touchSATELLITE SYMPOSIUM

Considering the complete picture in neuromyelitis optica spectrum disorder: Optimizing diagnosis and management to improve patient outcomes

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actrims 2022 FORUM
West Palm Beach, Florida
February 24-26

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Expert faculty

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Disclosures

Prof. Sean Pittock	*Advisory Board and panel fees from* Alexion Pharmaceuticals Inc., F. Hoffmann-La Roche AG, Genentech and UCB Pharma. *Consultant fees from* Alexion Pharmaceuticals Inc., EUROIMMUN, MedImmune/Viela Bio (all compensation paid directly to the Mayo Clinic); Prime Therapeutics, Roche/Genentech, Sage Therapeutics, UCB Pharma (personal compensation); Astellas Pharma Inc (compensation to the Mayo Clinic and personal). *Grants and research support from* AEA, Alexion Pharmaceuticals Inc., Grifols, Guthy-Jackson Charitable Foundation, MedImmune/Viela Bio and National Institutes of Health (all compensation is paid directly to the Mayo Clinic).
Dr Amy Kunchok	*Advisory board or panel fees from* Genentech.
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Agenda

Presentation	Speaker
Introduction and welcome	Prof. Sean Pittock
Applying diagnostic tools to recognize patients with NMOSD	Prof. Sean Pittock and Dr Amy Kunchok
Exploring emerging therapies to reduce relapse in NMOSD	Prof. Sean Pittock and Prof. Dean Wingerchuk
Adopting a holistic approach to improve quality of life for patients with NMOSD	All faculty
Summary and close	Prof. Sean Pittock

NMOSD, neuromyelitis optica spectrum disorder.

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Learning objectives

- Describe the clinical manifestations of NMOSD, the typical MRI findings and differential diagnoses
- Analyse the treatment options for the prevention of NMOSD attacks and their selection criteria
- Determine strategies for holistic management of the broad range of symptoms experienced by patients with NMOSD

MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder.

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Applying diagnostic tools to recognize patients with NMOSD

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NMOSD, neuromyelitis optica spectrum disorder.

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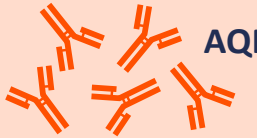
NMOSD, AQP4-IgG and MOGAD

NMOSD[1]



AQP4-IgG +ve plus ONE of:

AND no alternative diagnosis

AQP4-IgG –ve/unknown, no alternative diagnosis plus ≥2 of:
(but including optic neuritis, acute myelitis with LETM or APS)

AND additional MRI requirements for NMOSD

- Optic neuritis
- Acute myelitis
- Area postrema syndrome
- Acute brainstem syndrome
- Narcolepsy/acute diencephalic clinical syndrome
- Symptomatic cerebral syndrome

MOG antibody disorders[2]

MOG-IgG +ve plus ANY of:

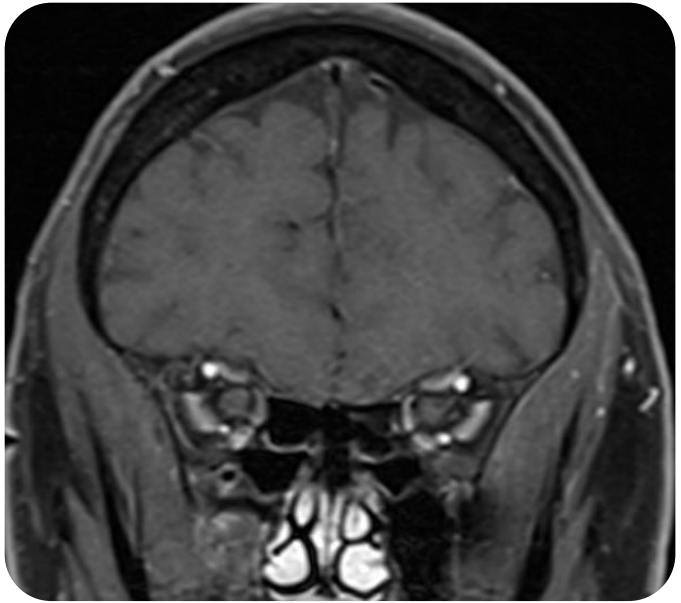
AND
no alternative diagnosis

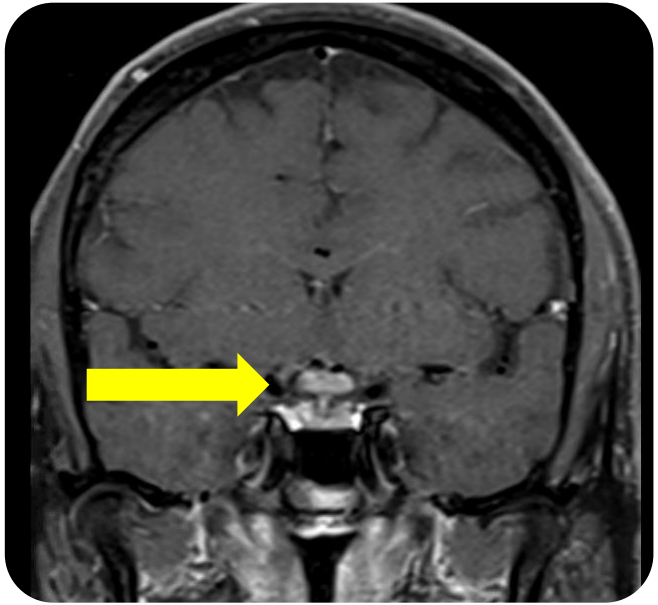
- Acute demyelinating encephalomyelitis
- Optic neuritis, including CRION
- Transverse myelitis (LETM or STM)
- Brain or brainstem syndrome compatible with demyelination

APS, area postrema syndrome; AQP4, aquaporin-4; CRION, chronic relapsing inflammatory optic neuropathy; IgG, immunoglobulin G; LETM, longitudinally extensive transverse myelitis; MOG(AD), myelin oligodendrocyte glycoprotein (antibody disorder); MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; STM, short-segment transverse myelitis.

1. Wingerchuk DM, et al. *Neurology*. 2015;85:177–89; 2. López-Chiriboga AS, et al. *JAMA Neurol*. 2018;75:1355–1363.

Optic neuritis



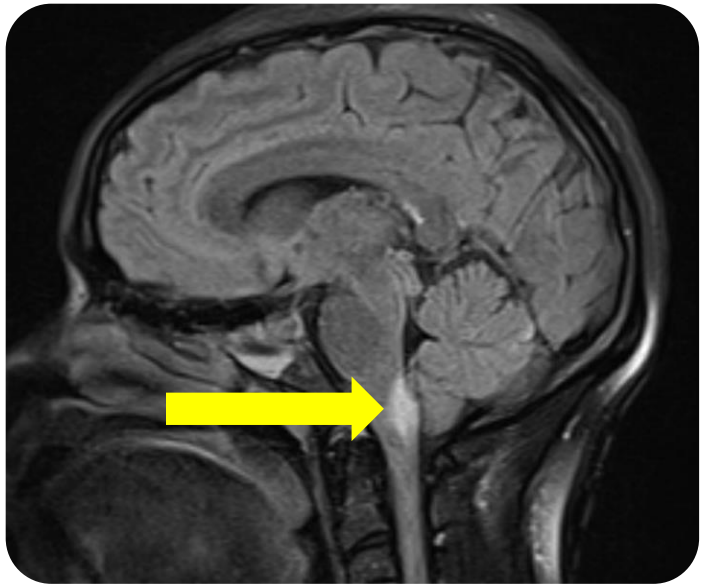


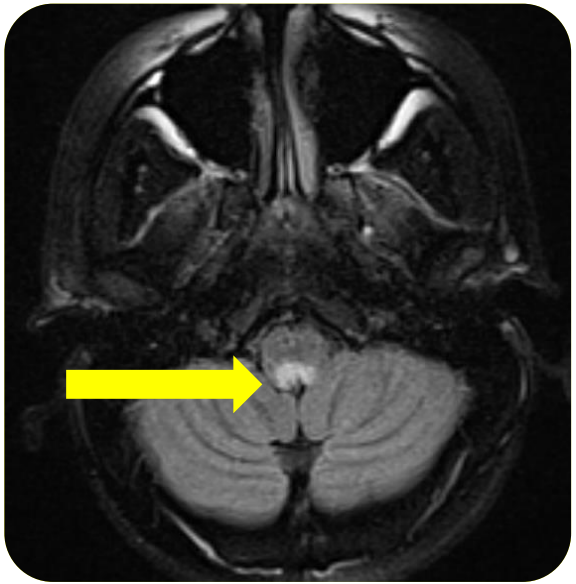
- 53-year-old male with prior transverse myelitis
- Presented with bilateral optic neuritis with optic chiasm involvement
- AQP4-IgG +ve

- Optic neuritis often involves the posterior optic nerve
- Chiasmal involvement can be seen in ~20%
- Bilateral optic neuritis is more common than in MS

AQP4-IgG, aquaporin 4-immunoglobulin G; MS, multiple sclerosis.
Slide provided courtesy of Dr Kunchok.

Area postrema syndrome



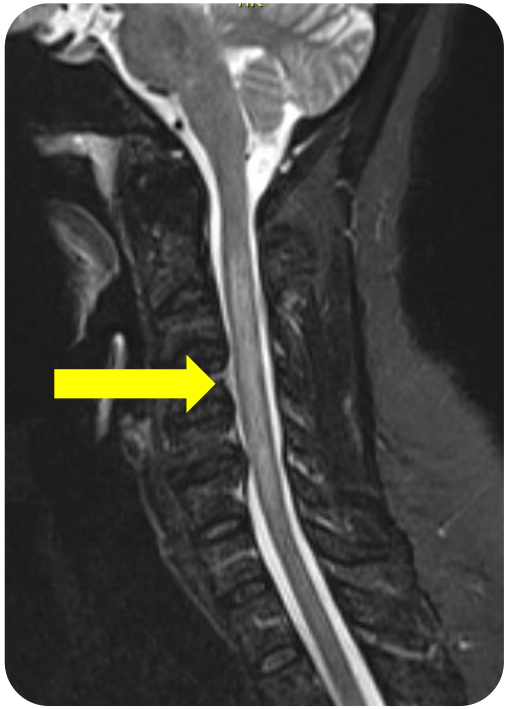


- 29-year-old African-American woman
- Persistent nausea and vomiting (2 months), labelled as gastroenteritis with two hospital presentations
- Second presentation: additional dysphagia and left-sided numbness
- AQP4-IgG +ve, coexistent ANA and SSA

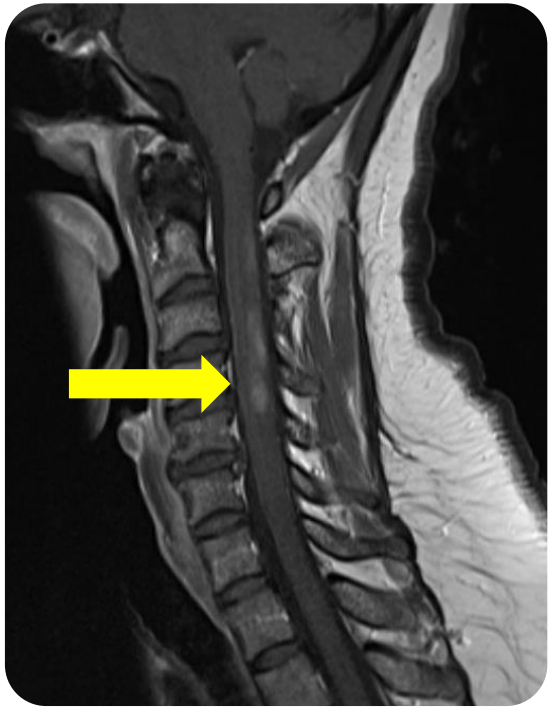
- Peri-ependymal lesions are common
- Highly vascular, devoid of blood-brain barrier
- APS: 7–10% at onset, 9–15% at subsequent attacks

ANA, antinuclear autoantibodies; AQP4-IgG, aquaporin 4-immunoglobulin G; SSA, Sjögren syndrome antibodies.
Slide provided courtesy of Dr Kunchok.

Longitudinally extensive transverse myelitis



- 49-year-old female
- Burning paresthesia in both legs that spread to the left arm followed by progressive weakness in the lower limbs and left arm
- AQP4-IgG +ve



- LETM ≥3 vertebral segments
- Central grey matter
- Ring enhancement
- Bright spotty T2 lesions

AQP4-IgG, aquaporin 4-immunoglobulin G; LETM, longitudinally extensive transverse myelitis.
Slide provided courtesy of Dr Kunchok.

MRI lesion diagnostic characteristics

Lesion characteristics	NMOSD	MS	MOGAD
Vertebral length	≥3 contiguous segments, some shorter	<3 contiguous segments, multiple	<3 contiguous segments more common than NMOSD
Location	Cervical/upper thoracic cord, central grey matter	Cervical cord, peripheral white matter	More caudal, may involve conus medullaris
Appearance	T2 bright spotty lesions T1 hypointense acute lesions, central location	Well demarcated, asymmetric T1 hypointensity rare, peripherally located	Axial T2 H-shaped hyperintensity
Post-attack	Change to short, distinct lesions or replacement by spinal cord atrophy	Complete lesion resolution possible, spinal cord atrophy rare	Lesions resolve; spinal cord atrophy rare

MOGAD, myelin oligodendrocyte glycoprotein antibody disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

Solomon JM, et al. *Ther Adv Neurol Disord.* 2021;14:1–18.

Serological testing: AQP4-IgG

Sensitivity and specificity of autoantibody assays[1]

	Tissue-based indirect immunofluorescence	ELISA	Euroimmun M1/M23 biochip slide	Euroimmun AQP4 fixed CBA	Oxford AQP4 live CBA
Specificity, % (True negative rate)	100	97	95	98	100
Sensitivity, % (True positive rate)	78	60	90	94	92

All methods have high specificity

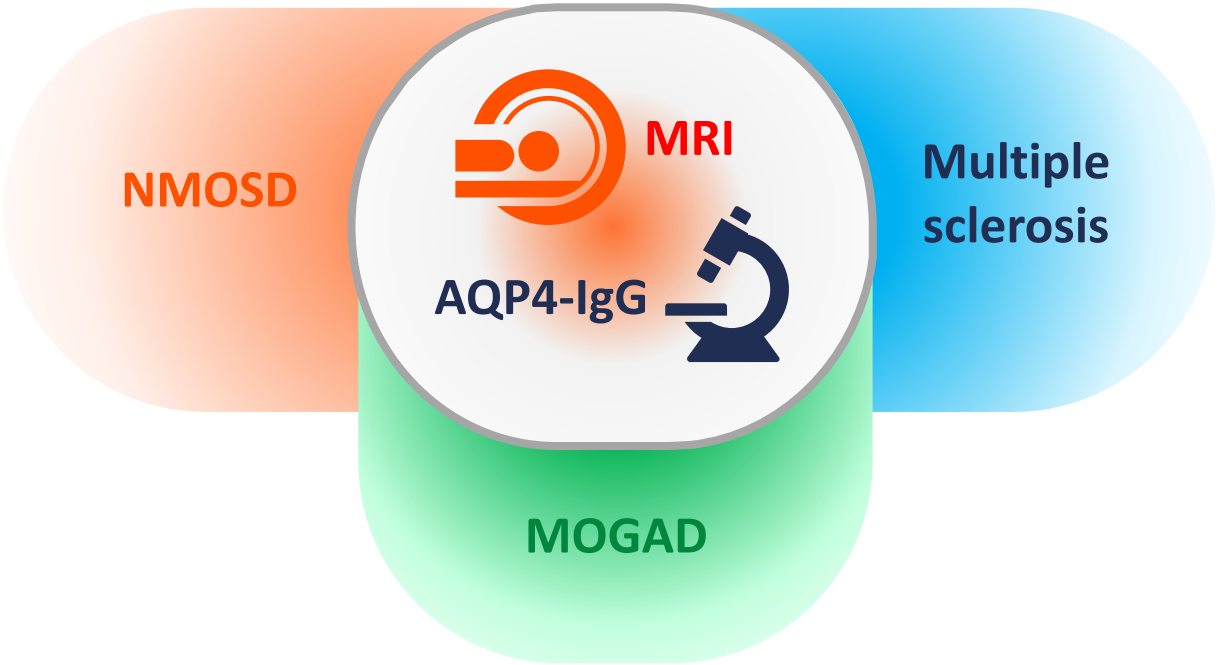
Low sensitivity is associated with false positives

- CBAs are highly specific and have not been associated with false positives[2]
- Anti-AQP4 titer by ELISA is not predictive of disease course[3]
- Serum testing is more sensitive than CSF[4]
- CSF findings in AQP4+ NMOSD:[5]
  - Lack of oligoclonal bands vs multiple sclerosis
  - Pleocytosis with predominance of neutrophils and eosinophils

AQP4, aquaporin-4; CBA, cell-based assay; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; NMOSD, neuromyelitis optica spectrum disorder.

1. Prain K, et al. *Front Neurol*. 2019;10:1028; 2. Redenbaugh V, et al. *Mult Scler J Exp Transl Clin*. 2021;7:20552173211052656;
3. Kessler RA, et al. *Mult Scler Relat Disord*. 2017;17:198–201; 4. Majed M, et al. *Neurol Neuroimmunol Neuroinflamm.* 2016;3:e231;
5. Jarius S, et al. *J Neurol Sci*. 2011;306:82–90.

Summary



AQP4-IgG, aquaporin 4-immunoglobulin G; MOGAD, myelin oligodendrocyte glycoprotein antibody disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

Exploring emerging therapies to reduce relapse in NMOSD

Prof. Sean Pittock

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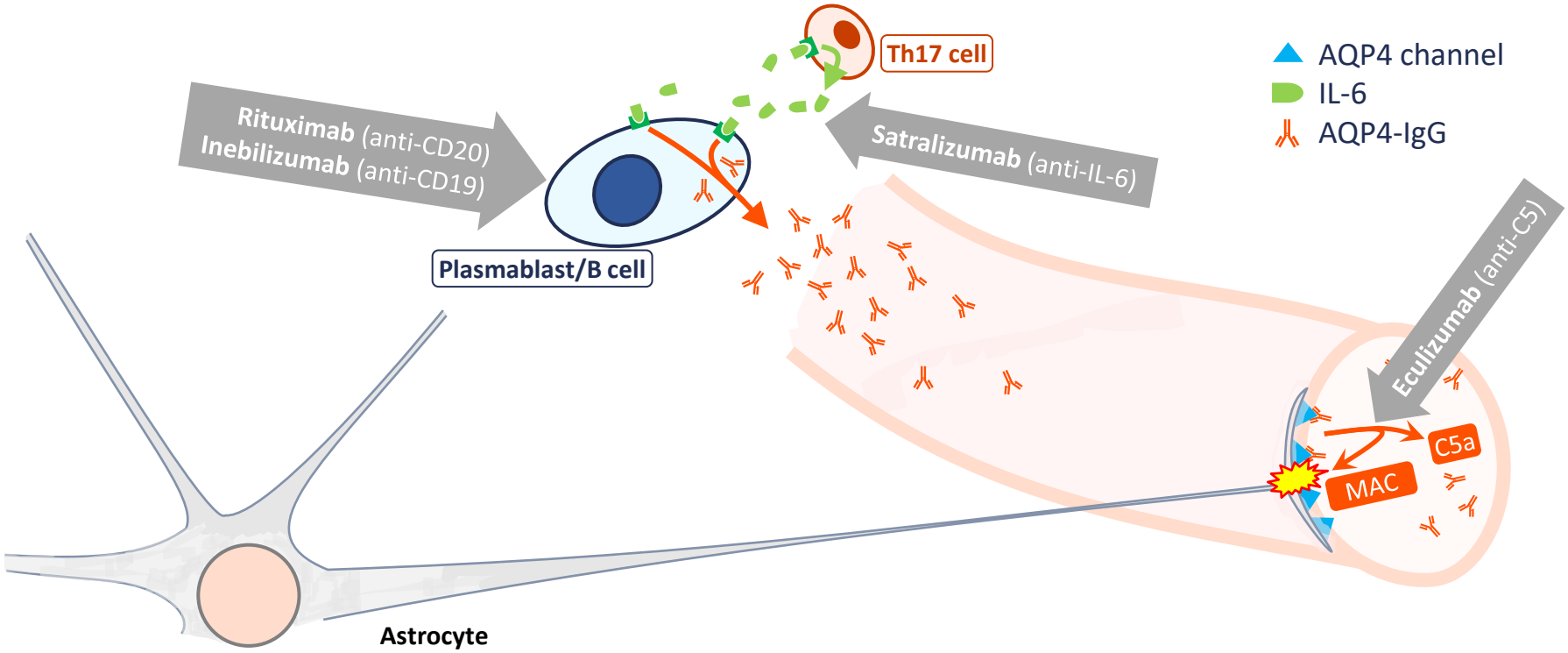
Rochester, MN, USA

Prof. Dean Wingerchuk

Mayo Clinic
Phoenix and Scottsdale
AZ, USA

NMOSD, neuromyelitis optica spectrum disorder.

Targets for approved NMOSD immunotherapies[1–3]



AQP4, aquaporin-4; C5(a), complement protein 5(a); CD19/20, cluster of diffentiation-19/20; IgG, immunoglobulin G; IL-6, interleukin-6; MAC, membrane attack complex; NMOSD, neuromyelitis optica spectrum disorder.

1. Weinshenker BG, et al. *Mayo Clin Proc.* 2017;92:663–79; 2. Chihara N, et al. *touchREVIEWS Neurol*. 2021;17:11–5; 3. Pittock SJ, et al. *Nat Rev Neurol.* 2021;17:759–73.

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Eculizumab: PREVENT study (AQP4-IgG +ve NMOSD)

PREVENT primary analysis[1]

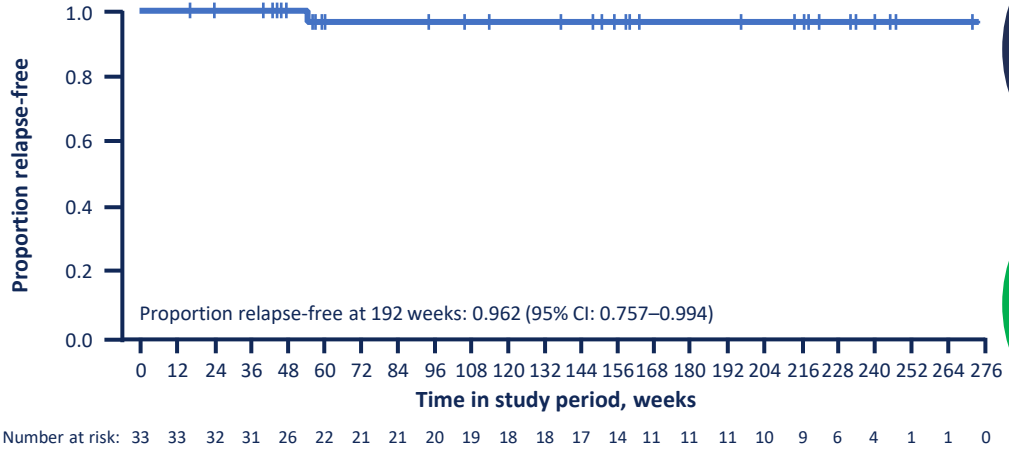
- 96 patients received eculizumab
- 47 patients received placebo
- Concomitant immunotherapy permitted

94%
reduction in risk of attack in AQP4-IgG +ve patients (p<0.001)

- **0/21** relapses at 144 weeks with eculizumab monotherapy vs **7/13** with placebo monotherapy

Open-label extension[2*]

- Crossover to eculizumab from placebo was permitted
- 33 patients with AQP4-IgG +ve NMOSD received eculizumab monotherapy



Median 2.8 years monotherapy duration

96% relapse-free at ~4 years

NCT01892345 (PREVENT); NCT02003144 (open-label extension). * Figure reproduced with permission from Pittock SJ, et al. *Mult Scler J. 2021;doi: 10.1177/13524585211038291.*
AQP4-IgG +ve, aquaporin-4-IgG-positive; CI, confidence interval; NMOSD, neuromyelitis optica spectrum disorder.
1. Pittock SJ, et al. *N Engl J Med.* 2019;381:614–25; 2. Pittock SJ, et al. *Mult Scler J. 2021;doi: 10.1177/13524585211038291.*

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Inebilizumab: N-MOmentum study

N-MOmentum primary analysis[1]

- 174 patients received inebilizumab
- 56 patients received placebo
- Concomitant immunotherapy not permitted; only oral prednisone permitted during first 3 weeks of study

77%
reduction in risk of attack in 161 AQP4-IgG +ve patients (p<0.0001)

Open-label extension[2]

- Crossover to open-label phase permitted
- 216 patients entered in total (91% of placebo group and 95% of inebilizumab group)

87.7%
of patients who originally received inebilizumab attack-free at up to 4 years

83.4%
of patients who originally received placebo attack-free at up to 4 years

- Not powered to assess efficacy in AGQ4-IgG –ve patients

NCT02200770.
AQP4-IgG +ve, aquaporin-4-IgG-seropositive; CI, confidence interval; IgG, immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder.
1. Cree BAC, et al. *Lancet.* 2019;394:1352–63; 2. Cree BAC, et al. Presented at 2021 American Academy of Neurology Annual Meeting; April 17-22. Abstract P15.076.

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Satralizumab: SAkuraSky and SAkuraStar studies

SAkuraSky study[1]

- 41 patients received satralizumab
- 42 patients received placebo
- Concomitant immunotherapy permitted

79% reduction in relapse risk in AQP4-IgG +ve (95% CI 0.06–0.75)[1]

89% of all patients attack-free at 48 weeks vs 66% in placebo group

SAkuraStar study[2]

- 63 patients received satralizumab
- 32 patients received placebo
- Concomitant immunotherapy prohibited

74% reduction in relapse risk in AQP4-IgG +ve (95% CI 0.11–0.63)[2]

76% of all patients attack-free at 48 weeks vs 62% in placebo group

Open-label extension[4]

- 166 patients from both studies
- Median satralizumab exposure was 96.1 weeks (randomized study period) and 131.9 weeks (open-label extension)

51% lower risk of relapse in patients originally randomized to satralizumab vs placebo

66% risk reduction in AQP4-IgG +ve patients (p<0.001)

No significant differences vs placebo in AQP4-IgG –ve populations[1,2]

Pooled analysis: 75% risk reduction in AQP4-IgG +ve patients vs 58% risk reduction overall[3]

AQP4-IgG +ve, aquaporin-4-IgG-seropositive; CI, confidence interval; IgG, immunoglobulin G.

1. Yamamura T, et al. *New Engl J Med.* 2019;381:2114–24; 2. Traboulsee A, et al. *Lancet Neurol.* 2020;19:402–12; 3. Haskova Z, et al. *Invest Ophthalmol Vis Sci.* 2020;61:3173.
4. Haskova Z, et al. *Invest Ophthalmol Vis Sci.* 2021;62:3475.

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AE profiles with immunotherapies for NMOSD

Eculizumab
PREVENT study

Compared with placebo:
- Similar overall AE (92% vs 91%) and SAE (16% vs 15%) rates[1]
- More upper RTIs 29% vs 13%[1]
- No meningococcal infections[1]
- One death from pulmonary empyema in the eculizumab group[2]
- Long-term monotherapy well tolerated in the OLE[2]

Inebilizumab
N-MOmentum study

Compared with placebo:
- Similar overall AE (72% vs 73%) and SAE (5% vs 9%) rates[3]
- More arthralgia 10% vs 4%[3]
- Similar rates of IRR (9% vs 11%) and infection (38% vs 41%)[2]
- Two deaths during the OLE (disease worsening in the context of pneumonia and an indeterminate brain lesion)[2]
- Treatment well tolerated over 4 years in the OLE[2]

Satralizumab
SAkuraSky and SAkuraStar studies

Compared with placebo:
- Similar overall AE (90% vs 95%[4] and 92% vs 75%[5]) and SAE (17% vs 21%[4] and 19% vs 16%[5]) rates
- Similar rates of serious infection (5% vs 7%[4] and 10% vs 9%[5])
- No anaphylactic reactions or opportunistic infections[2]
- No new safety signals reported in the OLE[6]

(S)AE, (serious) adverse event; IRR, infusion-related reaction; NMOSD, neuromyelitis optica spectrum disorder; OLE, open-label extension; RTI, respiratory tract infection.

1. Pittock SJ, et al. *N Engl J Med.* 2019;381:614–25; 2. Pittock SJ, et al. *Nat Rev Neurol.* 2021;17:759–73; 3. Cree BAC, et al. *Lancet.* 2019;394:1352–63;
4. Yamamura T, et al. *New Engl J Med.* 2019;381:2114–24; 5. Traboulsee A, et al. *Lancet Neurol*. 2020;19:402–12; 6. Haskova Z, et al. *Invest Ophthalmol Vis Sci.* 2021;62:3475.

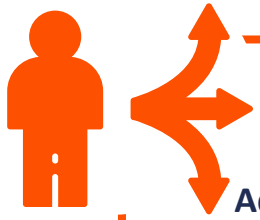
Factors influencing immunotherapy choice

Availability[1*]

- Eculizumab and satralizumab approved in several regions including the USA, Canada, Japan, Australia and some EU countries
- Inebilizumab approved in the USA and Japan

Testing

- Need for sensitive and specific cell-based AQP4-IgG assays[1]
- No agent has been approved for AQP4-IgG-negative NMOSD



Patient preference and adherence

Administration route and frequency

- Eculizumab: i.v. administration weekly for five doses then every 2 weeks[2]
- Inebilizumab: i.v. administration of two doses, 2 weeks apart, then one dose every 6 months[3]
- Satralizumab: s.c. injection every 2 weeks for three doses then every 4 weeks[4]

Willingness to switch if stable on older therapy[1]

Infection risk with lifelong therapy, and with concomitant immunosuppressives

Cost of lifelong therapy

*As of December 2021. AQP4-IgG, aquaporin-4 immunoglobulin; i.v., intravenous; NMOSD, neuromyelitis optica spectrum disorder; s.c., subcutaneous.

1. Pittock SJ, et al. *Nat Rev Neurol.* 2021;17:759–73; 2. Eculizumab prescribing information 2019. www.accessdata.fda.gov/drugsatfda_docs/label/2019/125166s431lbl.pdf;
3. Inebilizumab prescribing information 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/761142s000lbl.pdf;
4. Satralizumab prescribing information 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/761149s000lbl.pdf.

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Summary

Eculizumab

Inebilizumab

Satralizumab

OLE data

- Highly effective
- Persistent long-term benefits
- Well tolerated

Shared decision-making to individualise therapy

OLE, open-label extension.

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Adopting a holistic approach to improve quality of life for patients with NMOSD

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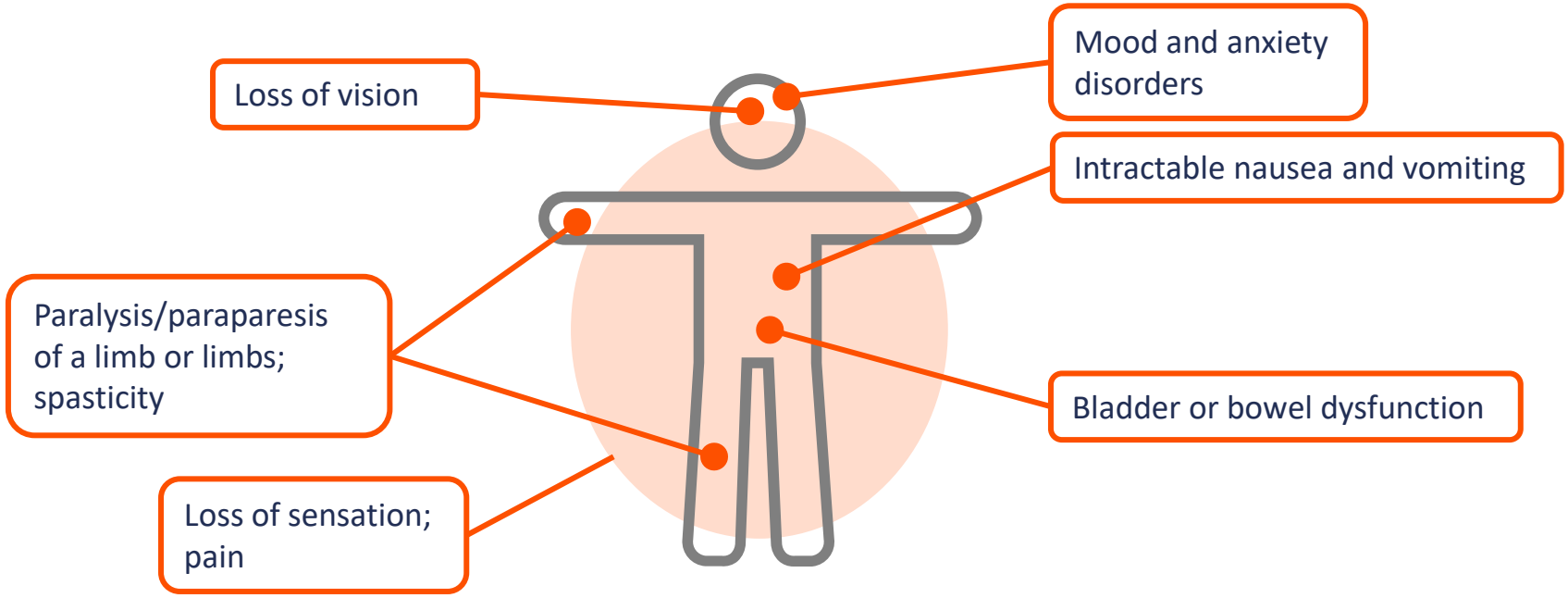
NMOSD symptoms



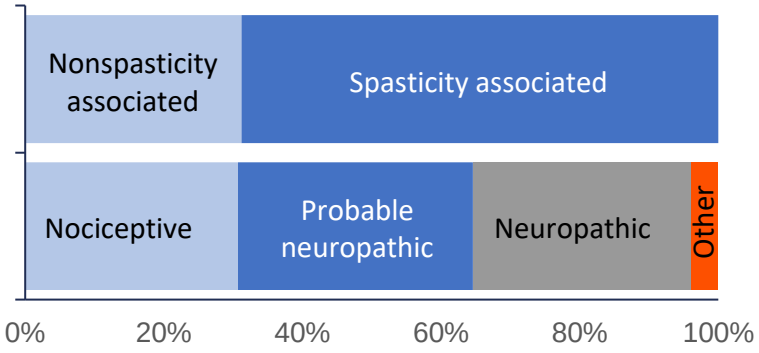
NMOSD, neuromyelitis optica spectrum disorder.

https://www.ohsu.edu/brain-institute/neuromyelitis-optica-spectrum-disorder-nmosd

Ayzenberg I, et al. *Neurol Neuroimmunol Neuroinflamm.* 2021;8:e985.

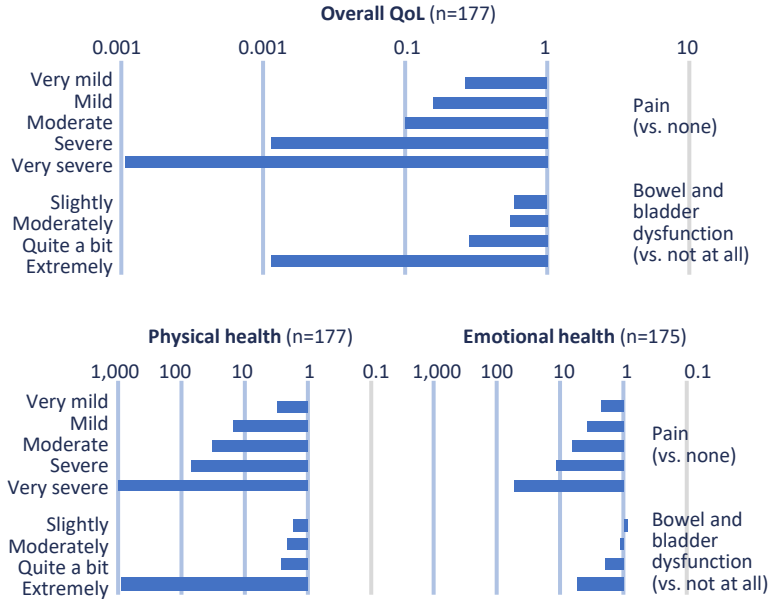
Pain, depression and quality of life

Character of pain in NMOSD and effect on daily living[1]



	Mean interference with daily activities*	
3.9/10	Work	6.6/10
2.8/10	Sleep	5.8/10
3.2/10	Walking	5.8/10
3.6/10	General activity	5.7/10

Impact of pain on QoL, physical and emotional health[2**]



*Measured using the short form of the Brief Pain Inventory questionnaire. **Figure reproduced with permission from Fujihara K, et al. *J Neurol Sci.* 2021;428:117546.
NMOSD, neuromyelitis optica spectrum disorder; QoL, quality of life.

1. Ayzenberg I, et al. *Neurol Neuroimmunol Neuroinflamm.* 2021;8:e985; 2. Fujihara K, et al. *J Neurol Sci.* 2021;428:117546.

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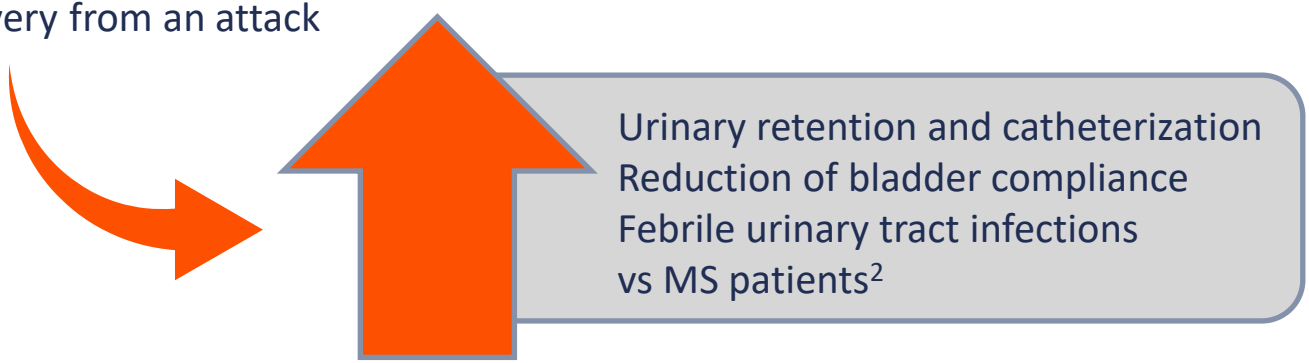
Neurogenic bladder in NMOSD

- Approximately 80% of patients with NMOSD have LUTS[1]
  - LUTS are more common and severe in NMOSD than in MS, and may persist after recovery from an attack

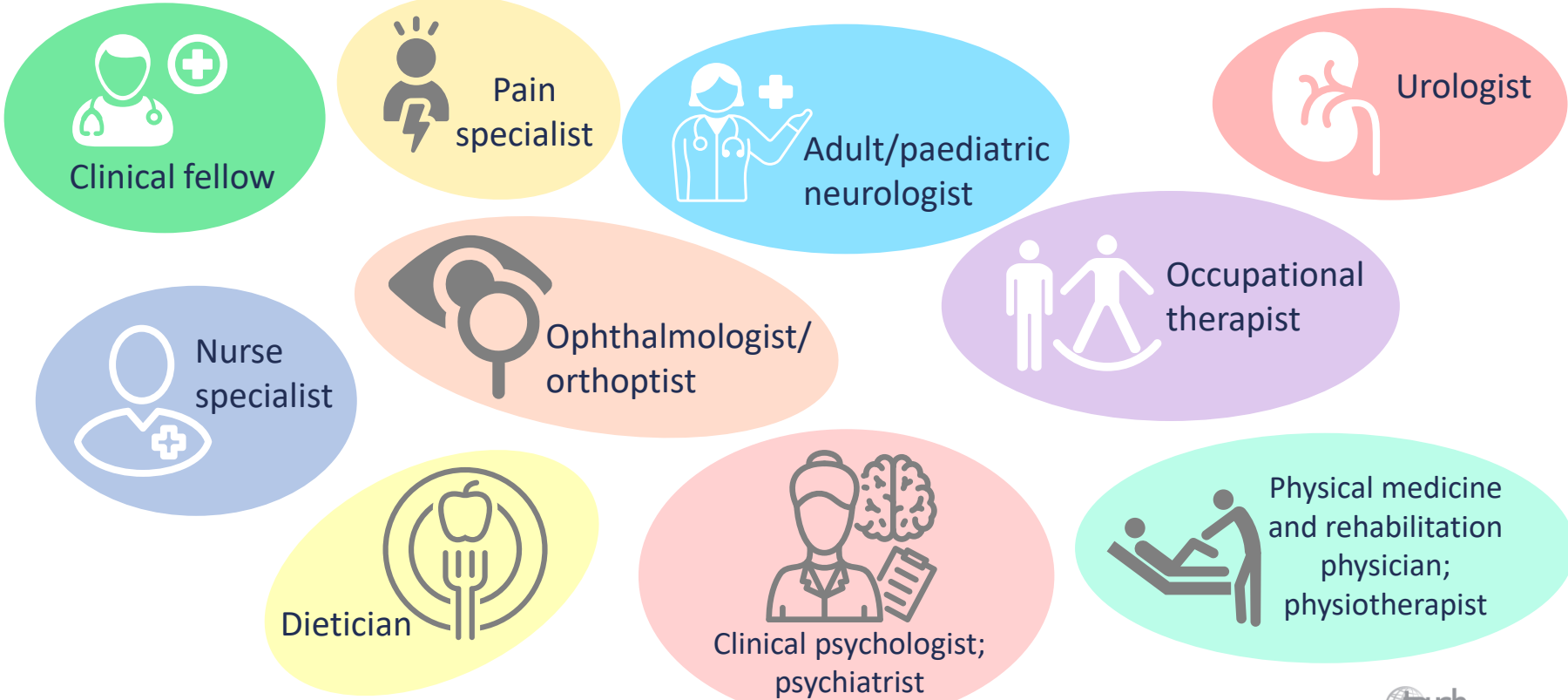


  - Ongoing management may therefore be required
  - Specialist referral should be considered

LUTS, lower urinary tract symptoms; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

1. Gupta A, et al. *J Neurosci Rural Pract*. 2020;11:245–49; 2. Declemy A, et al. *Int Neurourol J*. 2018;22:185–91.

MDT composition for NMOSD



MDT, multidisciplinary team; NMOSD, neuromyelitis optica spectrum disorder.
Huda S, et al. *Clin Med.* 2019;19:169–76.

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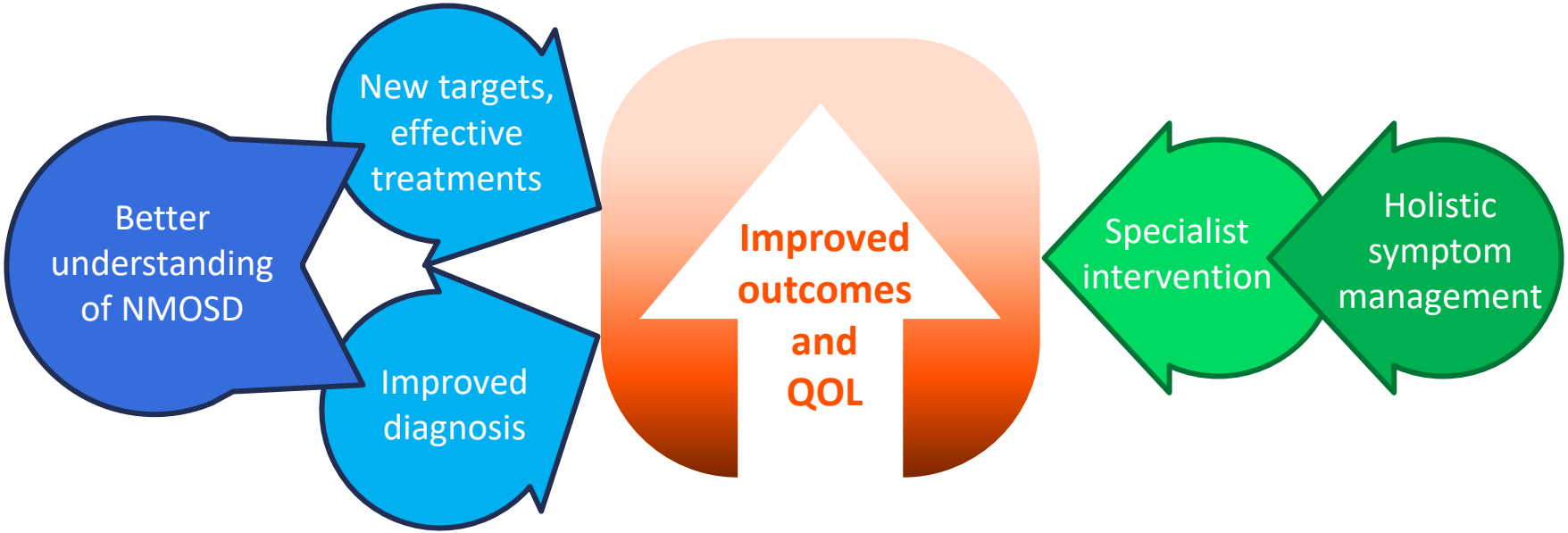
Summary and close

Prof. Sean Pittock

Mayo Clinic
Rochester, MN, USA

Summary

Significant progress in NMOSD research over the last 20 years



NMOSD, neuromyelitis optica spectrum disorder; QOL, quality of life.

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