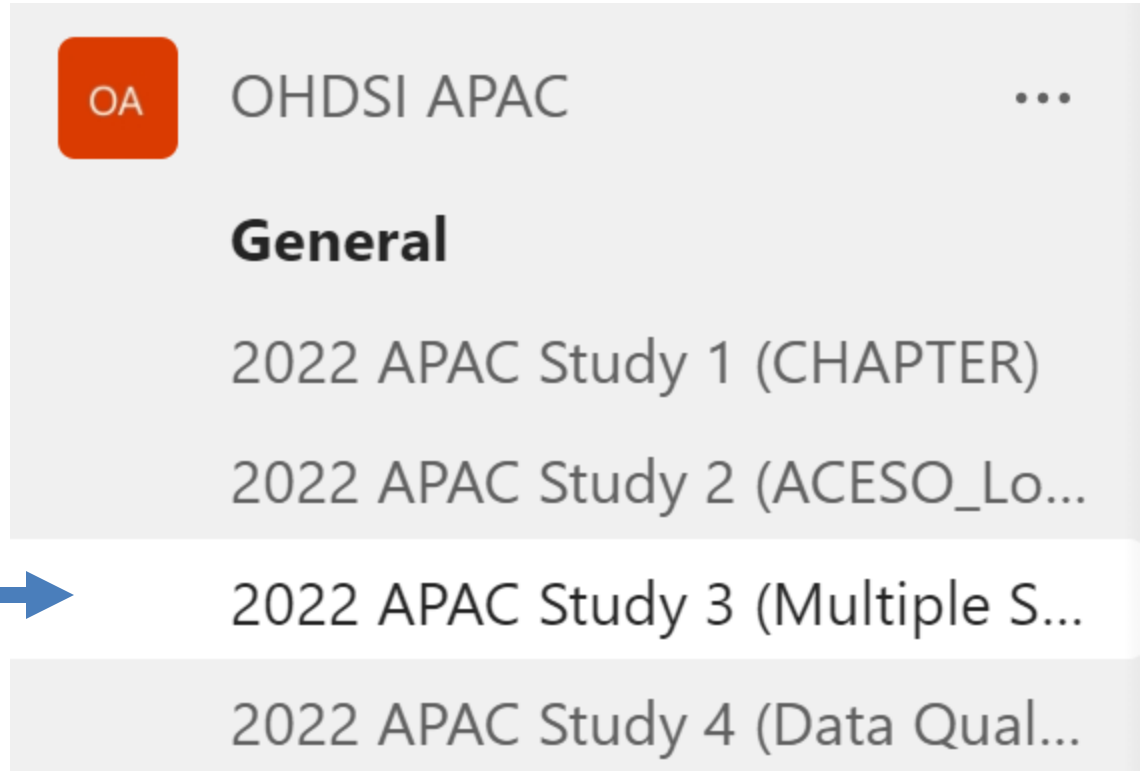
Has the increased use of High Efficacy treatments earlier in the treatment pathway led to better outcomes for patients diagnosed with MS?

RCTs that are investigating the effectiveness of traditional MS treatments with HET strategies

- *The 'Determining the Effectiveness of earLy Intensive Versus Escalation Approaches for the treatment of Relapsing-remitting MS' (DELIVER-MS) (NCT03535298) trial* will directly compare traditional MS with HET strategies and their impact on clinical and radiologic outcomes.
- *The 'TRaditional versus Early Aggressive Therapy for MS' (TREAT-MS*) (NCT03500328) trial aims to 1) evaluate, jointly and independently among patients deemed at higher risk vs. lower risk for disability accumulation, whether an "early aggressive" therapy approach, versus starting with a traditional, first-line therapy, influences the intermediate-term risk of disability, and 2) to evaluate if, among patients deemed at lower risk for disability who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy versus a new first-line therapy have different intermediate-term risk of disability."
- The DELIVER-MS study is due for completion in 2025 while the TREAT-MS study is due for completion in 2024.

Thank you!

- Next steps
  - Finalise MS Phenotype
  - Finalise MS medicines list
- Developing Protocol



- Fortnightly meetings at 11am Korean Time on Wednesday