

THE USE OF NATALIZUMAB (TYSABRI) FOR THE TREATMENT OF MULTIPLE SCLEROSIS

This is a summary of the American Academy of Neurology (AAN) guideline regarding recommended use and best practices for the use of natalizumab (Tysabri) for the treatment of multiple sclerosis.

Please refer to the full guideline for detailed findings and supporting evidence for the use of natalizumab for the treatment of multiple sclerosis at www.aan.com.

1. Does treatment with natalizumab reduce disease activity in RRMS by clinical and MRI measures?

Strong evidence	Strong evidence suggests that natalizumab reduces measures of disease activity such as clinical relapse rate, Gd-enhancement, and new and enlarging T2 lesions in patients with relapsing MS (Level A⁺).
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2. Does treatment with natalizumab reduce disease severity in RRMS by clinical and MRI measures?

Strong evidence	Strong evidence suggests that natalizumab improves measures of disease severity such as the EDSS progression rate and the T2-hyperintense and T1-hypointense lesion burden seen on MRI in patients with relapsing MS (Level A).
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Because of the possibility that natalizumab therapy may be responsible for the increased risk of PML, it is recommended that natalizumab be reserved for use in selected patients with relapsing remitting disease who have failed other therapies either through continued disease activity or medication intolerance, or who have a particularly aggressive initial disease course.

3. How does the efficacy of natalizumab compare with currently available disease-modifying therapies?

Insufficient evidence	Insufficient evidence to support the relative efficacy of natalizumab compared to other available disease-modifying therapies (Level U).
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4. Is natalizumab effective in other clinical types of MS such as SPMS?

Insufficient evidence	Insufficient evidence to support the value of natalizumab in the treatment of SPMS (Level U).
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5. In patients with RRMS, does the combination of natalizumab with other disease-modifying therapies improve efficacy?

Good evidence	Good evidence supports the value of adding natalizumab to patients already receiving IFN β -1a, 30 β g, IM once weekly (Level B).
Insufficient evidence	There is insufficient evidence regarding the value of adding IFN β therapy to patients already receiving natalizumab in the treatment of RRMS or the value of continuing IFN β therapy once natalizumab therapy is started (Level U).

6. In patients with MS, how safe is natalizumab, either alone or in combination with other immune modulating agents?

COMBINATION THERAPY

Strong evidence	Strong evidence suggests that there is an increased risk of developing PML in natalizumab-treated patients (Level A).
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MONOTHERAPY

Weak evidence	Weak evidence suggests that there is an increased risk of developing PML in natalizumab-treated patients (Level C).
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OPPORTUNISTIC INFECTIONS

Weak evidence	Weak evidence suggests that there may be an increased risk of other opportunistic infections (Level C).
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Because combination therapy with IFN β and natalizumab may increase the risk of PML, it should not be used. There are also no data to support the use of natalizumab combined with other disease-modifying agents as compared to natalizumab alone. The use of natalizumab in combination with agents not inducing immune suppression should be reserved for properly controlled and monitored clinical trials.

Since the development of this guideline, two cases of PML have been reported in patients receiving natalizumab monotherapy, one of whom had never previously received any immunomodulatory or immunosuppressive treatment. This observation indicates that natalizumab, by itself, is a risk factor for PML. However, the evidence has not been formally reviewed by the AAN's Therapeutics and Technology Assessment Subcommittee.

This guideline summary is evidence-based. The AAN uses the following definitions for the level of recommendations and classification of evidence for therapeutic intervention, prognosis, and screening.

***Classification of Recommendations:** **A** = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)* **B** = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.) **C** = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.) **U** = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. (Studies not meeting criteria for Class I–III).

* In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if (1) all criteria are met and/or (2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

AAN Classification of Evidence for Therapeutic Intervention: **Class I:** Randomized, controlled clinical trial with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required: (a) concealed allocation; (b) primary outcome(s) clearly defined; (c) exclusion/inclusion criteria clearly defined; and (d) adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias. **Class II:** Prospective matched group cohort study in a representative population with masked outcome assessment that meets b-d above OR a RCT in a representative population that lacks one criteria a-d. **Class III:** All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement. **** Class IV:** Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

** Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

This is an educational service of the American Academy of Neurology (AAN). It is designed to provide members with evidence-based guideline recommendations to assist with decision-making in patient care. It is based on an assessment of current scientific and clinical information and is not intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physicians caring for the patient, based on the circumstances involved. Physicians are encouraged to review carefully the full AAN guidelines so they understand all recommendations associated with care of their patients.

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