CADTH Health Technology Review

Interferons, Glatiramer Acetate, and Minocycline for Relapsing-Remitting Multiple Sclerosis and Clinically Isolated Syndrome

Rapid Review

Key Messages

What Is the Issue?

- Multiple sclerosis is a chronic autoimmune disorder that causes damage to central nervous system cells. Relapsing-remitting multiple sclerosis is characterized by relapses (episodes of new or worsening symptoms) followed by periods of partial or complete recovery (remission). A clinically isolated syndrome is the first episode of clinical symptoms and objective findings suggestive of multiple sclerosis. It lasts at least 24 hours and occurs without fever or infection.

- Disease-modifying therapies for multiple sclerosis include interferon beta-1a and interferon beta-1b, and glatiramer acetate.

- Minocycline is an antibiotic that may have a potential role in treating multiple sclerosis. Understanding its possible benefits and harms in clinically isolated syndrome and relapsing-remitting multiple sclerosis is important to clarify its potential role in these patients.

What Did We Do?

- The purpose of this report is to update 2 previous reports we conducted in 2019. We summarize the evidence regarding the clinical effectiveness of glatiramer acetate, interferon beta-1a, and interferon beta-1b for clinically isolated syndrome, as well as minocycline for clinically isolated syndrome and relapsing-remitting multiple sclerosis. Evidence-based guidelines were also summarized.

- We searched key resources, including journal citation databases, and conducted a focused internet search for relevant evidence published since 2019. One reviewer screened articles for inclusion based on predefined criteria, critically appraised the included studies, and narratively summarized the findings.

What Did We Find?

- We found 1 systematic review that evaluated the safety of interferon beta-1a and glatiramer acetate in patients with clinically isolated syndrome.

- Serious adverse events and withdrawals due to adverse events were similar in patients with clinically isolated syndrome who received interferon beta-1a and placebo.

- Serious adverse events were similar in patients with clinically isolated syndrome who received glatiramer acetate and placebo. Withdrawals due to adverse events were more common in patients with clinically isolated syndrome who received glatiramer acetate than placebo.

Key Messages

- We did not identify any studies that evaluated the clinical effectiveness of interferon beta-1a, interferon beta-1b, glatiramer acetate, or minocycline in patients with clinically isolated syndrome, or minocycline in patients with relapsing-remitting multiple sclerosis published since our previous reports. We did not identify any evidence-based guidelines published since our earlier reports.

What Does This Mean?

- It is uncertain if interferon beta-1a, interferon beta-1b, glatiramer acetate, and minocycline are effective treatments for clinically isolated syndrome, or if minocycline is an effective treatment for relapsing-remitting multiple sclerosis due to the lack of evidence identified in this report.

- Future studies are needed to understand the clinical effectiveness of interferon beta-1a, interferon beta-1b, glatiramer acetate, and minocycline in patients with clinically isolated syndrome, and minocycline in patients with relapsing-remitting multiple sclerosis.

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Abbreviations

CDEC   Canadian Drug Expert Committee

RCT   randomized controlled trial

Context and Policy Issues

What Are Relapsing–Remitting Multiple Sclerosis and Clinically Isolated Syndrome?

Multiple sclerosis is a chronic autoimmune disorder of the central nervous system that causes demyelination (damage to the protective cover [myelin sheath] around nerve cells) and neurodegeneration (damage and/or death of nerve cells).[1,2] Symptoms of multiple sclerosis can include constant fatigue, vision deficit, intense pain, sensory dysfunction, gait disturbances, cognitive impairment, urine incontinence, and spasticity.[1,3] The diagnosis of multiple sclerosis is based on clinical symptoms, cerebrospinal fluid analysis, and MRI.[3] It is estimated that more than 77,000 people older than 20 live with multiple sclerosis in Canada, and almost 75% of them are women.[4] The cause of multiple sclerosis is unknown, and the age of onset is typically between 20 and 40 years.[3]

Clinically isolated syndrome is the first episode of clinical symptoms and objective findings suggestive of multiple sclerosis. It lasts at least 24 hours and occurs without fever or infection.[3] Patients with clinically isolated syndrome may eventually convert to multiple sclerosis but do not yet fulfill the diagnostic criteria.[5] Clinically isolated syndrome is the first demyelinating event in 85% of patients with multiple sclerosis.[3] Relapsing-remitting multiple sclerosis, the most common form of the disease, is characterized by relapses (episodes of new or worsening symptoms) followed by periods of partial or complete recovery (remission).[1,6]

What Is the Current Practice?

There is no known cure for multiple sclerosis; however, treatments can decrease inflammation and reduce symptoms and the accumulation of disability.[7] Treatment of multiple sclerosis includes disease-modifying therapies, acute relapse treatment, comorbidity management, symptom control, psychological support, rehabilitative strategies, and lifestyle modifications.[2] The goal of disease-modifying therapies in relapsing-remitting multiple sclerosis is to decrease the frequency of relapses and reduce short-term disability.[2] Disease-modifying therapies for multiple sclerosis include injectable medications (e.g., interferons, glatiramer acetate), oral medications (e.g., siponimod, fumarates, teriflunomide), and monoclonal antibodies (e.g., natalizumab, ocrelizumab).[2]

The therapeutic approach in clinically isolated syndrome is similar to multiple sclerosis management; however, it does not include symptomatic treatment due to the lack of chronic and severe symptoms.[3] The goal of disease-modifying therapies in clinically isolated syndrome is to reduce the risk of conversion to multiple sclerosis.[3]

What Are Interferon Beta-1a and Interferon Beta-1b?

Interferons are naturally occurring cytokines (signalling proteins that affect the immune system) with complex effects on the central nervous system that are not fully understood.[8] The mechanism of action of interferon-beta includes the inhibition of T-cell (white blood cell that is part of the immune system) activation and proliferation as well as reduction of T-cells crossing the blood-brain barrier.[9] Interferon beta-1a is indicated for the treatment of relapsing forms of multiple sclerosis, including relapsing progressive multiple sclerosis and people who have experienced a single demyelinating event accompanied by

abnormal MRI scans with lesions typical of multiple sclerosis.[10] The recommended dosage is 30 mcg injected intramuscularly once a week.[10] Interferon beta-1b is indicated for treating patients with a single demyelinating event with at least 2 clinically silent lesions typical of multiple sclerosis on MRI, relapsing-remitting multiple sclerosis, and secondary-progressive multiple sclerosis.[11] The recommended dosage is 0.25 mg injected subcutaneously every other day.[11] In 2013, the Canadian Drug Expert Committee (CDEC) recommended that interferon beta-1a (Rebif) not be publicly reimbursed for clinically isolated syndrome.[12]

What Is Glatiramer Acetate?

Glatiramer acetate is a mixture of synthetic polypeptides (chains of amino acids) containing 4 naturally occurring amino acids (L-glutamic acid, L-alanine, L-tyrosine, and L-lysine).[8] Glatiramer acetate inhibits the activation of T-cells and prevents the entry of these cells into the brain.[8] Glatiramer acetate is indicated for the treatment of ambulatory patients with relapsing-remitting multiple sclerosis, including patients who have experienced a single demyelinating event and have lesions typical of multiple sclerosis on MRI.[13] Glatiramer acetate is available in 2 strengths, and the recommended dosage is 20 mg/mL once per day or 40 mg/mL 3 times per week at least 48 hours apart.[13] In 2017, CDEC recommended glatiramer acetate (Glatect) be reimbursed for its approved indication of ambulatory patients with relapsing-remitting multiple sclerosis, including patients who have experienced a single demyelinating event and have lesions typical of multiple sclerosis on MRI.[14] In contrast, in 2009, CDEC recommended glatiramer acetate (Copaxone) not be publicly reimbursed for the clinically isolated syndrome.[15]

What Is Minocycline?

Minocycline is a semisynthetic tetracycline antibiotic.[16] Minocycline is a potential option for chronic neurologic disorders such as multiple sclerosis due to its anti-inflammatory and neuroprotective effects.[16] Minocycline is indicated for treating various infections, including gall bladder infections, urinary tract infections, skin and soft tissue infections, and respiratory tract infections.[17] Minocycline is available in capsules intended for oral administration, and the recommended dosage for adults is 100 mg or 200 mg initially, followed by 100 mg every 12 hours.[17]

Why Is It Important to Do This Review?

The current report is an update to 2 of our previous reports published in 2019.[18,19] The 2019 report evaluating the clinical effectiveness of minocycline in patients with clinically isolated syndrome identified 1 randomized controlled trial (RCT).[19] Evidence from this RCT indicated that the risk of conversion from clinically isolated syndrome to multiple sclerosis at 6 months was statistically significantly lower in patients treated with minocycline versus placebo; however, this difference between groups was not sustained at 24 months.[19] The 2019 report that evaluated glatiramer acetate and interferon betas for clinically isolated syndrome identified 1 systematic review, 1 RCT, and 1 evidence-based guideline.[18] Evidence from these studies suggested that compared to placebo, glatiramer acetate and interferon betas slowed the conversion from clinically isolated syndrome to multiple sclerosis and reduced the development of new brain lesions.[18] Both previous reports outlined important limitations, including the limited quantity of available evidence and the risk of bias in the

included studies.[18,19] To inform decision-making, a request was made to determine whether new evidence has emerged since our previous reports.

Objective

The purpose of this report is to summarize new evidence regarding the clinical effectiveness of minocycline, glatiramer acetate, interferon beta-1a, and interferon beta-1b for clinically isolated syndrome and minocycline for relapsing-remitting multiple sclerosis as well as evidence-based guidelines.

Research Questions

1. What is the clinical effectiveness of minocycline for relapsing-remitting multiple sclerosis?
2. What is the clinical effectiveness of minocycline for clinically isolated syndrome?
3. What is the clinical effectiveness of glatiramer acetate for clinically isolated syndrome?
4. What is the clinical effectiveness of interferon beta-1a for clinically isolated syndrome?
5. What is the clinical effectiveness of interferon beta-1b for clinically isolated syndrome?
6. What are the evidence-based guidelines regarding minocycline for relapsing-remitting multiple sclerosis or clinically isolated syndrome?
7. What are the evidence-based guidelines regarding the use of glatiramer acetate and interferon beta-1a and 1b for clinically isolated syndrome?

Methods

Literature Search Methods

The literature search strategy used in this report is an update of searches developed for 2 of our previous reports.[18,19] For the current report, an information specialist conducted a literature search on key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were minocycline, glatiramer acetate, interferon beta-1a, interferon beta-1b, multiple sclerosis, and clinically isolated syndrome. Retrieval was limited to the human population. All searches were limited to English-language documents. For the initial search on glatiramer acetate, interferon beta-1a, or interferon beta-1b for clinically isolated syndrome, results were limited to documents published between January 1, 2014 and August 19, 2019. For the initial search on minocycline for clinically isolated syndrome or multiple sclerosis, results were limited to documents published between January 1, 2009 and August 16, 2019. For the current report, database searches were rerun on April 24, 2024 to capture any

articles published or made available since the initial search dates. The search of major health technology agencies was also updated to include documents published since August 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. As an update to 2 of our previous reports, articles were included if they were made available since the previous search date and were not included in the 2019 reports. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Q1 and Q6: Adult patients with relapsing-remitting multiple sclerosis Q2 to Q7: Adult patients with clinically isolated syndrome
Intervention	Q1, Q2, and Q6: minocycline Q3 and Q7: glatiramer acetate Q4 and Q7: interferon beta-1a Q5 and Q7: interferon beta-1b
Comparator	Q1: Multiple Sclerosis therapies (i.e., interferon beta-1a, interferon beta-1b, glatiramer acetate, dimethyl fumarate, ocrelizumab, teriflunomide, peginterferon beta), placebo Q2: Clinically Isolated Syndrome therapies (i.e., interferon beta-1a, interferon beta-1b, glatiramer acetate), placebo Q3: interferon beta-1a, interferon beta-1b, placebo Q4: glatiramer acetate, interferon beta-1b, placebo Q5: interferon beta-1a, glatiramer acetate, placebo Q6 and Q7: NA
Outcomes	Q1 to Q5: Clinical effectiveness (e.g., progression to clinically definite multiple sclerosis, time to progression to clinically definite multiple sclerosis, disability, relapse, changes in number and volume of lesions, health-related quality of life) and harms (e.g., adverse events) Q6: Guidelines regarding the use of minocycline for relapsing-remitting multiple sclerosis or clinically isolated syndrome Q7: Guidelines regarding the use of glatiramer acetate and interferon beta-1a and 1b for clinically isolated syndrome
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies, evidence-based guidelines

NA = not applicable.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or were duplicate publications. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included systematic reviews. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publication was critically appraised by 1 reviewer using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[20] as a guide. Summary scores were not calculated for the included study; instead, the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 356 citations were identified in the literature search. Following the screening of titles and abstracts, 317 citations were excluded, and 39 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for a full-text review. Of these potentially relevant articles, 42 publications were excluded for various reasons, and 1 systematic review met the inclusion criteria and was included in this report. Appendix 1 presents the PRISMA[21] flow chart of the study selection. Additional references of potential interest are provided in Appendix 2.

Summary of Study Characteristics

In total, 1 systematic review that evaluated safety was included in this report.[22] The systematic review had broader inclusion criteria than those identified in our research protocol. It included studies of any immunotherapy used as monotherapy. It included studies of the relevant interventions (interferon beta-1b, interferon beta-1a, glatiramer acetate) in patients with other types of multiple sclerosis (e.g., relapsing-remitting multiple sclerosis, progressive multiple sclerosis). Additional details regarding the characteristics of the included publication are provided in Appendix 3.

We did not identify any studies that evaluated the clinical effectiveness of interferon beta-1a, interferon beta-1b, glatiramer acetate, or minocycline in patients with clinically isolated syndrome, or minocycline in patients with relapsing-remitting multiple sclerosis published since our previous reports. We did not identify any evidence-based guidelines published since our earlier reports.

Study Design

The search for the systematic review by Tracamere et al. (2023)[22] included RCTs published up to March 4, 2022. The systematic review identified 123 RCTs, including 5 relevant to the present report.[22]

Country of Origin

Authors in Italy published the systematic review.[22]

Patient Population

The relevant population included in the systematic review was adults (aged 18 to 50 years) with clinically isolated syndrome.[22] The time since the patients' neurologic event ranged from 19 days to 3 months.[22] The mean baseline Expanded Disability Status Scale in the relevant population ranged from 1.0 to 1.5.[22.] The

Expanded Disability Status Scale measures how much someone is impacted by multiple sclerosis, and ranges from 0 to 10, with greater levels of disability corresponding to higher scores.[23]

Interventions and Comparators

In the relevant RCTs included in the systematic review, the interventions were interferon beta-1a and glatiramer acetate.[22] The dosages for interferon beta-1a ranged from 22 to 44 mcg.[22] In 3 of the RCTs, interferon beta-1a was administered once weekly, and in 1 RCT, it was administered either once weekly or 3 times weekly.[22] The dosage for glatiramer acetate was 20 mg daily.[22] The comparator in all the relevant RCTs was placebo.[22]

Outcomes

The systematic review by Tramacere et al. (2023) assessed serious adverse events and withdrawal due to adverse events.[22] The follow-up in the relevant RCTs ranged from 24 to 36 months.[22]

Summary of Critical Appraisal

An overview of the strengths and limitations of the included systematic review is provided in Table 2. Overall, the systematic review was well conducted with multiple strengths and no limitations based on the critical appraisal using AMSTAR 2.

Table 2: Strengths and Limitations of Systematic Review Using AMSTAR 2[20]

Strengths	Limitations
Tramacere et al. (2023)[22]	
• Clear objective and inclusion criteria that included components of population, intervention, comparator, and outcomes • The review methods were established before conducting the review, and the protocol was published • The choice of study designs included in the review (i.e., RCTs) was explained • The literature search was conducted in multiple databases and trial registries, reference lists from relevant SRs and included studies were handsearched for additional relevant literature, the search strategy was provided, and no language or date restrictions were imposed • Study selection and data extraction were performed independently by 2 reviewers • List of excluded studies and reasons for exclusion provided • Risk of bias was assessed independently by 2 reviewers using a satisfactory technique • Sources of funding for individual studies included in the review were reported • Authors reported potential competing interests and their funding sources	None

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; RCT = randomized controlled trial; SR = systematic review.

Summary of Findings

Appendix 4 presents the main study findings.

Safety of Interferon Beta-1a

Serious Adverse Events

Serious adverse events were more common in patients with clinically isolated syndrome who received interferon beta-1a than in those who received placebo in 2 of the RCTs identified in the Tramacere et al. (2023)[22] systematic review. In 2 other RCTs identified in the systematic review, serious adverse events were more common in patients with clinically isolated syndrome who received a placebo than in patients who received interferon beta-1a.[22] None of the differences between groups were statistically significant.[22]

Withdrawal Due to Adverse Events

Withdrawal due to adverse events was more common in patients with clinically isolated syndrome who received a placebo than interferon beta-1a (2 RCTs). However, the differences between groups were not statistically significant.[22]

Safety of Glatiramer Acetate

Serious Adverse Events

Serious adverse events were more common in patients with clinically isolated syndrome who received a placebo than patients who received glatiramer acetate in 1 RCT identified in the Tramacere et al. (2023)[22] systematic review. The difference in serious adverse events between treatment groups was not statistically significant.[22]

Withdrawal Due to Adverse Events

Withdrawal due to adverse events was statistically significantly more common in patients with clinically isolated syndrome who received glatiramer acetate than in those who received placebo (1 RCT).[22]

Limitations

This report is limited by the quantity of evidence identified. One systematic review was identified that evaluated the safety of interferon beta-1a and glatiramer acetate in patients with clinically isolated syndrome. We did not identify any studies that assessed the clinical effectiveness of interferon beta-1a, interferon beta-1b, glatiramer acetate, or minocycline in patients with clinically isolated syndrome. We did not identify any studies that evaluated the clinical effectiveness of minocycline in patients with relapsing-remitting multiple sclerosis. Additionally, we did not identify any evidence-based guidelines.

Conclusions and Implications for Decision- or Policy-Making

Due to the limited evidence identified since our last reports, it is difficult to draw conclusions on the clinical effectiveness and safety of interferon beta-1a, interferon beta-1b, glatiramer acetate, and minocycline for

the treatment of patients with clinically isolated syndrome as well as minocycline for the treatment of patients with relapsing-remitting multiple sclerosis. The safety of interferon beta-1a and glatiramer acetate was assessed in 1 systematic review, which reported no significant differences in serious adverse events or withdrawals due to adverse events between patients with clinically isolated syndrome treated with interferon beta-1a or placebo. Additionally, the systematic review reported no significant difference in serious adverse events in patients with clinically isolated syndrome treated with glatiramer acetate versus placebo. Withdrawals due to adverse events were more common in patients with clinically isolated syndrome who received glatiramer acetate than placebo.

Our 2 previous reports on interferon betas, glatiramer acetate, and minocycline identified 1 systematic review, 2 RCTs, and 1 evidence-based guideline.[18,19] Results from 1 RCT indicated that the risk of conversion from clinically isolated syndrome to multiple sclerosis at 6 months was statistically significantly lower in patients treated with minocycline versus placebo; however, this difference between groups was not sustained at 24 months.[19] Evidence from 1 systematic review and 1 RCT suggested that compared to placebo, glatiramer acetate and interferon betas slowed down the conversion from clinically isolated syndrome to multiple sclerosis and reduced the development of new brain lesions.[18] Both previous reports outlined important limitations, including the limited quantity of available evidence and the risk of bias in the included studies.[18,19]

Future studies and evidence-based guidelines on the use of interferon beta-1a, interferon beta-1b, glatiramer acetate, and minocycline in patients with clinically isolated syndrome, and minocycline in patients with relapsing-remitting multiple sclerosis would aid in decision-making around the use of these drugs.
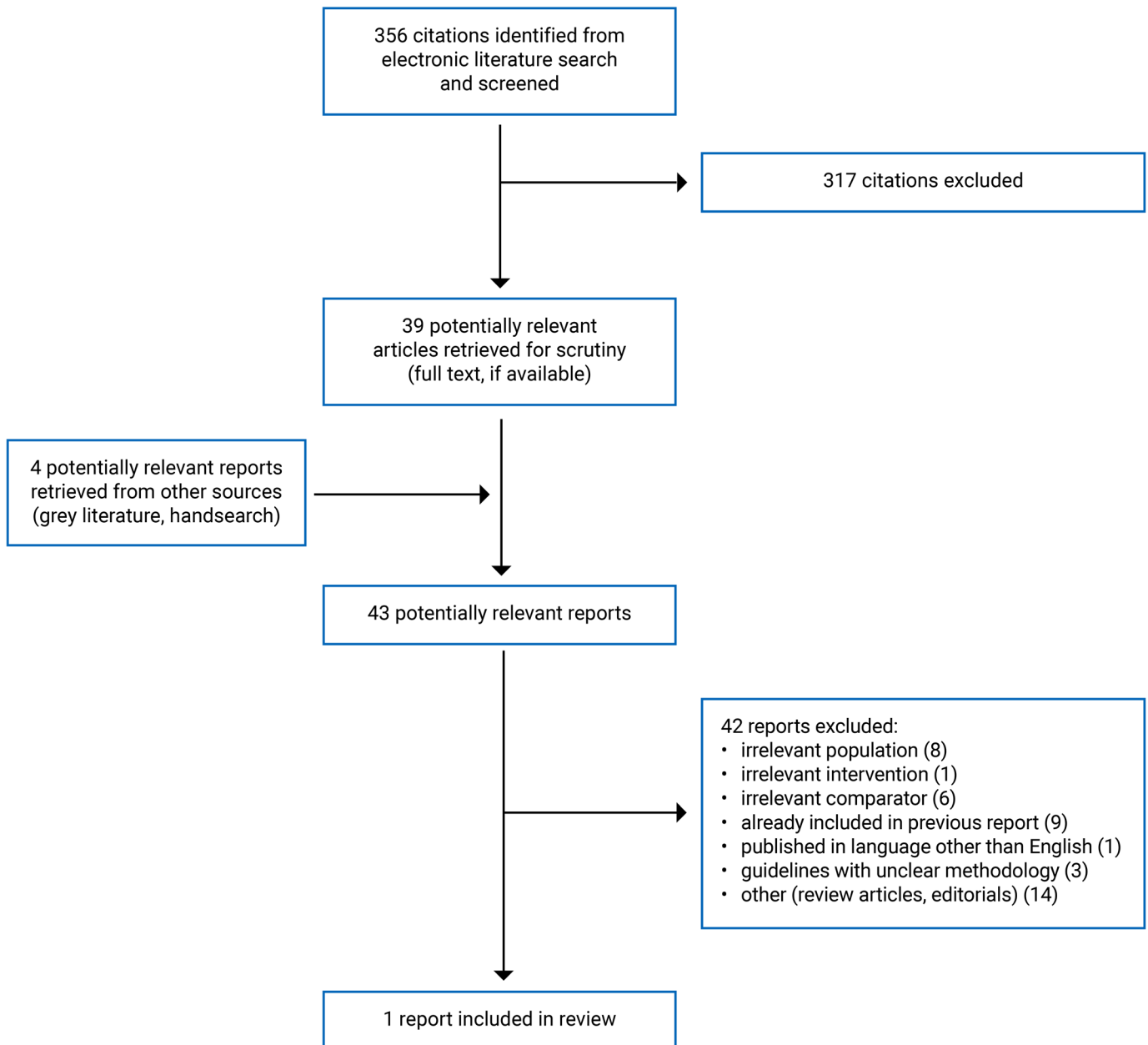
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11. Betaseron (interferon beta-1b): lyophilized powder for subcutaneous injection, 0.3 mg/vial [product monograph]. Mississauga (ON): Bayer Inc.; 2023: https://pdf.hres.ca/dpd_pm/00072199.PDF. Accessed 2024 May 15.

12. CADTH. CADTH Reimbursement Review: Rebif (Interferon beta-1a) for clinically isolated syndrome. 2013: https://www.cadth.ca/interferon-beta-1a. Accessed 2024 May 15.

13. Copaxone (glatiramer acetate): 20 mg / mL and 40 mg / mL single-use pre-filled syringes for subcutaneous injection; 40 mg / mL single-use pre-filled pens for subcutaneous injection [product monograph]. Toronto (ON): Teva Canada Limited; 2021: https://pdf.hres.ca/dpd_pm/00059892.PDF. Accessed 2024 May 15.

14. CADTH. CADTH Reimbursement Review: Glatect (glatiramer acetate) for relapsing remitting multiple sclerosis (RRMS). 2017: https://www.cadth.ca/glatiramer-acetate-0. Accessed 2024 May 15.

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Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies

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│   356 citations identified   │
│      from electronic         │
│   literature search and      │
│         screened             │
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              │                        │  317 citations excluded  │
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┌─────────────────────────────┐
│   39 potentially relevant    │
│  articles retrieved for      │
│  scrutiny (full text, if     │
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┌──────────────────────────┐  │
│ 4 potentially relevant    │──┘
│ reports retrieved from     │
│ other sources (grey        │
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│  43 potentially relevant     │
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              │                        │ 42 reports excluded:                       │
              │                        │ • irrelevant population (8)                │
              │                        │ • irrelevant intervention (1)              │
              │                        │ • irrelevant comparator (6)                │
              │                        │ • already included in previous report (9)  │
              │                        │ • published in language other than English │
              │                        │   (1)                                      │
              │                        │ • guidelines with unclear methodology (3)  │
              │                        │ • other (review articles, editorials) (14) │
              ▼                        └──────────────────────────────────────────┘
┌─────────────────────────────┐
│  1 report included in review │
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Appendix 2: References of Potential Interest

Note that this appendix has not been copy-edited.

Guidelines With Unclear Methodology

Yamout B, Al-Jumah M, Sahraian MA, et al. Consensus recommendations for diagnosis and treatment of Multiple Sclerosis: 2023 revision of the MENACTRIMS guidelines. *Mult Scler Relat Disord*. 2024 Mar;83:105435. PubMed

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Appendix 3: Characteristics of Included Publications

Table 3: Characteristics of Included Systematic Review

Study citation, country, funding source	Study design, outcomes	Intervention and comparators	Included studies	Population characteristics
Tramacere et al. (2023)[22] Italy **Funding source:** Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, Milan, Italy and the Neurologic Institute Carlo Besta	Systematic review and network meta-analysis of RCTs **Outcomes:** serious adverse events, withdrawals due to adverse events	**Eligible interventions:** immunotherapies used as monotherapies **Eligible comparators**: placebo or another active drug **Relevant interventions and comparators:** • CHAMPS 2000: interferon beta-1a 30 mcg intramuscularly weekly vs placebo • ETOMS 2001: interferon beta-1a 22 mcg subcutaneously once weekly vs placebo • Pakdaman 2007: interferon beta-1a 30 mcg intramuscularly once weekly vs placebo • PreCISe 2009: glatiramer acetate 20 mg subcutaneously daily vs placebo • REFLEX 2012: interferon beta-1a 44 mcg subcutaneously once weekly or 3 times weekly vs placebo	123 RCTs in total, 5 RCTs relevant to the present report	**Eligible population:** adults with multiple sclerosis or CIS **Relevant population:** adults with CIS **Age range:** • CHAMPS 2000: 18 50 years • ETOMS 2001: 18 to 40 years • Pakdaman 2007: 19 to 50 years • PreCISe 2009: 18 to 45 years • REFLEX 2012: 18 to 50 years **Time since the neurologic event:** • CHAMPS 2000: median = 19 days • ETOMS 2001: within 3 months • Pakdaman 2007: within 3 months • PreCISe 2009: mean = 74 days • REFLEX 2012: 58 days **Mean baseline EDSS:** • CHAMPS 2000: NR • ETOMS 2001: 1.2 • Pakdaman 2007: NR • PreCISe 2009: 1.0 • REFLEX 2012: 1.5

CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; NR = not reported; RCT = randomized controlled trial.

Note that this appendix has not been copy-edited.

Appendix 4: Main Study Findings

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Table 4: Summary of Findings by Outcome — Serious Adverse Events

Citation	Primary study	Follow-up	Intervention		Control		Risk ratio (95% CI)
			Events	Total	Events	Total	
Interferon beta-1a vs placebo							
Tramacere et al. (2023)[22] (SR)	CHAMPS 2000 (RCT)	36 months	12	193	19	190	0.62 (0.31 to 1.25)
	ETOMS 2001 (RCT)	24 months	6	154	5	155	1.21 (0.38 to 3.87)
	REFLEX 2012 (RCT)	24 months	14	344	12	171	0.58 (0.27 to 1.23)
	Pakdaman 2007 (RCT)	36 months	9	104	7	98	1.21 (0.47 to 3.13)
Glatiramer acetate vs placebo							
Tramacere et al. (2023)[22] (SR)	PreCISe 2009 (RCT)	36 months	11	243	19	238	0.57 (0.28 to 1.17)

CI = confidence interval; RCT = randomized controlled trial; SR = systematic review.

Table 5: Summary of Findings by Outcome — Withdrawal Due to Adverse Events

Citation	Primary study	Follow-up	Intervention		Control		Risk ratio (95% CI)
			Events	Total	Events	Total	
Interferon beta-1a vs placebo							
Tramacere et al. (2023)[22] (SR)	CHAMPS 2000 (RCT)	36 months	2	193	7	190	0.28 (0.06 to 1.34)
	REFLEX 2012 (RCT)	24 months	9	344	8	171	0.56 (0.22 to 1.42)
Glatiramer acetate vs placebo							
Tramacere et al. (2023)[22] (SR)	PreCISe 2009 (RCT)	36 months	15	243	4	238	3.67 (1.24 to 10.91)

CI = confidence interval; RCT = randomized controlled trial; SR = systematic review.