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Glatiramer Acetate and Interferon Beta 1a and 1b for Clinically Isolated Syndrome: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

AAN	American Academy of Neurology
AE	adverse event
AGREE II	appraisal of guidelines for research evaluation II
AMSTAR	assessing the methodological quality of systematic reviews
CDMS	clinically definite multiple sclerosis
CIS	clinically isolated syndrome
CUA	combined unique active
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
GA	glatiramer acetate
IFN	interferon
IM	intramuscularly
mcg	microgram
mg	milligram
MRI	magnetic resonance imaging
MS	multiple sclerosis
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RCT	randomized controlled trial
SC	subcutaneously

Context and Policy Issues

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, degenerative disease of the central nervous system characterized by axonal injury and loss.[1] Approximately 77,000 Canadians aged 20 years and older live with MS and almost 75% are women.[2] The majority of new patients are aged 20 to 49 years. A possible precursor of MS is clinically isolated syndrome (CIS) which refers to a single demyelinating event lasting at least 24 hours.[3] As with MS, patients with CIS may present with optic neuritis or symptoms suggestive of a brain stem syndrome, a cerebellar syndrome, or a spinal cord disorder.[4]

Disease-modifying therapies (DMTs) such as glatiramer acetate, interferon beta-1a (IFN β‑1a), and IFN β-1b have been used to treat patients with MS and are therefore potential therapies for patients with CIS.[5,6] Glatiramer acetate is an immunomodulatory agent that is made of alanine, lysine, glutamate, and tyrosine amino acids.[7] β-IFNs are naturally occurring cytokines that facilitate the growth of anti-inflammatory agents.[8] Though DMTs may be useful in managing patients with CIS, their mechanisms of action and safety profiles are not well-understood.[6,9] Findings from the PreCISe trial – a double-blind, placebo-controlled RCT – suggested that 20 mg of glatiramer acetate administered subcutaneously once a day was superior to placebo in prolonging the time to conversion from CIS to clinically definite MS (CDMS) but its effect on disability was unclear.[10] Based on this evidence, the Canadian Drug Expert Committee (CDEC) recommended in 2009 that glatiramer acetate (Copaxone) not be reimbursed for CIS.[11] A 2012 review by CADTH found that no new evidence regarding the efficacy of glatiramer acetate for treating patients with CIS had been published since the completion of PreCISe.[10] In 2013, based on a systematic review which retrieved one placebo-controlled RCT of IFN β‑1a 44mcg administered subcutaneously, CDEC recommended that it not be reimbursed for CIS. Again, the benefit on disability was unclear.[12]

This review aims to summarize and evaluate evidence regarding the clinical effectiveness and safety of glatiramer acetate, IFN β‑1a, and IFN β-1b, in treating patients with CIS. The review also aims to summarize and assess relevant evidence-based guidelines.

Research Questions

1. What is the clinical effectiveness of glatiramer acetate for clinically isolated syndrome?
2. What is the clinical effectiveness of interferon beta-1a for clinically isolated syndrome?
3. What is the clinical effectiveness of interferon beta-1b for clinically isolated syndrome?
4. What are the evidence-based guidelines regarding the use of glatiramer acetate and interferon beta-1a and 1b for clinically isolated syndrome?

Key Findings

Sparse evidence was found in the published literature. One systematic review and one randomized controlled trial provided evidence on the clinical effectiveness of glatiramer, interferon beta-1a, and interferon beta-1b in people with clinically isolated syndrome. One set of evidence-based guidelines provided relevant recommendations. The evidence on each treatment regimen was derived from no more than two RCTs, suggesting a lack of diversity in the patient populations, and limiting opportunities for meaningful meta-analyses. Three of the five RCTs that were included in the systematic review reported on interferon beta-1a; in two trials the drug was delivered intramuscularly and in one, subcutaneously and at two dosages. One of the remaining RCTs reported on patients treated with glatiramer acetate while the other reported on patients treated with interferon beta-1b.

Manufacturers of the interventions of interest sponsored the included studies and as such may have had opportunities to influence the selection of patients, comparators, and outcomes. Incidentally, there was some evidence of patient selection bias and discrepancy in the reporting of results between the systematic review and the randomized controlled trial. For these and other reasons, considerable caution must be taken in making inferences from the results presented in this report.

Treatment effect was assessed with measurements of time to multiple sclerosis conversion, relative number of new brain lesions that developed during the study period, the change in volume of lesions that existed at study baseline, and the incidence of discontinuation due to adverse events. Overall, relative to placebo, specific doses of glatiramer acetate and beta-interferons slowed down the conversion from clinically isolated syndrome to clinically definite multiple sclerosis or McDonald multiple sclerosis and reduced the development of new brain lesions. Safety outcomes favoured glatiramer acetate and beta-interferons over placebo. The authors did not report on the statistical significance of these effects, nor was there direct comparison of active therapies.

Based on a limited quantity of evidence from four randomized controlled trials, a guideline development group provided recommendations on discussing the benefits and risks of disease-modifying therapies, prescribing, monitoring patients with CIS, and stopping therapies.

There was no identified evidence on incidence of progression to clinically definite multiple sclerosis, mortality, hospitalizations, quality of life, disability, time to disability, long-term disability progression, or relapse. None of the studies directly compared glatiramer acetate

and beta-interferons. Recommendations on switching between therapies that were specific to patients with CIS were not found.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were glatiramer acetate or interferon beta 1-a or interferon beta 1-b and clinically isolated syndrome. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and August 19, 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. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1-Q4: Adult patients with clinically isolated syndrome
Intervention	Q1&Q4: Glatiramer acetate Q2&Q4: Interferon beta-1a Q3&Q4: Interferon beta-1b
Comparator(s)	Q1: Interferon beta-1a, Interferon beta-1b, placebo Q2: Glatiramer acetate, Interferon beta-1b, placebo Q3: Glatiramer acetate, Interferon beta-1a, placebo Q4: Not applicable
Outcome(s)	Q1 – Q3: Clinical effectiveness: Progression to clinically definite multiple sclerosis, time to progression to clinically definite multiple sclerosis; Mortality; Hospitalizations; Quality of life, health related quality of life; Disability, time to disability, long-term disability progression; Relapse Changes in number and volume of lesions (observed on magnetic resonance imaging); Harms: Adverse events

	Q4: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology and studies comparing immediate to delayed therapy were also excluded. An additional reference of interest is listed in Appendix 6.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised by one reviewer using the AMSTAR 2 checklist,[13] the network meta-analysis that was embedded in the systematic review was critically appraised using the ISPOR Task Force's Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making,[14] the randomized controlled trial (RCT) was critically appraised using the Downs and Black checklist,[15] and the guideline document was appraised using the AGREE II instrument.[16] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 322 citations were identified in the literature search. Following screening of titles and abstracts, 306 citations were excluded and 16 potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature search and other sources for full text review. Of these 22 potentially relevant articles, 3 publications met the inclusion criteria for this report and 19 publications were excluded for various reasons. Appendix 1 presents the PRISMA[17] flowchart of the study selection.

Summary of Study Characteristics

Study characteristics are summarized below, and details are available in Appendix 2.

Study Design

One systematic review (with an embedded network meta-analysis),[18] one RCT[19] and one set of guidelines[20] were included in this review. The systematic review and guidelines were published in 2018, whereas the RCT was published in 2014. The systematic review and the RCT included partially overlapping groups of patients but reported on different sets of outcomes. The RCT compared two active therapy groups with one group of patients treated with placebo while the systematic review compared one of these active therapy groups with one group of patients treated with placebo.

The systematic review[18] was conducted as part of a larger review on glatiramer acetate and β-interferons that included patients with relapsing-remitting MS and secondary progressive

MS along with CIS.[18] The authors limited their analysis to the subset of patients with CIS and to specific treatment regimens. The authors searched multiple databases in February 2016 and conducted a network meta-analysis of data from five double-blinded RCTs with open label study extensions; the search time frame was not reported. Information relevant to this report was recorded in the double-blind portion of the studies prior to open label crossover of patients into alternate intervention groups (primarily, from placebo to active treatment). The RCTs were: Rebif flexible dosing in early MS (REFLEX), CHAMPS, Pakdaman, BENEFIT, and PRECISE RCTs. The analysis of the treatment effect was conducted in two stages: first, a conventional pairwise meta-analysis was completed wherein active therapies were compared individually against placebo and where active therapies were compared as a group against placebo. At the next stage, following an assessment of heterogeneity, summary estimates for pairwise comparisons were calculated for each outcome of interest using a network meta-analysis.

The RCT[19] reported on results from the REFLEX trial. The authors compared two dosages of one drug and placebo in patients with CIS. They calculated treatment effects as ratios of outcome measures between pairs of interventions and conducted pairwise comparisons based on an adjusted negative binomial model. The authors conducted subgroup analyses based on age, incidence of gadolinium-enhancing (Gd+) lesions at baseline, incidence of T2 non-enhancing lesions at baseline, focality of the presentation and steroid use at the time of the first demyelinating episode.

The guidelines were developed by a panel of 12 physician and nurse members of the American Academy of Neurology (AAN), two members from the Consortium of Multiple Sclerosis Centers, and three adults with an MS diagnosis who represented patients.[20] The guideline developers followed the AAN's guideline development process.[20] The process started with searches of the MEDLINE, CENTRAL, and EMBASE databases from inception to November 2016. The developers then extracted evidence of the clinical effectiveness of DMTs from RCTs (when possible) while they extracted evidence of harms from RCTs, cohort studies, case series, and case reports. They considered whether the DMTs were superior to placebo in decreasing the risk of conversion from CIS to MS. A subset of the panel consulted other guideline panelists to ascertain the importance of certain outcome measures. Each recommendation in the guidelines was assigned a level of obligation (A, B, C, U or R) based on confidence in the evidence, soundness of inference assuming all premises are true, acceptance of axiomatic principles, and anticipated magnitude of benefit relative to harms. The level of obligation rating was determined in three stages: initial level, mandatory modification, and optional modification. The initial level of obligation was rated level A if the developers had high confidence in the evidence, if 100% of the developers were convinced of the soundness of inference assuming all premises were true, and if 100% of the developers accepted the axiomatic principles. The initial level of obligation was rated level B if the developers had moderate confidence in the evidence, if at least 80% and less than 100% of the developers were convinced of the soundness of inference assuming all premises were true and accepted the axiomatic principles, and it at least 80% of the developers believed that evidence cited from rerated conditions was strong. The initial level of obligation was rated level C if the developers had low confidence in the evidence, and if at least 50% up to less than 80% of the developers were convinced of the soundness of inference assuming all premises were true, accepted the axiomatic principles, and believed that the evidence cited from rerated conditions was strong. The initial level of obligation was rated level U or R if the developers had very low confidence in the evidence, and if less than 50% of the developers were convinced of the soundness of inference assuming all

premises were true, accepted the axiomatic principles, and believed that the evidence cited from rerated conditions was strong.

The level of obligation was modified to level A, B, C, or U if there was a large benefit relative to harm, moderate benefit relative to harm, small benefit relative to harm, or it was too close to call, respectively. The level of benefit was large if there was large benefit and no harm; moderate, if there was large benefit and minimal harm or moderate benefit and no harm; and small, if there was large benefit and moderate harm, moderate benefit and minimal harm, or small benefit and no harm. The benefit was determined too close to call if benefit and harm were substantially similar.

The developers could optionally downgrade the level of obligation based on the importance of the outcome, expected variation in patient preferences, financial burden relative to expected benefits, and availability of the intervention.

AAN staff sent invitations asking key stakeholders, including all AAN section members, and pertinent external physician and patient organizations, including the Consortium of Multiple Sclerosis Centers, the Multiple Sclerosis Association of America, the Multiple Sclerosis Coalition, and the National Multiple Sclerosis Society to review drafts of the guidelines. The drafts were reviewed by at least three AAN committees, a network of neurologists, peer reviewers solicited through the *Neurology* journal, and representatives from related fields. The panel modified the draft or updated the systematic review, accordingly. The guideline was reviewed by the AAN's Guideline Development, Dissemination, and Implementation Subcommittee before and after the public comment period. Individuals with perceived conflicts of interest were engaged as advisors to help validate key questions, assess the scope of the literature search, identify seminal articles, and participate in the recommendation development process. To mitigate their influence, individuals with conflicts of interest were not permitted to review or rate evidence.

Country of Origin

The systematic review[18] was conducted by authors in the United Kingdom and the RCT[19] was conducted by authors in Italy. The guidelines[20] were developed in the United States.

Patient Population

All the studies reported on the treatment of people with a single clinical episode diagnosed as having CIS. The systematic review[18] reported on 1845 patients with a single clinical event and evidence of clinically silent lesions based on magnetic resonance imaging (MRI). In one study that was included in the systematic review, 171 patients were enrolled in each arm, but 146 patients completed the study in each arm. Some outcome measurements were taken in 146 patients while others were reported for 171 patients in each arm.[18] The RCT[19] enrolled 517 patients between the ages of 24 and 37 years who had an Expanded Disability Status Scale (EDSS) score between 0 and 5, a CIS episode within 60 days prior to study entry, and at least two clinically silent lesions visible on a T2-weighted brain MRI scan. The lesions had to be at least 3 mm in diameter and at least one of them had to be ovoid, located within white matter, or located below the tentorium cerebelli of the brain. No exclusion criteria were disclosed. The guidelines[20] focused on DMTs in people with MS (including CIS and relapsed MS). While the systematic review[18] and guidelines[20] covered patients with a range of MS diagnoses, only information relevant to patients with CIS was considered for this report.

Interventions and Comparators

The interventions of interest in the included studies were glatiramer acetate, IFN β-1a, and IFN β-1b. The systematic review[18] included one RCT in which patients had 20 mg of glatiramer acetate (Copaxone) subcutaneously once a day, one in which patients received 44 mcg of IFN β-1a (Rebif) subcutaneously three times weekly, two in which patients received 30 mcg of IFN β-1a (Avonex) intramuscularly (IM) once a week, and another in which patients received 250 mcg of IFN β-1b (Betaferon, Extavia) subcutaneously every other day. The comparator in these studies was placebo.

The RCT reported on three groups of patients who received 44 mcg IFN β-1a (Rebif) subcutaneously three times a week, 44 mcg IFN β-1a (Rebif) subcutaneously once a week, or placebo.

The guideline developers considered a broad range of therapies, including but not limited to glatiramer acetate, IFNs, and steroids.[20]

Outcomes

The clinical effectiveness of glatiramer acetate and β-IFNs relative to placebo was assessed by the authors of the systematic review,[18] RCT,[19] and the guidelines[20] through the following outcomes and outcome measures:

Clinical effectiveness: Time to develop MS

- Time to clinically definite MS (CDMS [hazard ratio, pooled hazard ratio])[18]. CDMS was indicated by Poser criteria and a second relapse or neurological deterioration, Poser criteria were not described.
- Time to McDonald MS (pooled hazard ratio)[18]. McDonald MS was based on MRI and clinical findings; the specific criteria were not described.
- Incidence of conversion to MS (relative risk ratio).[20] MS was defined as an immune-mediated demyelinating disease of the CNS, characterized on histopathology by focal perivenular infiltrates of leukocytes (primarily macrophages and lymphocytes) and plaque formation.[20]

Clinical effectiveness: Change in MRI-sensitive lesions

- Mean number of combined unique active (CUA), new T2 non-enhancing, new T1 Gd+, and new T1 non-enhancing lesions per patient per scan (difference, relative risk ratio, hazard ratio)[19]
- Median change in the volume of T2, T1 Gd+ and T1 non-enhancing lesions from baseline (absolute value)[19]
- Neuroimaging changes[20]

A CUA lesion was defined as a new or persisting Gd+ lesion on T1 MRI or a new or enlarging lesion on T2 MRI (non-enhancing on T1 MRI).[19]

The authors of the RCT conducted subgroup analyses based on age (that is, less than 30 years old versus at least 30 years old), steroid use at first attack, monofocal/multifocal presentation of first attack, presence or absence of Gd+ lesions at baseline, sex, and number of T2 lesions at baseline (that is, fewer than 9 or at least 9 lesions).[19]

Safety

- Discontinuation due to adverse events (proportion of study group or incidence)[18]
- New or unexpected safety signals (count)[19]
- Incidence of serious adverse effects.[20] The serious adverse effects were not described.

Follow-up periods

The studies included in the systematic review[18] and guidelines[20] reported on short-term clinical effectiveness outcomes 24 months or 36 months after the study started. The authors of the RCT reported on outcomes 24 months after randomization or at conversion to CDMS, whichever occurred first.[19]

Treatment effect

The authors of the systematic review[18] reported on the clinical treatment effects as hazard ratios between active therapies and placebo. Safety outcomes were reported as proportions.[18] The authors of the RCT presented clinical treatment effects as differences, risk ratios and hazard ratios between pairs of interventions.[19] Effect sizes with corresponding 95% CIs were estimated using an adjusted negative binomial model that included treatment and randomization factors as covariates. The effect sizes were not calculated for the median change in volume of lesions from baseline.

Summary of Critical Appraisal

The critical appraisal of the studies is summarized below, and details are available in Appendix 3.

Systematic Review and Network Meta-Analysis

The authors of the systematic review[18] registered a protocol on a publicly-available database and included the population, interventions, and outcomes of interest in the statement of objectives, suggesting that elements of the review had been determined before the review started. Literature was acquired from multiple databases and study selection, data extraction, and quality assessment were conducted in duplicate. The sources of funding of the primary studies were disclosed enabling an accurate assessment of potential sources of bias. These characteristics presumably enhanced the credibility of the systematic review but not sufficiently to offset the serious limitations that were observed.

The systematic review was conducted as part of a larger review of patients with relapsing–remitting MS, secondary progressive MS, and CIS and in which glatiramer acetate and all forms of IFNs were compared against each other or placebo/best supportive care, and where clinical outcomes were reported such as relapse rates, progression to multiple sclerosis, or disability progression as measured by the EDSS.

The relevance of the patient population, interventions, and outcomes that were included in the network meta-analysis is driven by the interests of decision-makers. The results from the network meta-analysis are relevant to decision-makers who are interested in the relative clinical effectiveness (i.e., time to CDMS) of 44 mcg of IFN β-1a taken subcutaneously thrice weekly, 250 mcg of IFN β-1b taken subcutaneously every other day, 30 mcg of IFN β-1a injected intramuscularly weekly and 20 mg of glatiramer acetate taken subcutaneously

daily in patients with CIS and clinically-silent lesions based on MRI examinations, prior to open-label extension periods. Decision-makers who are interested in the clinical effectiveness of other doses and forms of interferon or other therapies, patients with relapsing–remitting MS, secondary progressive MS, and other outcomes may find this network meta-analysis irrelevant. It is unclear whether the results of the network meta-analysis will hold in Canadian settings given that data was collected from patients being treated with multiple different regimens and in different countries.

Regarding credibility of the network meta-analysis, the authors attempted to identify all relevant RCTs by conducting searches of multiple databases; however they omitted some details of their literature searches such as keywords, results from a group of patients that were treated with 44 mcg of IFN β-1a weekly in the REFLEX trial, and outcomes such as change in lesion size following treatment.[19] The authors provided insufficient information to ascertain whether statistical methods were used that preserved within-study randomization. No rationale was given for the use of a random-effects model. Regarding reporting quality and transparency, the authors reported individual study results and results of direct comparisons with measures of uncertainty (for some outcomes). The effect of important patient characteristics on treatment effects was not reported. The authors reported that they conducted an appraisal of the quality of the included RCTs, but they did not provide their findings nor results of an overall assessment of the quality of the body of evidence for each outcome. One of eight authors and a clinician received funding from the manufacturer of one of the therapies under evaluation, giving the manufacturer an opportunity to exert undue influence in exchange for financial compensation. The treatment effects of four different DMTs regimen were pooled in the meta-analysis. Since the DMTs might have unique mechanisms and effects, the pooled DMT comparison versus placebo is of debatable benefit.

Randomized controlled trial

The RCT[19] exhibited some strengths that similarly were insufficient to offset its serious limitations. Registration of the RCT on a publicly-accessible database suggests that the authors were transparent in their research and minimized patient selection. The authors clearly described their objective and main outcomes. The patients and outcome assessors were blinded to the treatment options, accurate outcome measures were used, and patients were recruited from the same population over the same time frame. Estimates of random variability were reported in the form of 95% confidence intervals for the main outcomes and the statistical significance of the estimated treatment effects were indicated with *P* values. The following limitations were observed.

The authors omitted details when describing their population, study group sizes, interventions, potential confounders and main findings as follows: descriptions of patient characteristics were limited to age, sex, steroid use, disability score, and number of MRI-sensitive lesions. Importantly, it is unclear how many patients were enrolled at the time that measurements were recorded, suggestive of reporting bias. The authors indicate in their text that 146, 156, and 146 patients, respectively completed the study in the 44 mcg SC IFN β-1a thrice weekly, 30 mcg SC IFN β-1a weekly, and placebo groups. However, a figure in the article suggests that at 24 months, the number of patients in each group was 113, 119, and 88, respectively. The number of patients who converted to MS in each group prior to the follow-up timepoint was not disclosed. It is unclear how many patients in each group provided viable outcome measurements. Subgroup analyses were conducted for age, number of Gd+ lesions and number of T2 non-enhancing lesions; however, the choices of thresholds for these parameters were not justified suggesting post-hoc analyses may have

been conducted. Regarding reporting of findings, the estimates of treatment effect were determined through pairwise comparisons based on an adjusted negative binomial model that was not described. As such, it is unclear how the point estimates were derived. The authors indicated that they assessed the quality and potential likelihood of bias of the included RCTs using the Cochrane Risk of Bias tool but did not discuss the quality of the body of evidence for each clinical outcome.

External validity could not be evaluated given that details of the recruitment process were unavailable. It does appear that patients were selected to be at high risk of conversion to MS. The apparent use of stringent inclusion criteria means the generalizability of the results may be limited because the patients may not be representative of the general population of patients with CIS. Other than conversion to MS, the rates and reasons for dropping out in less than 24 months were not discussed; therefore, it is unclear whether the patients who were prepared to participate were representative of the population of patients from which they were recruited. Details of the staff and location of treatment were missing, precluding an assessment.

Some elements that are required to assess the risk to internal validity were missing such as the number of patients who converted to MS prior to 24 months and information on whether any adjustment was made to account for different lengths of follow-up. Finally, the authors did not discuss compliance with the intervention or statistical power of the study. Some of the missing information may be available in companion reports on the REFLEX trial.

Guideline

The included set of guidelines had more strengths than limitations.[20] The scope and purpose were well-defined, stakeholders appeared to be inclusive although it was not possible to assess whether all relevant professional groups were represented. All elements of a rigorous development process were present such as systematic selection of evidence, clear descriptions of the strengths and limitations of the included RCTs and the process through which recommendations were formulated, explicit links between the recommendations and the supporting evidence, an outline of an external peer-review process, and guidance for future updates. The key recommendations were specific, unambiguous and clearly identifiable.

The guideline's quality was weakest in the applicability domain. The developers did not provide advice on and/or tools for implementing their recommendations, nor did they describe facilitators and barriers to implementation. They also did not discuss potential resource implications of applying the recommendations nor monitoring and/or auditing criteria. Given the evidence on the use of glatiramer acetate and β-INF in treating patients with CIS was limited to four RCTs, users of the guidelines will likely need substantial support in implementing the recommendations.

Summary of Findings

The main study findings are summarized below while details and authors' conclusions are provided in Appendix 4.

Clinical effectiveness at 24 months and/or 36 months

One systematic review[18] and one RCT[19] provided evidence on the clinical effectiveness of glatiramer acetate, IFN β-1a, and IFN β-1b in people with CIS. The RCT reported on a set of patients who were included in the systematic review, i.e., patients who were treated with

IFN β-1a once a week.[19] The guideline developers considered evidence from four of the five RCTs that were included in the systematic review.[20]

Time to develop multiple sclerosis

Authors of the systematic review concluded that each of the active interventions, glatiramer acetate, IFN-1a, and IFN β-1b, reduced the short-term risk of developing CDMS relative to placebo.[18] Pooled hazard ratios of the time to convert to CDMS or McDonald MS calculated across five RCTs favoured active therapy over placebo.[18] No discussion of the minimal clinically important difference in the time to convert to CDMS or McDonald MS was provided.

Change in MRI-sensitive lesions

A comparison of the difference in the number of CUA lesions, T2 non-enhancing lesions, T1 Gd+ lesions, and T1 non-enhancing lesions per patient per scan between active therapy and placebo led the authors of the RCT[19] to conclude that a thrice weekly regimen of 44 mcg subcutaneous IFN β-1a was (indirectly) more effective in reducing the number of new lesions than the weekly regimen of 30 mcg subcutaneous IFN β-1a.[19] Both regimens were more effective than placebo in reducing the number of new lesions.[19] The adjusted negative binomial model favoured active therapy over placebo, although the statistical significance of the effect size was not reported.[19] The model also favoured the higher dose regimen over the lower.[19] Subgroup analysis favoured patients 30 years or older over younger patients, patients with no Gd+ lesions over those with at least one lesion, and patients with fewer than nine T2 non-enhancing lesions over those with more lesions. Focality of lesions, use of steroids during the first episode or sex has no statistically significant impact on the risk of developing new lesions within 24 months of treatment. The analysis of the change in volume of lesions from baseline favoured both active therapies over placebo. No discussion of minimal clinically important differences in the number or volume of lesions was provided.

Safety

The systematic review reported mixed results on the incidence of discontinuation due to adverse events.[18] Comparisons of the proportion of patients who discontinued the study due to adverse events favoured 44 mcg of SC IFN β-1a thrice weekly and 30 mcg of IM IFN β-1a weekly over placebo. Similar calculations favoured placebo over 250 mcg of SC IFN β-1b and 20 mg of SC glatiramer acetate daily. The authors did not quantitatively synthesize the evidence from the RCTs nor did they asses the statistical significance of the differences in outcome measures between the active therapies and placebo. Further, the authors did not describe the specific events that led to patients discontinuing treatment. The authors of the RCT did not identify any safety signals, in direct contradiction to the findings on the incidence of discontinuation due to adverse events in the systematic review.[19]

There was no evidence identified on incidence of progression to CDMS, mortality, hospitalizations, quality of life, disability, time to disability, long-term disability progression, or relapse.

Guidelines

The evidence on clinical effectiveness for the single set of guidelines was extracted from four of the five RCTs that were included in the systematic review.[18] Appendix 5 outlines the overlap among the studies that are included in this review.

The evidence favoured glatiramer acetate, IFN β-1a, and IFN β-1b over placebo. Relative to placebo, the risk of conversion to MS over 3 years was significantly lower with 20 mg of glatiramer acetate taken subcutaneously daily, with an RR of 0.58 (95% CI, 0.44 0.75). Relative to placebo, the risk of conversion to MS over 2 years was significantly lower with 44 mcg of IFN β-1a taken subcutaneously thrice weekly, with an RR of 0.55 (95% CI, 0.38 0.78). Relative to placebo, the risk of conversion to MS over 3 years was significantly lower with 30 mcg IFN β-1a injected intramuscularly weekly, with an RR of 0.71 (95% CI, 0.56 0.89%), Relative to placebo, the risk of conversion to MS over 2 years was significantly lower with 250 mcg of IFN β-1b taken subcutaneously every other day, with an RR of 0.59 (95% CI, 0.46 0.76). The risk of harms from initiating DMTs (such as adverse events, major adverse events, and burden of taking a long-term medication) relative to the benefit of reducing relapse rate in patients with CIS or relapsing forms of MS who have not had relapses in two or more years and do not have active new MRI lesion activity on recent imaging is unknown.

The guidelines included four relevant recommendations:

- *"Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with [two] or more brain lesions that have imaging characteristics consistent with MS"* (page 174)[20]
- *"After discussing the risks and benefits, clinicians should prescribe DMT to people with a single clinical demyelinating event and two or more brain lesions characteristic of MS who decide they want [DMT]"* (page 175)[20]
- *"Clinicians may recommend serial imaging at least annually for the first five years and close follow-up rather than initiating DMT in people with CIS or relapsing forms of MS who are not on DMT, have not had relapses in the preceding two years, and do not have active new MRI lesion activity on recent imaging"* (p 176)[20]
- *"Clinicians should [compare] the associated risks of continuing DMTs [with] those risks that are associated with stopping DMTs in people with CIS (who have not been diagnosed with MS)."* (page 212)[20] There was some uncertainty in the level of consensus achieved for this recommendation.

Recommendations on switching between therapies specifically for patients with CIS were not found although there were recommendations for patients diagnosed with MS.

Limitations

There are multiple limitations of note in the published body of evidence on clinical effectiveness and safety of DMTs in patients diagnosed with CIS that was identified for this report. The evidence on each treatment regimen was derived from no more than two RCTs, suggesting a lack of diversity in the patient populations, and limiting opportunities for meaningful meta-analyses. Three of the five RCTs that were included in the systematic review[18] reported on interferon beta-1a; in two trials the therapy was delivered intramuscularly and in one, subcutaneously and at a different dose. One of the remaining RCTs reported on patients treated with glatiramer acetate while the other reported on patients treated with interferon beta-1b.

Patient selection bias was evident, given the narrow inclusion criteria of the clinical trials. Outcomes were reported over relatively short and variable time-frames of two[18-20] or three years.[18,20] Reliable measures of outcomes such as, mortality, relapse, and long-term

disability progression could not have been captured in these short time frames. Regarding variability in reporting time-frames, authors of the RCT[19] indicated that outcomes were reported for some patients when they converted to CDMS and not at the targeted timeframe of 24 months. It is unclear whether adjustments were made for a range of follow-up times. Each study reported on a subset of relevant outcomes and details on adverse events were sparse. To comprehensively assess the impact of the therapies of interest, all important outcomes should be studied.

Another important limitation was related to potential conflicts of interest by authors of the RCTs from which all evidence was derived.[18,19] Manufacturers of the DMTs that were under evaluation sponsored majority of the RCTs (sponsorship was unclear in one of five trials) and as such, may have influenced the design of the study and reporting. Specifically, manufacturers may have influenced the selection of patients, comparators, and outcomes in order to demonstrate findings in favour of products from which they could gain financial benefit. Importantly, the authors of the systematic review selectively reported on RCTs evaluating groups of patients with CIS, interventions at specific doses, and outcomes. Given that DMTs have unique effects, the pooled DMT comparison versus placebo that was conducted by the authors of the systematic review[18] is of debatable benefit.

Lastly, there were some gaps in the evidence. Of note, direct comparisons between the DMTs were lacking except for a comparison of relative number of MRI-sensitive lesions and changes in the volume of lesions between two doses of IFN β-1a.[19] None of the studies reported on incidence of progression to CDMS, mortality, hospitalizations, quality of life, disability, time to disability, long-term disability progression, or relapse. The guideline developers followed a rigorous development process, however, they provided insufficient information on implementing their recommendations. These limitations along with those outlined in the quality assessment section suggest that considerable caution must be taken in making inferences about the clinical effectiveness and safety of glatiramer acetate, IFN β-1a, and IFN β-1b for patients diagnosed with CIS, specifically in relation to the Canadian context.

Conclusions and Implications for Decision or Policy Making

The evidence on the clinical effectiveness and safety of glatiramer acetate, IFN β-1a, and IFN β-1b for treating patients diagnosed with CIS is limited in quantity and quality. One systematic review,[18] one RCT[19], and one set of guidelines[20] were included in this review. The RCT[19] exhibited more limitations than strengths. Serious weaknesses in reporting and internal validity were observed. The authors incompletely described the patients' characteristics, study group sizes, interventions, potential confounders, main findings, incidence of conversion to MS prior to 24 months, or compliance with the intervention.[19] The guideline developers[20] followed a rigorous process, however, they did not provide advice and/or tools on implementing their recommendations.

Results from the systematic review[18] suggested that, relative to placebo, specific doses of glatiramer acetate, IFN-1a, and IFN β-1b slowed down the speed of conversion from CIS to CDMS or McDonald MS and reduced the development of new MRI-sensitive brain lesions. Findings from the RCT[19] similarly favoured IFN β-1a over placebo. Additionally, a higher dose of IFN β-1a offered some benefits over a lower dose.[19] The systematic review that was conducted as part of the guideline development process derived evidence from the same pool of randomized controlled trials that were included in other studies in this review; as such, it provided little additional knowledge regarding comparative effectiveness of the

active regimens. The set of guidelines included recommendations for physicians to discuss with patients the benefits and risks of prescribing and stopping disease-modifying therapies, and for physicians to monitor patients with CIS. The recommendations for switching therapies were not included in this review as they were not specific to patients with CIS. The limited availability of published evidence on the use of glatiramer acetate, IFN β-1a, and IFN β-1b in treating patients with CIS suggests a general lack of experience in this area. As such, users of the guidelines will likely need substantial support in implementing the recommendations. However, the developers did not provide advice on and/or tools for implementing their recommendations, nor did they describe facilitators and barriers to implementation. They also did not discuss potential resource implications of applying the recommendations nor monitoring and/or auditing criteria.

This current review compiled evidence for glatiramer acetate from the same RCT that was referenced in the recommendations made by the Canadian Drug Expert Committee in 2009. Relative to the systematic review from which 2013 recommendations on IFN β-1a (Rebif) were drawn, new evidence on the impact of 44 mcg of IFN β-1a administered thrice weekly subcutaneously on the number and volume of new MRI-sensitive lesions compared with that of 44 mcg of IFN β-1a administered once weekly subcutaneously was included.[19] No new information on the impact of DMTs on disability was found.

Caution must be taken in interpreting the evidence presented in this review due to potential conflicts of interest from sponsorship by the manufacturers of the interventions that were under evaluation, the sparsity of evidence, and apparent selection of patients, and selective measurement and reporting of outcomes. While contemplating the lack of robust findings in the literature, decision-makers and policy makers may also consider that evidence on patients with confirmed MS may be needed alongside evidence on patients with CIS to construct a comprehensive picture of the true treatment effects of glatiramer acetate and β-IFNs. Additional research involving other comparators (e.g., direct comparisons of drugs indicated for CIS or other treatment regimens) and additional clinical sites in Canada may help to produce evidence that will be useful in informing public health policies that are relevant to the Canadian population.

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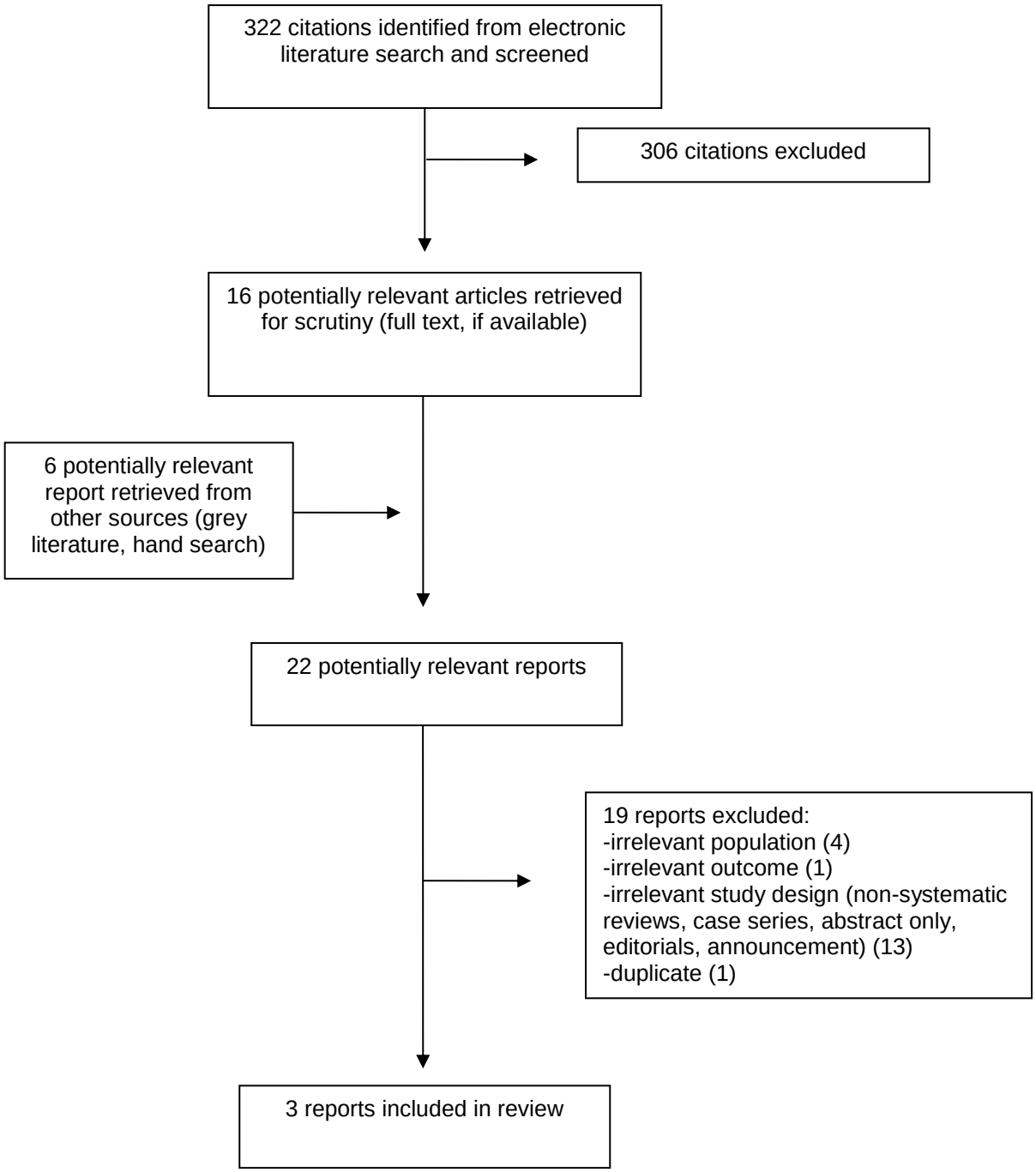
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of the Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country Funding	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Armoiry et al., 2018[18] **United Kingdom** One of eight authors received funding from a manufacturer	A systematic review and network meta-analysis of the short- and long-term clinical effectiveness of first-generation DMTs in people with CIS Included: Five RCTs (PReCISe, REFLEX, CHAMPS, Pakdaman, BENEFIT) with short-term results from double-blinded periods and long-term results from open-label extensions; published between 2000 and 2012.[a] Excluded: Long-term follow-up studies of immediate versus delayed therapy	Patients with a single clinical event and evidence of clinically silent lesions based on MRI Mean age (PreCISe, n=481): 31.2±6.9 years Mean age (REFLEX, n=292): 30.7 years Mean age (CHAMPS, n=383): 33.0±0.7 years Mean age (Pakdaman, n=202): 28.0 years Median age (BENEFIT, n=487): 30 years OR Mean age (CHAMPS, Pakdaman, PreCISe, REFLEX, n=1358): 31.1 years Median age (BENEFIT, n=487): 30 years % female (PreCISe, n=481): 67% % female (REFLEX, n=292): 66% % female (CHAMPS, n=383): 75% % female (Pakdaman, n=202): 67.8% % female (BENEFIT, n=487): 70.7% OR % female (n=1845): 69% Exclusion criteria: NR	Intervention: 20 mg SC GA daily (PreCISe, n=243) 44 mcg IFN β-1a SC thrice weekly (REFLEX, n=146)[b] 30 mcg IFN β-1a IM weekly (CHAMPS, Pakdaman, n=297) 250 mcg IFN β-1b SC every other day (BENEFIT, n=305) Comparator: Placebo (n=854)	Time to CDMS, discontinuation due to AEs Follow-up: 2 years (REFLEX, BENEFIT), 3 years (PreCISe, CHAMPS, Pakdaman) Results of long-term outcomes from the open-label extension periods were not included in this report

AE = adverse events; BENEFIT = Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment; CDMS = clinically definite multiple sclerosis; CHAMPS = Controlled High Risk Avonex Multiple Sclerosis Prevention Study; CIS = clinically isolated syndrome; DMT = disease-modifying therapy; GA = glatiramer acetate; IFN = interferon; MRI = magnetic resonance imaging; NR = not reported; PreCISe = Evaluate Early Glatiramer Acetate Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis of Subjects Presenting With Clinically Isolated Syndrome; RCT = randomized controlled trial; REFLEX = Rebif flexible dosing in early MS; SC = subcutaneously.

[a] Included one group of patients that were included in the RCT[19].

[b] Based on cross-referencing, a total of 171 patients were enrolled at the start of the study and 146 remained at the 2 year follow-up time point[19]

Table 3: Characteristics of the Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
De Stefano et al., 2014[19] **Italy** The study was funded by a manufacturer	The REFLEX RCT[a]	517 patients aged 18 to 50 years with an EDSS score of 0 to 5, with a history of a single demyelinating event suggestive of MS within 60 days prior to study entry and ≥2 clinically silent lesions on a T2-weighted brain MRI scan ≥3 mm, ≥ 1 ovoid, periventricular or infratentorial; time of enrollment NR Median age: 29 years (range, 24 to 37) % female: 64.2% Exclusion criteria: NR	Intervention: IFN β-1a 44 mcg SC thrice weekly (n = 171), IFN β-1a 44 mcg SC once a week (n = 175) Comparator: placebo (n = 171)	Mean number of lesions per patient per scan, change in lesion volume from baseline Follow-up: 24 months or conversion to CDMS, whichever occurred first Change in brain volume from baseline was not included in this review

CDMS = clinically definite multiple sclerosis; EDSS = Expanded Disability Status Scale; IFN = interferon; MRI = magnetic resonance imaging; MS = multiple sclerosis; NR = not reported; RCT = randomized controlled trial; REFLEX = Rebif flexible dosing in early MS; SC = subcutaneous.

[a] This RCT was included in the systematic review[18]

Table 4: Characteristics of Included Guideline

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Rae-Grant et al., 2018[20] American Academy of Neurology						
AAN members and other clinicians committed to the delivery of optimal care to people with MS. Separate recommendations were made for patients with CIS.	Disease-modifying therapies in people with MS	Clinical effectiveness	AAN 2011 guideline development process	The AAN therapeutic classification of evidence	AAN 2011 guideline development process including Delphi process	An outline of an external peer-review process, and guidance for future updates were provided

AAN = American Academy of Neurology; MS = multiple sclerosis.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Quality Assessment of the Systematic Review using AMSTAR 2[13]

Strengths	Limitations
Armoiry et al., 2018[18]	
• The statement of objectives included the population, interventions, and outcomes of interest • The authors searched multiple databases and performed study selection, data extraction and quality assessment in duplicate • The study eligibility criteria included the population, intervention (at authorized dosages), study types, outcomes, blinding • The review was conducted as part of a larger review that was registered on a publicly-available database • The sources of funding of the primary studies were disclosed	• Details of the methodology were omitted such as keywords and a search strategy • The authors did not provide an explanation for limiting the design of included studies to randomized controlled trials • The authors did not provide a list of excluded studies nor justification for the exclusion criteria • The outcome of the risk of bias assessment for each study was not described • The authors did not critically assess the body of evidence of the outcomes • One of eight authors received funding from a manufacturer

Table 6: Quality Assessment of the embedded Meta-Analysis using the ISPOR Task Force questionnaire[14]

Question	Armoiry et al., 2018[18]
Relevance	
1. Is the population relevant?	Cannot answer
2. Are any relevant interventions missing?	Cannot answer
3. Are any relevant outcomes missing	Cannot answer
4. Is the context (settings and circumstances) applicable ?	Cannot answer
Credibility	
5. Did the researchers attempt to identify and include all relevant RCTs?	Yes
6. Do the trials for the interventions of interest form one connected network of RCTs?	Yes
7. Is it apparent that poor quality studies were included, thereby leading to bias?	No
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Yes
9. Are there systematic differences in treatment effect modifiers across the different treatment comparisons in the network?	Cannot answer
10. Were these imbalances in effect modifiers across the different treatment comparisons identified before comparing individual study results?	Cannot answer
Analysis	
11. Were statistical methods used that preserve within-study randomization?	Cannot answer

Question	Armoiry et al., 2018[18]
12. If both direct and indirect comparisons are available for pairwise contrasts was agreement in treatment effects evaluated or discussed?	Not applicable
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize bias with the analysis?	Not applicable
15. Was a valid rationale provided for the use of random-effects or fixed-effect models?	No
16. If a random-effects model was used, were assumptions about heterogeneity explored or discussed?	No
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Not applicable
Reporting quality and transparency	
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes
19. Are the individual study results reported?	Yes
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Yes
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes
23. Is the effect of important patient characteristics on treatment effects reported?	No
Interpretation	
24. Are the conclusions fair and balanced?	Cannot answer
Conflict of interest	
25. Were there any potential conflicts of interest?	Yes
26. If yes, were there steps taken to address these?	Yes

Table 7: Quality Assessment of the Randomized Controlled Trial using the Downs and Black checklist[15]

Criteria	De Stefano et al., 2014[19]
Reporting	
27. Is the hypothesis/aim/objective of the study clearly described?	Yes
28. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes
29. Are the characteristics of the patients included in the study clearly described?	No
30. Are the interventions of interest clearly described?	No
31. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	No
32. Are the main findings of the study clearly described?	No
33. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes
34. Have all important adverse events that may be a consequence of the intervention been reported?	No
35. Have the characteristics of patients lost to follow-up been described?	No
36. Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?	Yes
External validity	
37. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unable to determine
38. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unable to determine
39. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unable to determine
Internal validity - bias	
40. Was an attempt made to blind study subjects to the intervention they have received?	Yes
41. Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes

Criteria	De Stefano et al., 2014[19]
42. If any of the results of the study were based on "data dredging", was this made clear?	Unable to determine
43. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Unable to determine
44. Were the statistical tests used to assess the main outcomes appropriate?	Yes
45. Was compliance with the intervention(s) reliable?	Unable to determine
46. Were the main outcome measures used accurate (valid and reliable)?	Yes
Internal validity – confounding (selection bias)	
47. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes
48. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes
49. Were study subjects randomised to intervention groups?	Yes
50. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Yes
51. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Unable to determine
52. Were losses of patients to follow-up taken into account?	Unable to determine
Power	
53. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Unable to determine

Table 8: Strengths and Limitations of Guidelines using AGREE II[16]

Item	Guideline
	Rae-Grant et al., 2018[20]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Cannot assess
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes
14. A procedure for updating the guideline is provided.	Yes
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	No

Table 8: Strengths and Limitations of Guidelines using AGREE II[16]

Item	Guideline
	Rae-Grant et al., 2018[20]
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No
20. The potential resource implications of applying the recommendations have been considered.	No
21. The guideline presents monitoring and/or auditing criteria.	No
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	Unable to assess
23. Competing interests of guideline development group members have been recorded and addressed.	Yes

Appendix 4: Main Study Findings and Authors' Conclusions

Table 9: Summary of Findings of the Systematic Reviews

Main Study Findings	Authors' Conclusion
DMT vs. placebo	
Armoiry et al., 2018[18]	
Clinical effectiveness - Time to CDMS @ 24 months and/or 36 months **GA 20 mg SC daily (n = 243) vs. placebo (n = 238) @ 36 months; 1 study** • HR: 0.55 (CI, 0.40 to 0.76); in favour of active treatment **IFN β-1a 44 mcg SC thrice weekly (n = 171)[a] vs. placebo (n = 171) @ 24 months; 1 study** • HR: 0.48 (CI, 0.31 to 0.74); in favour of active treatment **IFN β-1a 30 mcg IM weekly (n = 297) vs. placebo (n = 288) @ 36 months; 2 studies** • HR: 0.52 (CI, 0.39 to 0.68); I^2 = 0%, P = 0.72; in favour of active treatment **IFN β-1b 250 mcg SC every other day (n = 305) vs. placebo (n = 182) @24 months; 1 study** • HR: 0.50 (CI, 0.36 to 0.70); in favour of active treatment *Network meta-analysis* **Clinical effectiveness - Time to CDMS @ 24 months and/or 36 months** **Grouped DMT (n = 1016) vs. placebo (n = 879); 5 studies** • Pooled HR: 0.51 (CI, 0.44 to 0.61); I^2 = 0%, P = 0.98; in favour of grouped DMT results There was no evidence from indirect comparisons suggesting superiority of any one active therapy over another **Clinical effectiveness - Time to McDonald MS @ 24 months and/or 36 months** **Grouped DMT (n = 1016) vs. placebo (n = 879); 5 studies** • Pooled HR: 0.52 (CI, 0.46 to 0.60); I^2 = 0%; P = 0.93; in favour of grouped DMT results **Safety - Discontinuation due to AEs @ 24 months or 36 months[b]** **IFN β-1a 44 mcg SC thrice weekly (n = 171) vs. placebo (n = 171) @ 24 months; 1 study** • Incidence: 2.9% vs. 3.5%; in favour of active therapy **IFN β-1a 30 mcg IM weekly (n = 193) vs. placebo (n = 190) @ 36 months; 1 study** • Incidence: 0.5% vs. 3.7%; in favour of active therapy **IFN β-1b 250 mcg SC every other day (n = 292) vs. placebo (n = 176) @24 months; 1 study** • Incidence: 8.2% vs. 0.6%; in favour of placebo **GA 20 mg SC daily (n = 243) vs. placebo (n = 238) @ 36 months; 1 study**	*"…IFN-β and GA reduce the short-term (up to 2–3 years) risk of a second clinical attack after CIS and so delay the diagnosis of CDMS"* (p 1007)

Main Study Findings	Authors' Conclusion
• Incidence: 5.8% vs. 1.7%; in favour of placebo A network meta-analysis of safety outcomes was not conducted	

AE = adverse event; CDMS = clinically diagnosed MS; CI = 95% confidence interval; DMT = disease modifying therapy; GA = glatiramer acetate; HR = hazard ratio; IFN = interferon; IM = intramuscularly; MS = multiple sclerosis; NR = not reported; RCT = randomized controlled trial; SC = subcutaneously

[a] Authors listed the number of patients enrolled as 146, yet indicated that 171 were available for assessment of discontinuation due to AEs
[b] Different numbers of patients were available for the assessment of discontinuation due to AEs. One of the included studies did not report on AEs

Table 10: Summary of Findings of the Primary Studies

Main Study Findings	Authors' Conclusion
De Stefano et al., 2014[19,a]	
Clinical effectiveness @ 24 months (REFLEX trial) **IFN β-1a 44 mcg SC thrice weekly (n = 171) vs. IFN β-1a 30 mcg SC weekly (n = 175) vs. placebo (n = 171)** Study completion rates: 146 (85.4%) vs. 156 (89.1%) vs. 146 (85.4%), respectively; *P* = NR **Mean number of lesion per patient per scan[b]** Mean (±SD) number of CUA lesions: 0.6±1.15 vs. 1.23±4.26 vs. 2.70±5.23, respectively; indicating that both regimen were more effective than placebo Relative reduction in the number of CUA lesions compared to placebo: 2.10 vs. 1.47**;** *P* = 0.002; indicating that the thrice weekly regimen is more effective than the weekly regimen *Analysis using an adjusted negative binomial model (P* = NR*)* CUA lesions: 0.50 vs. 0.95 vs. 2.58, respectively New T2 non-enhancing lesions: 0.17 vs. 0.24 vs. 0.55, respectively New T1 Gd+ lesions: 0.06 vs. 0.17 vs. 0.72, respectively New T1 non-enhancing lesions: 0.18 vs. 0.26 vs. 0.41, respectively All results favour active therapy (statistical significance of the effect size was not reported) **IFN β-1a 44 mcg SC thrice weekly vs. placebo[b]** RR of CUA lesions: 0.19 (CI, 0.14 to 0.26); *P* <0.001 RR of new T2 non-enhancing lesions: 0.30 (0.23 to 0.40); *P* <0.001 RR of new T1 Gd+ lesions: 0.08 (CI, 0.05 to 0.13); *P* <0.001 RR of new T1 non-enhancing lesions: 0.43 (CI, 0.33 to 0.57); *P* <0.001 All results favour active therapy **IFN β-1a 30 mcg SC weekly vs. placebo[b]** RR of CUA lesions: 0.37 (CI, 0.27 to 0.50); *P* <0.001 RR of new T2 non-enhancing lesions: 0.43 (CI, 0.32 to 0.57); *P* <0.001 RR of new T1 Gd+ lesions: 0.24 (CI, 0.16 to 0.35); *P* <0.001	*"This secondary analysis of REFLEX found improved MRI outcomes in patients treated with both dosing regimens compared with placebo, and also found additional benefit of the higher-dose regimen. Together, these data support the rationale for early subcutaneous IFN β-1a treatment of patients with CIS suggestive of MS; however, these potential benefits of early treatment have to be balanced against the risk of treatment."* (p 652)

Main Study Findings	Authors' Conclusion
RR of new T1 non-enhancing lesions: 0.63 (CI, 0.48 to 0.81); *P* 0.004 All results favour active therapy **IFN β-1a 44 mcg SC thrice weekly vs. IFN β-1a 30 mcg SC weekly[b]** RR of CUA lesions: 0.52 (CI, 0.38 to 0.71); *P* = 0.002 RR of new T2 non-enhancing lesions: 0.71 (CI, 0.53 to 0.95); *P* = 0.012 RR of new T1 Gd+ lesions: 0.35 (CI, 0.23 to 0.54); *P* <0.001 RR of new T1 non-enhancing lesions: 0.69 (CI, 0.53 to 0.91); *P* = 0.008 All results favour higher dose (statistical significance of the effect size was not reported) *Subgroup analysis* HR for age <30 years vs ≥30 years: 1.69 (CI, 1.31 to 2.18); favouring the older group HR for ≥1 vs 0 Gd+ lesions: 2.67 (CI, 2.05 to 3.47); favouring those with no lesions HR for ≥9 vs <9 T2 non-enhancing lesions: 4.93 (CI, 3.66 to 6.63); favouring those with fewer than 9 lesions There was no significant effect of monofocal versus multifocal presentation, use of steroids during the first event or patient sex. **Median (IQR) change in volume from baseline[b] (*P* = NR)** T2 non-enhancing lesions: −128.7 mm^3 (−721.0 to 42.5) vs. −37.9 mm^3 (−609.3 to 177.4) vs. +51.5 mm^3 (−194.6 to 617.3), respectively; favouring active therapies over placebo T1 Gd+ lesions: 0 mm^3 (−88.7 to 0.0) vs. 0 mm^3 (−71.55 to 0.00) vs. 0 mm^3 (−54.40 to 11.40), respectively; slightly favouring active therapies over placebo T1 non-enhancing lesions: No change vs. no change vs. +31.5 mm^3, respectively; favouring active therapies over placebo **Safety** No new or unexpected safety signals were found	

CI = 95% confidence interval; CIS = clinically isolated syndrome; CUA = combined unique active; Gd+ = gadolinium-enhancing; IFN = interferon; HR = hazard ratio; IQR = interquartile range; MRI = magnetic resonance imaging; MS = multiple sclerosis; NR = not reported; REFLEX = Rebif flexible dosing in early MS; RR = relative risk; SC = subcutaneously; SD = standard deviation

[a] Reported on a subset of patients included in the systematic review[18]
[b] It is unclear how many patients were enrolled at the time that measurements were recorded. The authors indicate in their text that 146, 156, and 146 patients, respectively completed the study in the 44 mcg SC IFN β-1a thrice weekly, 30 mcg SC IFN β-1a weekly, and placebo groups. Meanwhile, figure 1 suggests that at 24 months, the number of patients were 113, 119, and 88, respectively.

Table 11: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations[a]
Rae-Grant et al., 2018[20]	
"Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS" (page 174)	Level of obligation: B
"After discussing the risks and benefits, clinicians should prescribe DMT to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want [DMT]" (page 175)	Level of obligation: B
"Clinicians may recommend serial imaging at least annually for the first 5 years and close follow-up rather than initiating DMT in people with CIS or relapsing forms of MS who are not on DMT, have not had relapses in the preceding 2 years, and do not have active new MRI lesion activity on recent imaging" (page 176)	Level of obligation: C – given the lack of evidence in these populations and inference made about the risk of harm from initiating DMTs
"Clinicians should [compare] the associated risks of continuing DMTs [with] those of stopping DMTs in people with CIS (who have not been diagnosed with MS)"[b] (page 212) Only recommendations for starting, switching, and stopping therapies for patients with CIS are reported here. Recommendations for other therapies and populations that did not meet the inclusion criteria for this review are excluded	Level of obligation: B – given that there is evidence that DMTs delay progression to MS but not all cases of CIS progress to MS. Inferences were made about people with CIS' attitudes toward indefinite treatment and the lack of evidence regarding stopping treatment in this population. Consideration was also given to good clinical practice of discussing risks of treatment with patients

CIS = clinically isolated syndrome; DMT = disease-modifying therapy; MRI = magnetic resonance imaging; MS = multiple sclerosis

[a] The level of obligation was based on confidence in the evidence, soundness of inference assuming all premises are true, acceptance of axiomatic principles, and anticipated magnitude of benefit relative to harms, among other criteria

[b] There was some uncertainty regarding consensus

Appendix 5: Overlap between Included Systematic Reviews

Table 12: Primary Study Overlap Among the Included Studies

Primary Study Citation	Article Citation		
	Armoiry et al, 2018[18]	De Stefano et al., 2014[19]	Rae-Grant et al., 2018[20]
PRECISE	X	-	X
REFLEX	X	X	X
CHAMPS	X	-	X
Pakdaman et al.	X	-	-
BENEFIT	X	-	X

Table 13: Characteristics of Primary Studies Included in the Systematic Review and Guidelines

Primary Study Citation	Characteristics				
	Intervention	Comparator(s)	Country	Length of time prior to cross-over	Sponsor
PreCISe	GA 20 mg SC daily (n=243)	Placebo (n=238)	Australia, Canada, United State, and 13 European countries	3 years	Manufacturer
REFLEX	IFN β-1a 44 mcg SC thrice week (n=171)[a]	Placebo (n=171)	Canada, Lebanon, Morocco, Suadi Arabia, Turkey, and 21 European countries	2 years	Manufacturer
CHAMPS	IFN β-1a 30 mcg IM weekly (n=193)	Placebo (n=190)	Canada, United States	3 years	Manufacturer
Pakdaman et al.	IFN β-1a 30 mcg IM weekly (n=104)	Placebo (n=98)	Iran	3 years	Unclear
BENEFIT	IFN β-1b 250 mcg SC every other day (n=305)	Placebo (n=182)	Israel, Canada, and 18 European countries	2 years	Manufacturer

BENEFIT = Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment; CHAMPS = Controlled High Risk Avonex Multiple Sclerosis Prevention Study; GA = glatiramer acetate; IFN = interferon; IM = intramuscularly; PreCISe = Evaluate Early Glatiramer Acetate Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis of Subjects Presenting With Clinically Isolated Syndrome; REFLEX = Rebif flexible dosing in early MS; SC = subcutaneously

[a] The systematic review did not report on 175 patients who were treated with IFN β-1a 44 mcg SC weekly. The number of patients who were enrolled at 24 months in the IFN β-1a thrice weekly, IFN β-1a weekly, and placebo groups were 146, 156, and 146, respectively[19]

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Appendix 6: Additional References of Potential Interest

Review with unclear methodology

Freedman MS, Comi G, De Stefano N, et al. Moving toward earlier treatment of multiple sclerosis: Findings from a decade of clinical trials and implications for clinical practice. *Mult Scler Relat Disord*. 2014 Mar;3(2):147-155.
PubMed: PM25878002