The Evolving Landscape of MS Treatment

Hosted by

Alberta and Northwest Territories Division

Tuesday May 29, 2018



Multiple Sclerosis Society of Canada

The MS Society of Canada gratefully acknowledges the educational grant received from Biogen which makes possible this educational session.

The MS Society does not approve, endorse or recommend any specific product or therapy but provides information to assist individuals in making their own decisions.

Identification of needs, determination of objectives, selection of content and speakers, educational methods and materials are the sole responsibility of MS Society staff and advisors.

MS Society of Canada

- Mission Statement: To be a leader in finding a cure for multiple sclerosis and enabling people affected by MS to enhance their quality of life.

THE EVOLVING LANDSCAPE OF MS TREATMENT

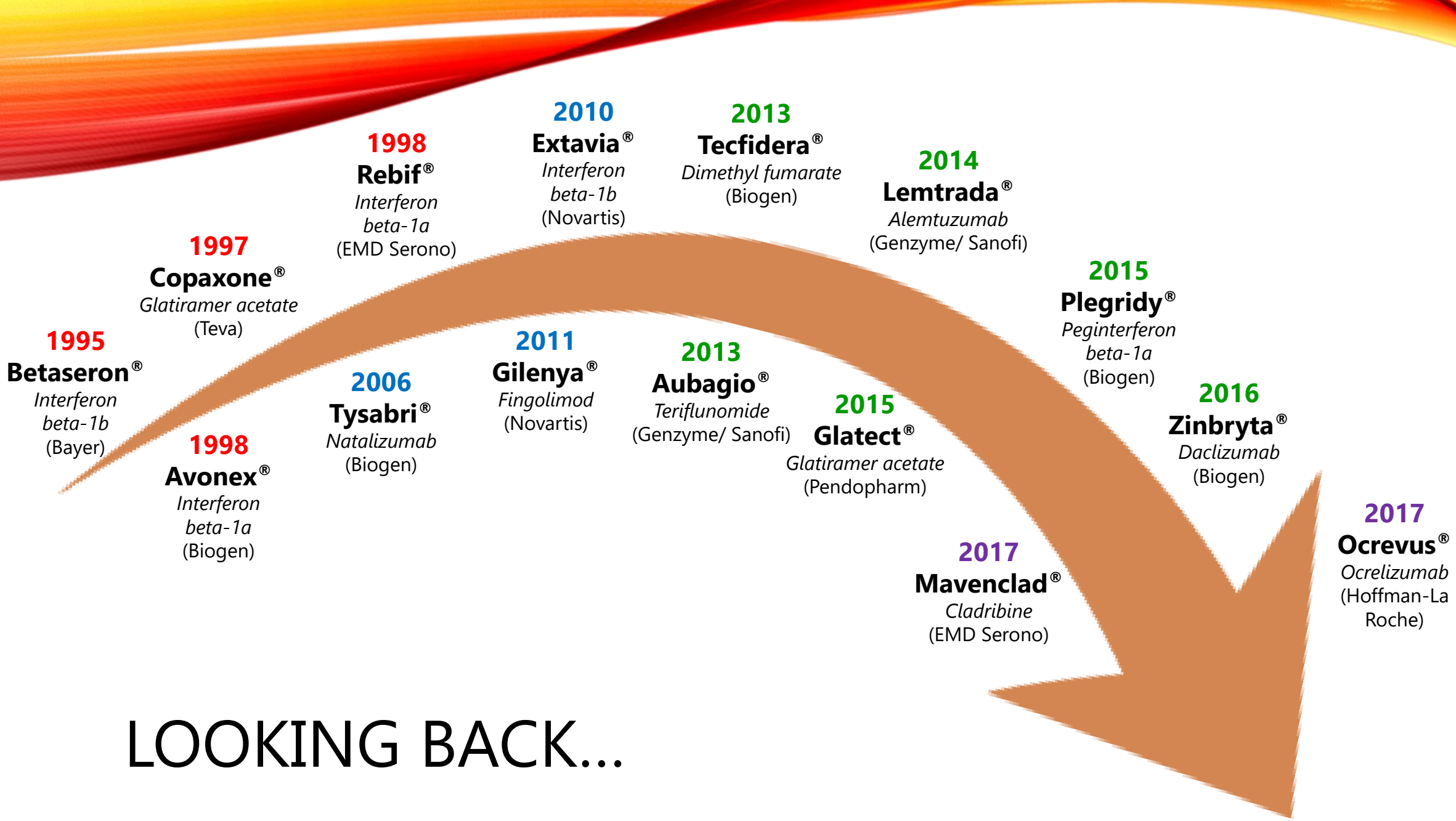
May 29, 2018 – National Webinar

Amy Semaka, BScPharm, PharmD

asemaka@ualberta.ca

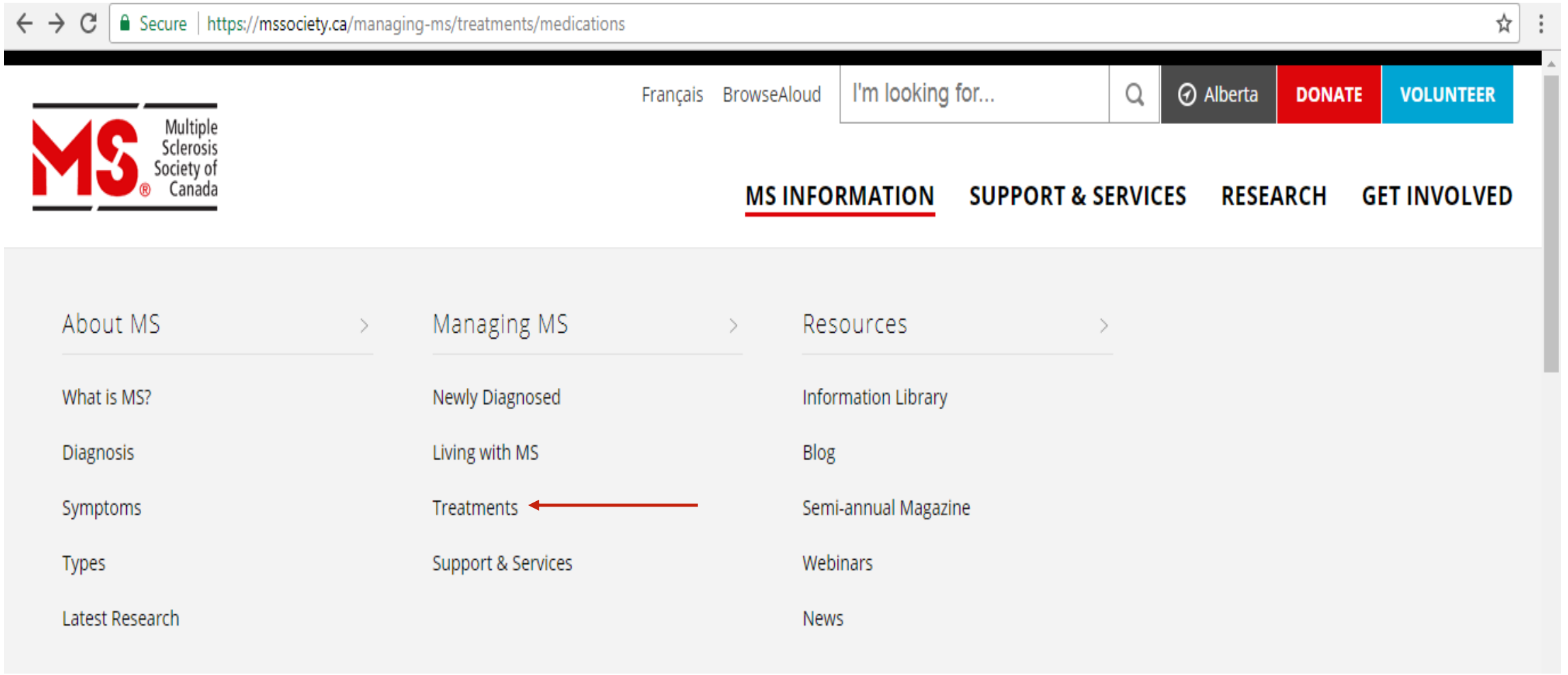
DISCLOSURES

- I have no commercial or monetary relationships that would influence this presentation.
- I met with representatives from the pharma industry for the purpose of seeking relevant and privileged presentation material, but I was in no way biased by these meetings.
- I am a member of the Board of Directors for the MS Society (Edmonton Chapter), but I receive no compensation as a member of this Board.



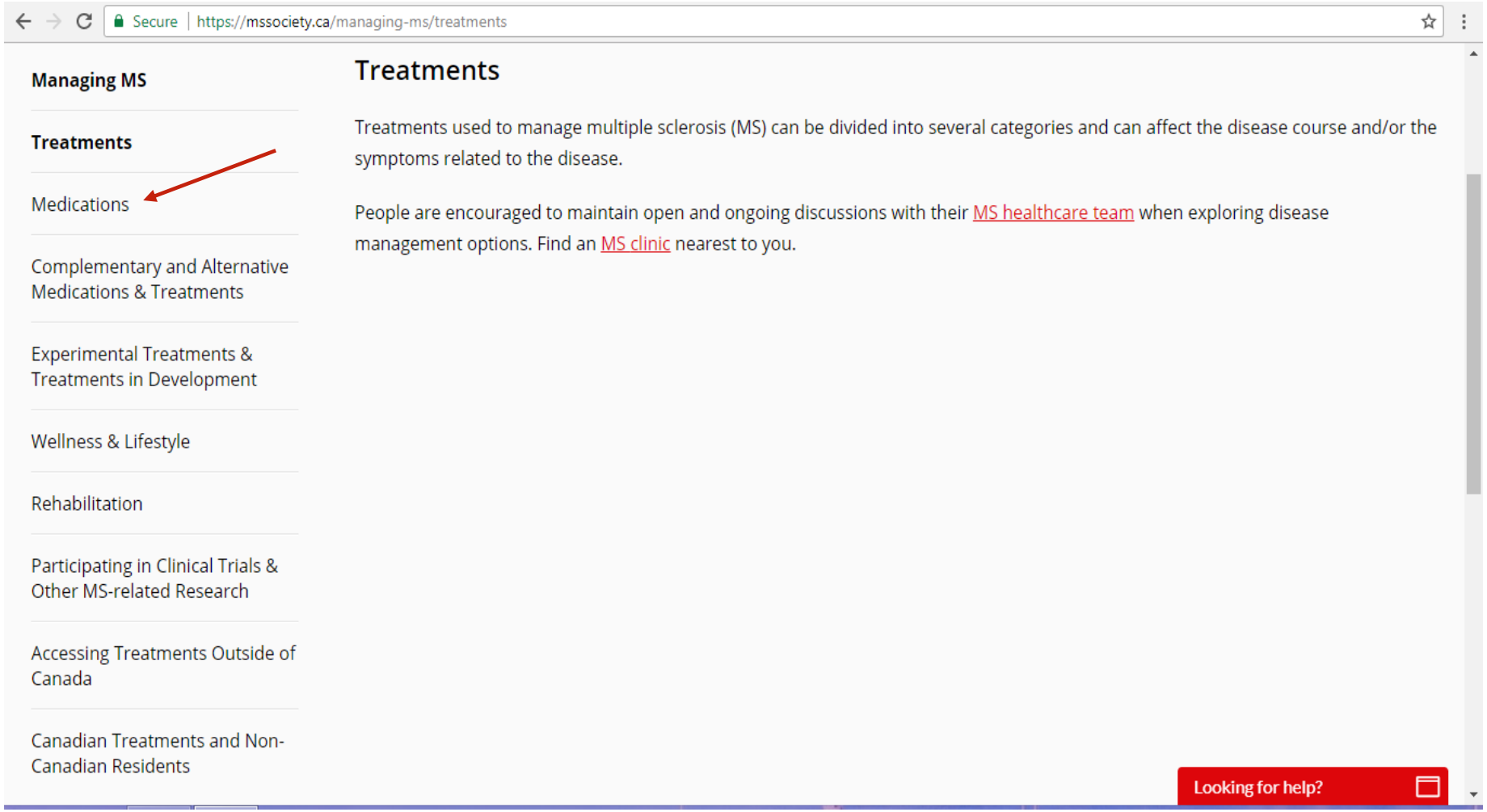
LOOKING BACK…

MED INFO

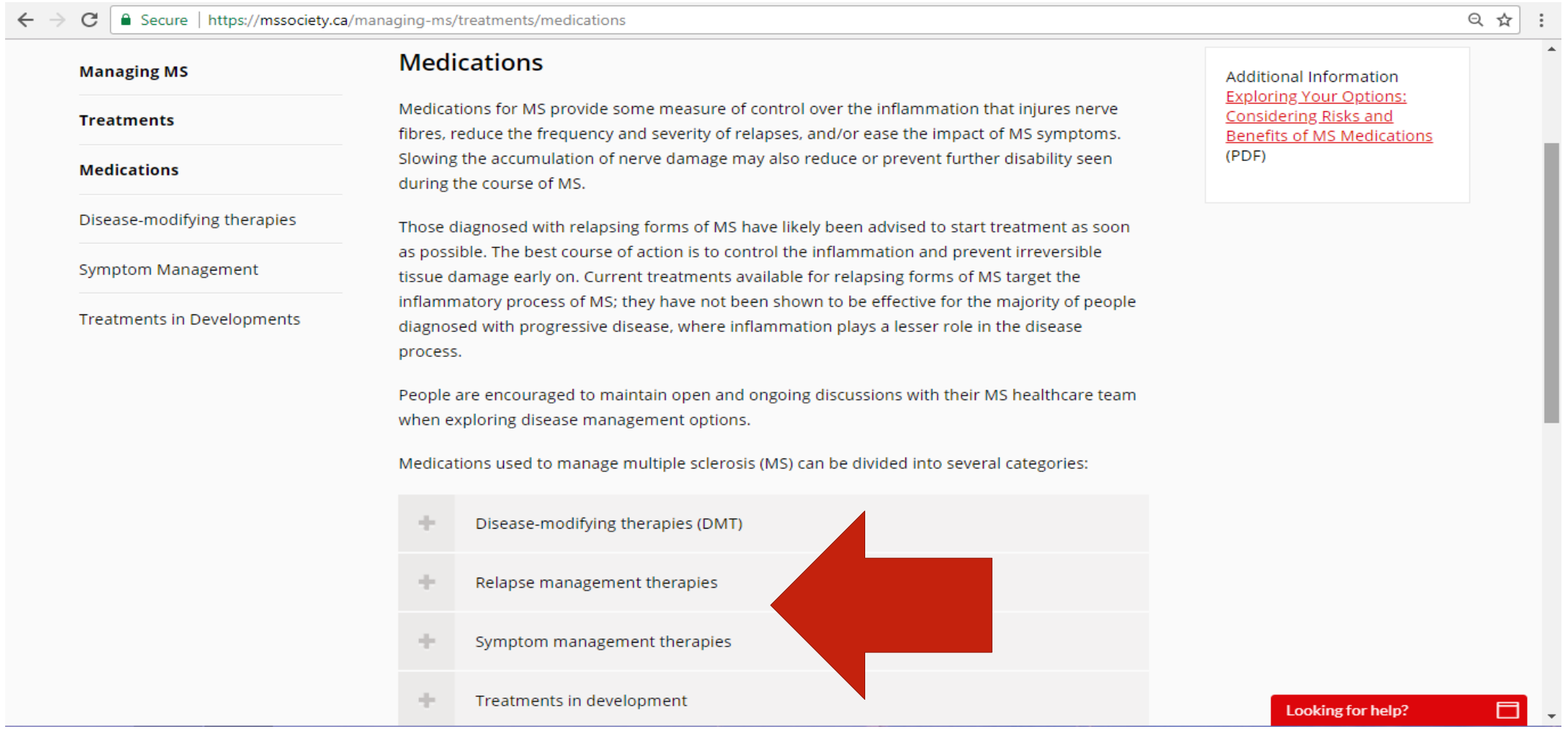


www.mssociety.ca

MED INFO


Secure | https://mssociety.ca/managing-ms/treatments
Managing MS
Treatments
Medications
Complementary and Alternative Medications & Treatments
Experimental Treatments & Treatments in Development
Wellness & Lifestyle
Rehabilitation
Participating in Clinical Trials & Other MS-related Research
Accessing Treatments Outside of Canada
Canadian Treatments and Non-Canadian Residents
Treatments
Treatments used to manage multiple sclerosis (MS) can be divided into several categories and can affect the disease course and/or the symptoms related to the disease.
People are encouraged to maintain open and ongoing discussions with their MS healthcare team when exploring disease management options. Find an MS clinic nearest to you.
Looking for help?

MED INFO


Secure | https://mssociety.ca/managing-ms/treatments/medications
Managing MS
Treatments
Medications
Disease-modifying therapies
Symptom Management
Treatments in Developments
Medications
Medications for MS provide some measure of control over the inflammation that injures nerve fibres, reduce the frequency and severity of relapses, and/or ease the impact of MS symptoms. Slowing the accumulation of nerve damage may also reduce or prevent further disability seen during the course of MS.
Those diagnosed with relapsing forms of MS have likely been advised to start treatment as soon as possible. The best course of action is to control the inflammation and prevent irreversible tissue damage early on. Current treatments available for relapsing forms of MS target the inflammatory process of MS; they have not been shown to be effective for the majority of people diagnosed with progressive disease, where inflammation plays a lesser role in the disease process.
People are encouraged to maintain open and ongoing discussions with their MS healthcare team when exploring disease management options.
Medications used to manage multiple sclerosis (MS) can be divided into several categories:
Disease-modifying therapies (DMT)
Relapse management therapies
Symptom management therapies
Treatments in development
Additional Information
Exploring Your Options: Considering Risks and Benefits of MS Medications (PDF)
Looking for help?

LOOKING FORWARD…

Clinical trials query results

From Health Canada

New search

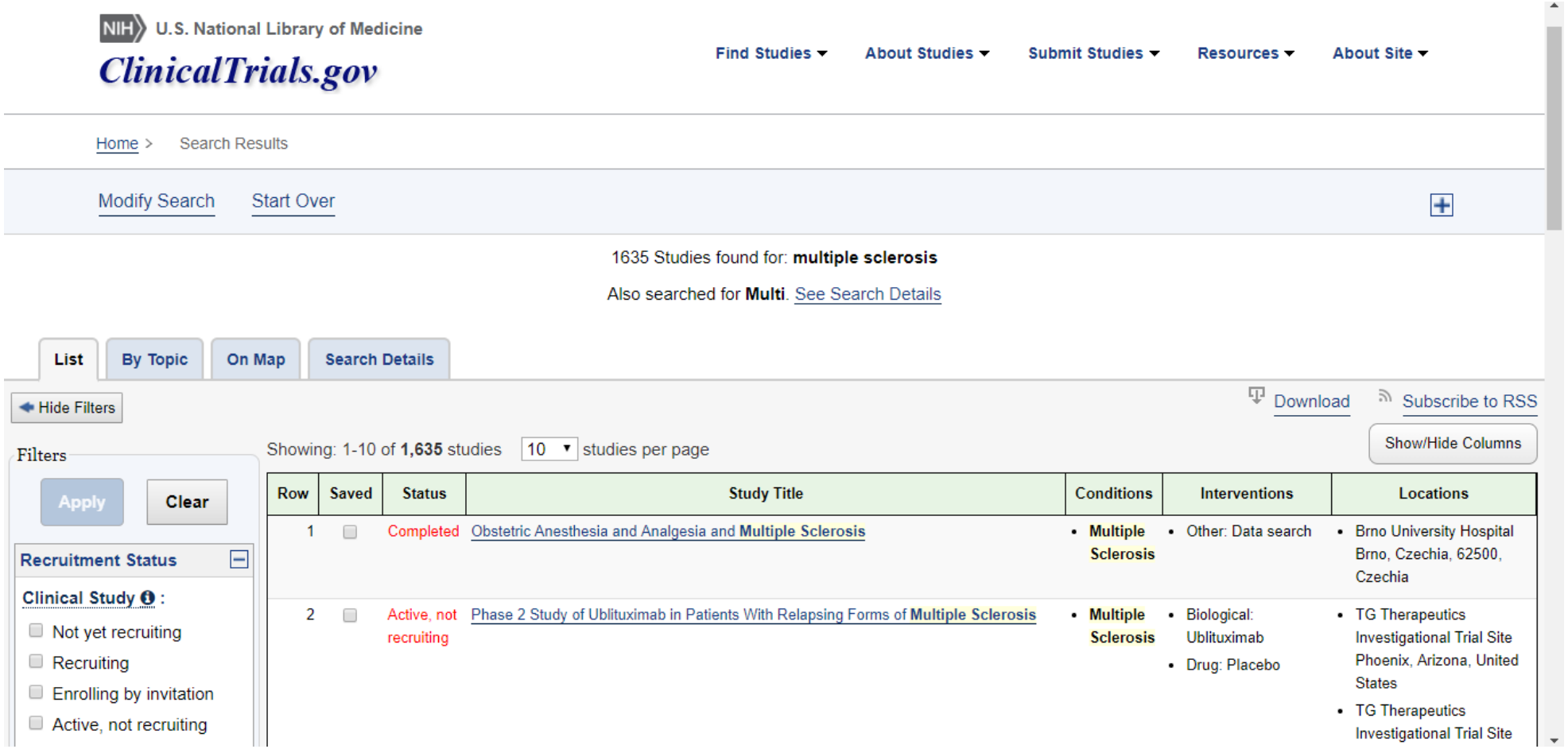
Filter items | Showing 1 to 10 of 36 entries | Show 10 entries

Clinical trials query results.

Drug name	CTA protocol title	Medical condition	Study population	Trial status
AIN457	A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO-CONTROLLED, ADAPTIVE DOSE-RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AIN457 (SECUKINUMAB) IN PATIENTS WITH RELAPSING MULTIPLE SCLEROSIS.	MULTIPLE SCLEROSIS	ADULT FEMALE, ADULT MALE	PENDING
ALKS 8700	A PHASE 3 OPEN LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ALKS 8700 IN ADULTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS	RELAPSING-REMITTING MULTIPLE SCLEROSIS	ADULT FEMALE, ADULT MALE	ONGOING
AMPHETAMINE-DEXTROAMPHETAMINE	A DOUBLE-BLIND PLACEBO CONTROLLED STUDY OF MIXED-AMPHETAMINE SALTS, EXTENDED RELEASE (ADDERALL XR) FOR COGNITIVE IMPAIRMENT IN MS	MULTIPLE SCLEROSIS	ADULT FEMALE, ADULT MALE	ONGOING

Health Canada Clinical Trials Database

LOOKING FORWARD…



ClinicalTrials.gov

LOOKING FORWARD…

World Health Organization

International Clinical Trials Registry Platform
Search Portal

Home | Advanced Search | List By | Search Tips | UTN | ICTRP website | Contact us

Back to Search | Export to CSV | Export results to XML

3857 records for 2314 trials found for: multiple sclerosis (What is this?)

Show 10 records per page

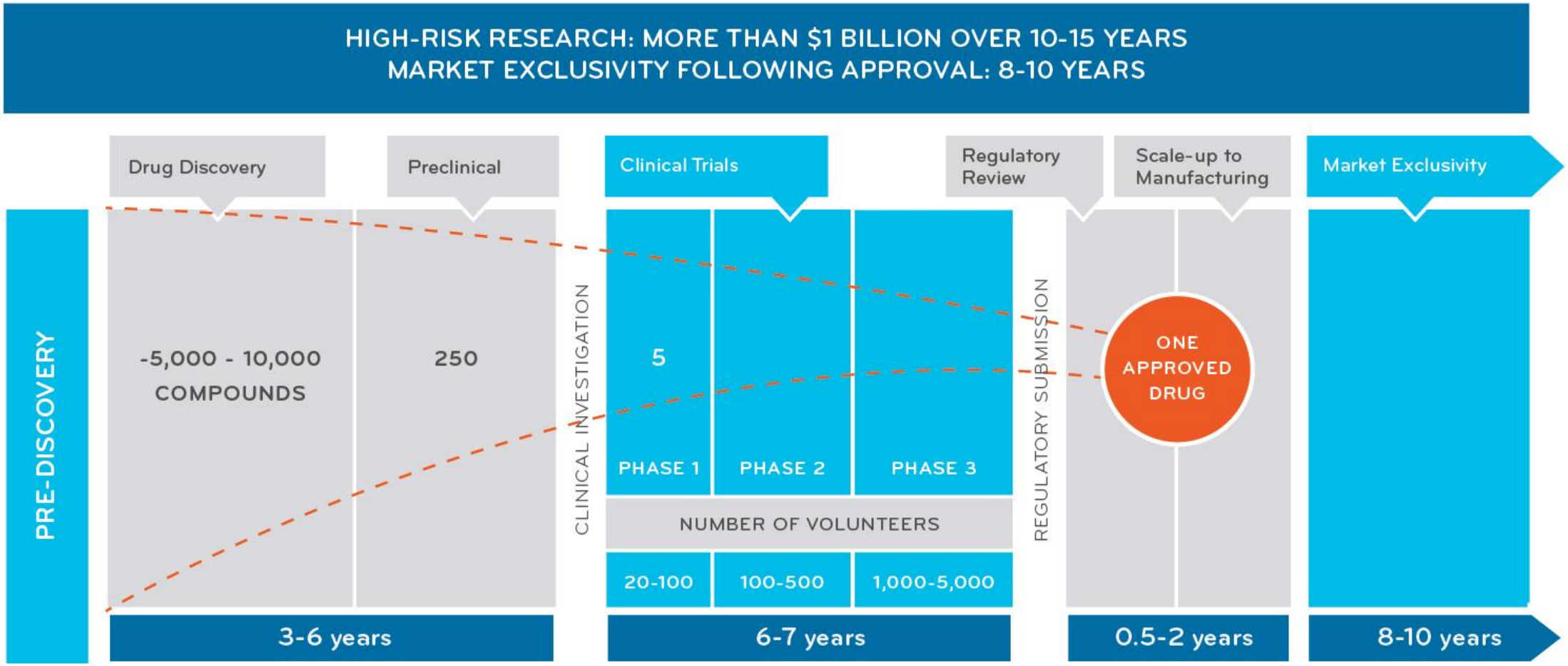
1 2 3 4 5 6 7 8 9 10 ... >>

Recruitment status	Prospective Registration	Main ID	Public Title	Date of Registration	Results available
Not Recruiting	Yes	IRCT20120227009157N7	Effect of nano formulation of saffron crocin in patients with multiple sclerosis	2018-02-16	Yes
Recruiting	No	IRCT20170128032241N2	Effect of oral curcuden on multiple sclerosis patients	2018-02-16	Yes
Recruiting	Yes	IRCT20170404033212N2	Effect of Spirituality Education Program on Depression and Anxiety	2018-02-16	Yes
Recruiting	Yes	ISRCTN17924218	Validating a self-adminstered, language-independent iPad-based test for assessment and monitoring of cognitive impairment in patients with multiple sclerosis (MS)	16/02/2018	Yes
Not recruiting	Yes	NCT03436199	Safety and Efficacy of ADS-5102 in Multiple Sclerosis Patients With Walking Impairment	12/02/2018	
Authorised	No	EUCTR2016-001515-20-IT	nd	07/02/2018	
Recruiting	Yes	NCT03429062	Comparison of Two Community Based Exercise Protocols in People With Multiple Sclerosis	05/02/2018	
Not recruiting	No	NCT03434873	Effect of Motor Cortex Versus Sacral Magnetic Stimulation in Multiple Sclerosis Patients With Urinary Tract Dysfunction	02/02/2018	
Not recruiting	Yes	NCT03438357	Evaluation of an Automatic Segmentation Software (Pixyl.Neuro) to Track Lesions in Multiple Sclerosis Patients Via Cerebral MRI	02/02/2018	
Not recruiting	Yes	NCT03444454	Telerehabilitation in Multiple Sclerosis	02/02/2018	

1 2 3 4 5 6 7 8 9 10 ... >>

WHO ICTRP Search Portal

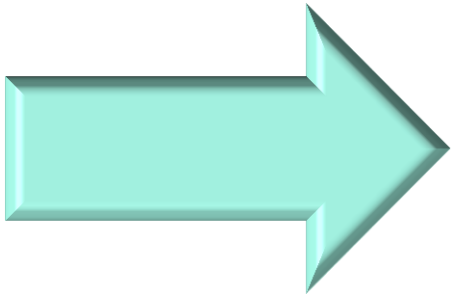
DRUG DISCOVERY TIMELINE



www.innovativemedicines.ca

Ref 1-4

‘FROM MOLECULE TO MEDICINE’



Roche Drug Development Video

BIOLOGIC VS CHEMICAL DRUGS

BIOLOGIC DRUGS (Avonex, Betaseron, Extavia, Lemtrada, Ocrevus, Plegridy, Rebif, Tysabri, Zinbryta)	CHEMICAL DRUGS (Aubagio, Copaxone, Gilenya, Glatect, Mavenclad, Tecfidera)
Manufactured using biological or "living" source and often employing recombinant DNA technology	Manufactured by combining specific organic and/or inorganic ingredients in an ordered process
Recombinant proteins (i.e. hormones, growth factors, enzymes), antibodies, interferons, vaccines, blood products, gene therapies, tissues, stem cells, allergenics	Tablets, capsules, suspensions, solutions, certain injectable products, patches
Large, complex molecules, difficult to characterize using current analytics due to size and variable numbers of components within them	Small-molecule drugs, easier to characterize using current analytics (more uniform and pure)
Costly production process that tends to yield small quantities and requires many testing steps (>25)	Well-defined, cheaper production process that allows for large quantities and requires fewer testing steps (~50)
Very sensitive to changes in manufacturing processes, physical conditions (i.e. heat, shear forces), contamination	Less sensitive to changes in manufacturing processes, physical conditions, and microbial contamination
More likely to induce immune reaction (immune system may consider large molecules to be foreign substances)	Less likely to induce immune reaction due to small size
Often cannot administer orally as they would be destroyed by factors within the stomach (acid, enzymes)	Less susceptible to factors within the stomach so oral administration is an option
Comprise ~10% of drugs on the market today	Comprise ~90% of drugs on the market today

Ref 5-8

BIOLOGIC VS CHEMICAL DRUGS

- Biologics are difficult to characterize so their manufacturing process must remain essentially unchanged over time to ensure consistency, quality, and purity
- The living systems used to produce biologics can be sensitive to even minor changes in the manufacturing process
  - The slightest change in manufacturing can impact the nature of the finished biologic and ultimately, its function in the body
- Changes in processes are less of a concern for chemical drugs as the final product can be extensively analyzed for purity, concentration, and batch-to-batch consistency

Ref 5-8

BIOSIMILARS

- A biosimilar “behaves in a similar way” to a reference biologic drug
  - Previously known as “subsequent entry biologics” in Canada
- Generally made by different manufacturers once the patent for the reference biologic expires
  - Approved based on a thorough comparison to the reference drug which must include clinical data showing that the biosimilar has the same mechanism, efficacy, safety, potency, and purity as the reference drug
  - There must be “no clinically meaningful differences” between the biosimilar and the reference drug
    - This includes no difference in immunogenicity
    - Minor differences in clinically inactive components are allowed

Ref 9-11

BIOSIMILARS VS GENERICS

- Biosimilars are sometimes mistakenly called “generic” versions of biologics
- Generic products have an identical chemical makeup to their brand name counterparts
- Since biologic drugs are uniquely derived from living systems which are prone to natural variability from cell to cell, and taking into account the complexity of biologic development, biosimilars cannot be identical to their reference biologics
  - They can be shown to be similar, but cannot be exact copies of each other
  - Because of this, they cannot accurately be shown to be pharmaceutically or therapeutically equivalent, and thus are not interchangeable with one another

Ref 9-11

MAKING HEADLINES: OCREVUS® (OCRELIZUMAB)

- On February 15, Hoffman-La Roche announced Health Canada's approval of ocrelizumab (Ocrevus®), the first disease-modifying therapy to be approved in Canada for primary progressive MS
  - Also approved for relapsing forms of MS
  - Ocrelizumab binds to a molecule (CD20) on the surface of B cells, inducing their lysis and causing a depletion of them from the circulation
    - By selectively targeting CD20 B cells, it may preserve B cell reconstitution (by not affecting stem cells) and long-term immune memory (by not affecting plasma cells)
- ORATORIO trial studied 732 participants with PPMS
  - Treatment with ocrelizumab significantly reduced the proportion of individuals that experienced disability progression at 12 weeks compared to placebo (32.9% vs 39.3% respectively, as measured by the Expanded Disability Status Scale (EDSS))
  - Reduction was sustained at 24 weeks (29.6% vs 35.7%, respectively)

Ref 12-16

MAKING HEADLINES: OCREVUS® (OCRELIZUMAB)

- At 120 weeks, 38.9% of individuals on ocrelizumab vs 55.1% on placebo had declined on the time required to walk 25 feet
- Ocrelizumab also significantly decreased the volume of brain lesions on MRI by 3.4% (increased 7.4% in placebo group), and significantly reduced the percentage of volume loss in the brain (0.90% vs 1.09% with placebo)
- The most common adverse events associated with ocrelizumab were mild-moderate infusion-related reactions (39.9% vs 25.5% with placebo)
  - No clinically significant differences in rates of serious adverse events/infections
  - There were 2 malignancies in the placebo group, and 11 in the ocrelizumab group
    - 4/11 in the ocrelizumab group were breast cancers; further safety analyses are ongoing
- The Canadian Drug Expert Committee had a meeting on March 21, 2018
  - The Committee recommends that ocrelizumab be reimbursed for the management of adult patients with early PPMS, pending certain criteria and conditions are met

Ref 12-16

FUTURE PROSPECTS FROM /GENENTECH

- More data on ocrelizumab to come
  - Efficacy for improving upper body function/cognition
  - Use of ocrelizumab in patients between 55-65 years of age and patients with EDSS score between 6.5-8.0
  - Long-term efficacy/safety results
  - Potential of ocrelizumab in other neurological diseases
- Studies on neuroregeneration
- 'Brain shuttle' to improve drug delivery to the brain → **Roche Brain Shuttle Video**
- "FLOODLIGHT" app → uses smartphone sensors to monitor MS patients and employs active and passive measures

Ref 17

MAKING AN EXIT: ZINBRYTA® (DACLIZUMAB)

- Antibody that targeted CD25, a subunit of the interleukin-2 receptor on T cells (prevented activation and caused a net reduction in T cell responses)
- Voluntarily withdrawn by Biogen and Abbvie in March 2018 due to increasing safety concerns
  - Severe liver damage
  - Reports of encephalitis (inflammation of the brain) in patients in Europe
- Over 8,000 patients had been treated with Zinbryta® worldwide
  - Patients stopping treatment are to be monitored with regular blood tests (at least monthly) and more frequently as indicated up to 6 months after their last dose
  - Patients who were doing well on the drug would still have to stop treatment and potentially start an alternate agent, upon discussion with their doctor

Ref 18, 19

HEALTH CANADA ADVERSE REACTION REPORTING

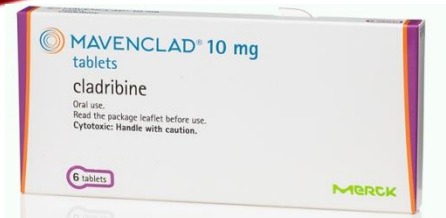
- Patients, caregivers, health care providers, and the general public can voluntarily report adverse reactions to medications (prescription/non-prescription), biologics, natural health products, etc. to the Canada Vigilance Program
  - Reports can be done online, by phone, or submitting a form via fax or mail
  - Health Canada wants to know about all suspected adverse reactions, but especially if they are unexpected (regardless of severity), serious, or related to a product that has been on the market for less than 5 years
- It is mandatory for manufacturers and distributors to have a system for monitoring side effects, submit adverse reaction reports to Health Canada, and notify Health Canada about studies with new safety information
- There is also an online searchable database that contains information about reported adverse reactions

Ref 20-23

FUTURE PROSPECTS FROM Biogen

- New and improved version of Tecfidera® (dimethyl fumarate)
  - "ALKS 8700" is a monomethyl fumarate (MMF) prodrug
    - Designed to provide an improved side effect profile, namely ↓ gastrointestinal (GI) side effects
    - Tecfidera®: diarrhea (13.9%), nausea (12.1%), abdominal pain (9.5%), vomiting (8.5%)
    - Safety data from the first month of EVOLVE-MS-1 are promising – ALKS 8700 had low rates of adverse GI events leading to discontinuation (0.5%); incidence of diarrhea also reduced – 6.6%
  - For relapsing forms of MS; currently in phase 3 trials
- A re-myelinating antibody
  - Opicinumab is an antibody against LINGO-1, a CNS-specific protein that suppresses myelination and axonal regeneration by preventing the development of young cells into oligodendrocytes
    - By blocking LINGO-1, opicinumab can potentially promote re-myelination, restoration of nerve communication, and ultimately the prevention or reversal of disability
  - For relapsing forms of MS; currently in phase 2 trials

Ref 24-29



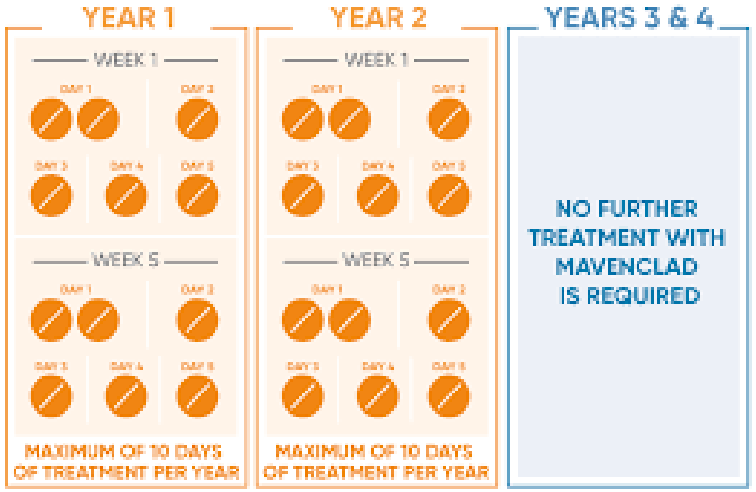
MAVENCLAD ® (CLADRIBINE)

- Indicated as monotherapy for adults with RRMS, in patients who have had an inadequate response to, or are unable to tolerate, 1 or more therapies for MS
- Interferes with normal production of DNA in B cells, leading to cell death
  - Activated only by lymphocytes so very little non-target cell damage
- Rejected for FDA approval in the 90s on the grounds that more data was needed
- Rejected by EMA in 2010 due to concerns of cancer cases arising in CLARITY trial
- Studied in 5 clinical trials – significantly reduced disability progression, annualized relapse rates, and brain atrophy
- Meta-analysis showed risk of cancer is not increased vs that seen with other DMTs
  - Cannot rule out risk entirely – need long-term follow-up
- Most common adverse effect = lymphopenia = more prone to infections, i.e. shingles

Ref 30-34

MAVENCLAD ® (CLADRIBINE)

- Recommended dose is 3.5mg/kg body weight over 2 years, administered as 1 treatment course of 1.75mg/kg per year (2 courses total)
- Treatment beyond 2 years has not been established
  - Continuing treatment for a 3rd or 4th year offers no additional benefit
- Long-term inhibition of lymphocytes with effect persisting months after drug is cleared from the body
  - Resistance to degradation
  - Effects on resting and proliferating cells
  - Effects on memory B cells
  - Cells unable to repair damage done



Illustrative example based on the average patient weight in the CLARITY study (67kg)
Re-initiation of therapy after Year 4 has not been studied

Ref 30-34

DRUG SUPPORT PROGRAMS

ATYPICAL THERAPIES - MINOCYCLINE

- Antibiotic most commonly used for moderate to severe acne and rosacea
- Antibacterial effects: binds to a specific genetic machine (ribosome) within bacteria and prevents protein synthesis, thereby killing the bacteria
- Also has anti-inflammatory effects: not fully understood in MS but believed to suppress the activity of pro-inflammatory cells/molecules, and prevent the migration of disease-causing T cells into the CNS by interfering with certain compounds that disrupt the blood-brain barrier
- Also thought to have neuroprotective benefits in MS including inhibiting the death of myelin-producing cells, reducing damage to nerve fibers through antioxidant activity, and protecting against excitotoxicity (overstimulation of nerve fibers)

Ref 35-39

ATYPICAL THERAPIES - MINOCYCLINE

- When given to mice with both mild and severe forms of MS-like disease, symptom severity was significantly reduced and symptom onset was delayed
- 2008 Dr. Metz clinical trial:
  - 142 participants at 12 Canadian MS clinics
  - Minocycline 100mg twice daily vs placebo
  - Studied reduction in proportion of participants with CIS who converted to MS at 6 mos.
- 61% of placebo-treated participants converted to MS at 6 mos. vs 33.4% of minocycline-treated participants (27.6% reduction, significant)
  - Maintained at 12 mos. but not enough participants for conclusive results at 24 mos.

Ref 35-39

ATYPICAL THERAPIES - MINOCYCLINE

- Most common side effects: diarrhea, dizziness, ataxia (latter = gait abnormalities, difficulty walking, poor balance/coordination, changes in fine motor skills)
- Less common side effects: bluish-grey discoloration of skin, nails, teeth, tissue ("black thyroid") – more so with long-term use
  - Linked to cases of lupus and auto-immune hepatitis – recovery is possible if minocycline is stopped
- Resistance likely not significant but still possible – may affect susceptibility to other drugs in the class
  - Can also pass on resistance to other bacteria besides acne-causing bacteria
- Costs ~20 cents per 100mg capsule

Ref 35-39

MEDICAL CANNABIS

- Two (most common) cannabis varieties – sativa and indica
  - Many different strains with different concentrations of two active chemicals known as cannabinoids – THC (tetrahydrocannabinol-commonly known to cause the "high" effects) and CBD (cannabidiol-minimizes the "high" from THC)
- Evidence base for cannabis is weak – objective measures often fail to demonstrate a benefit, but patient self-report or subjective measures suggest a benefit
  - Cannabis "probably" has a benefit i.e. for spasticity and pain associated with MS
- Difficult to conduct good quality studies – many strains of cannabis, many ways to use it, very patient-specific effects
  - Difficult to disguise cannabis i.e. in placebo-controlled trial, because smell, taste, and side effects are challenging to mask
- Typical use is ~1 gram/day with varying percentages of THC and CBD recommended
  - "Start low, go slow"
- Cost? ~$5-$15/gram (average user spends ~$30-$150/week)

Ref 40-44

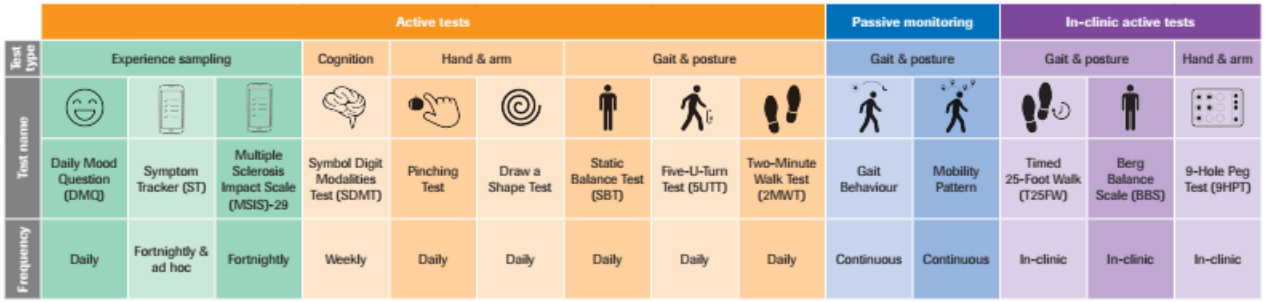
MEDICAL CANNABIS

- Available as edible products or oils, sublingual tinctures, or it may be vaporized or dried for smoking/inhalation (among other formulations/methods)
  - Edible products = delayed onset, long-lasting, more discreet use
  - Inhalation = quick onset of effect, shorter-acting, may cause bronchial irritation/cough
  - Sativex® is an oral spray approved for spasticity and neuropathic pain associated with MS and cancer – usual dose is 4-8 sprays per day
  - Cesamet® is synthetic THC indicated for nausea/vomiting associated with chemotherapy – 1-2mg 2-3 times per day
- Range of adverse effects associated with cannabis that depend on the product (%THC vs %CBD, amount used, method of use, etc.) and the user (cannabis-aware vs naïve, sensitivity, tolerance, other medications/medical conditions)
  - Dizziness, drowsiness, headache are most common, plus cognitive impairment
  - Reported that 1 in every 11 users (9%) become dependent

Ref 40-44

PATIENT ADVOCACY

- Keep an organized, updated record of your medical history
  - Current medications, past medications (include dates when meds were changed, reason why they were stopped), detailed allergies, blood test results, imaging, surgeries, hospital admissions with notes about the admission, health/drug insurance information, drug support enrolment information, names/numbers of other professionals involved in your care (i.e. physiotherapist, occupational therapist, social worker, psychologist)
  - Make brief notes after all your appointments – what was talked about, changes made, plans for next visit, etc.
- Monitor your symptoms/progression
  - You know your body better than your doctor does
  - Online sheets, "Floodlight" (at right)
  - Keep track and tell your doctor



Symptom trackers: https://www.msonetoone.com/ms-symptom-tracker
https://www.msonetoone.com/doctor-discussion-guide

Ref 45

PATIENT ADVOCACY

- Be informed and use reputable sources
  - Do a little research of your own
  - MS Society, National MS Society, MS Trust, Medscape, Mayo Clinic, NHS, MS News Today, etc., even Wikipedia or drug company websites
- Write your questions down
  - Limited appointment time with doctor/neurologist but there should be a balance between their checklist and yours
  - No question is a stupid question
- Speak up
  - Don’t be afraid to state what is bothering you, and don’t ever think that you are a bother to your doctor
  - Speaking up and stating your concerns helps you be your own advocate

ROLE OF THE PHARMACIST IN MS MANAGEMENT

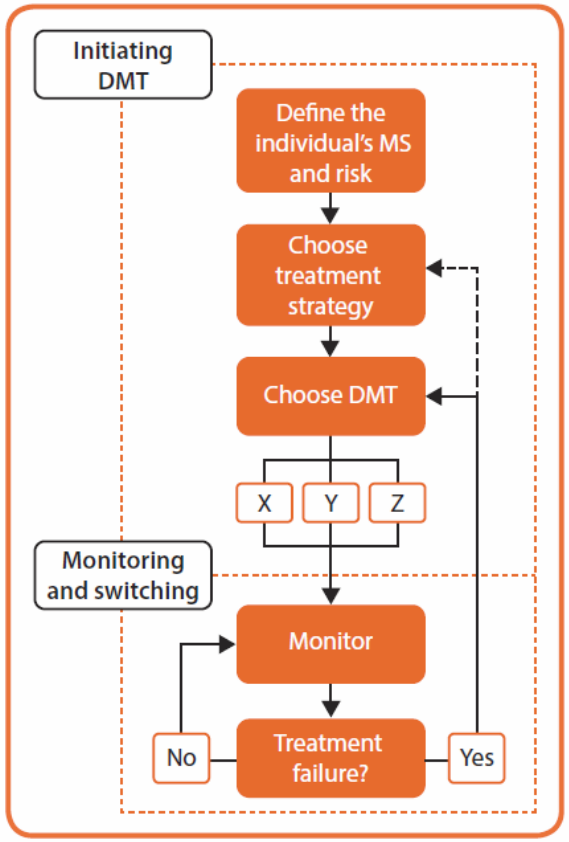
- Assist with choosing an appropriate disease-modifying therapy based on a patient's diagnosis, symptoms, goals for the therapy, other medical conditions and medications, side effect tolerance, and ability to take/use the medication
- Advise on side effect management including finding alternate therapies, modifying the dose/schedule of a therapy, suggesting non-drug measures, or adding on another medication to counteract the side effect
- Determine appropriate medications for symptom management including treatments for pain, spasticity, depression, anxiety, insomnia, etc.
- Monitor patients for progress on their therapy and changes in their condition
- Assess for drug interactions and advise on their management
- Help coordinate drug coverage or enrolment in drug support programs
- Be an advocate for patients and support them to advocate for themselves

PATIENT CASE

Ms. G is a 27-year-old female who presented to her neurologist appointment for evaluation of her neurological symptoms. For the past 3 years, she has noticed a persistent stumbling gait and tendency to fall, along with periodic changes in her visual acuity and feeling exhausted much earlier in the day than usual. Over Christmas, she realized she was having a hard time holding objects in her hands and she developed bilateral tingling in her feet over the past 2 months. Upon further work-up and investigation, the neurologist diagnosed her with MS.

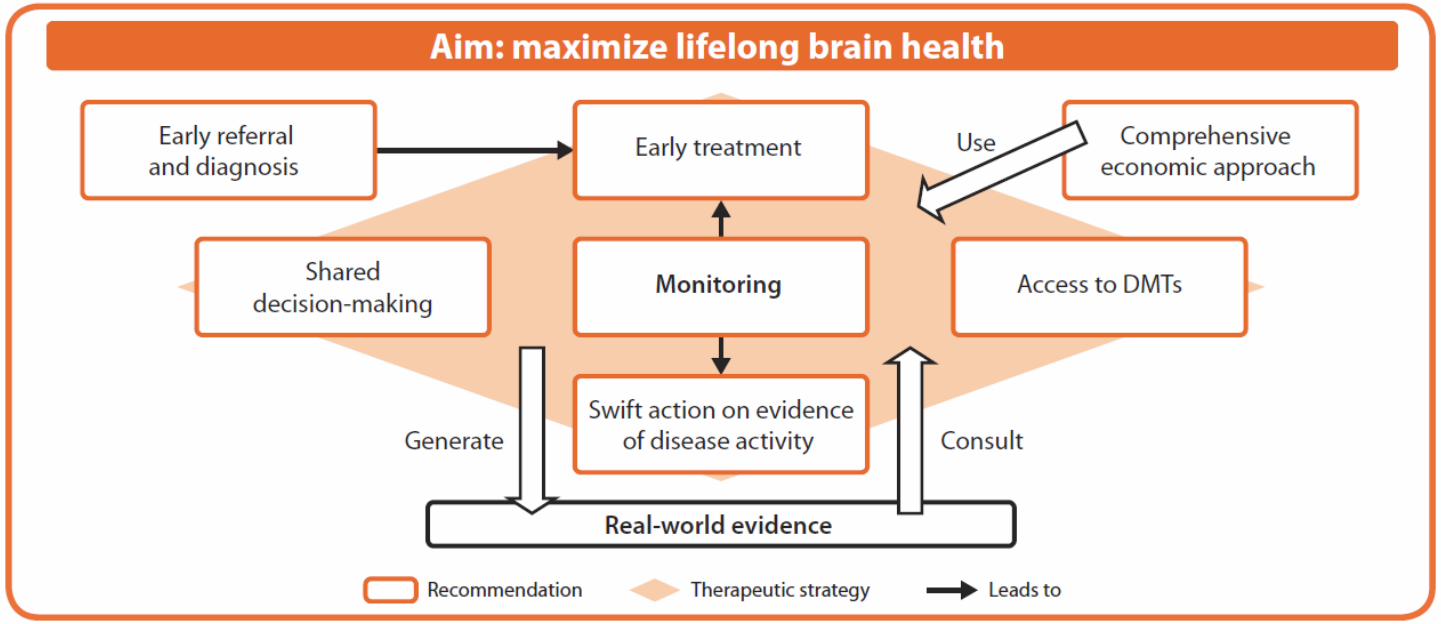
THE RIGHT IDEA

Monitoring is crucial to identifying treatment failure and enabling timely switching to a different DMT



X, Y and Z represent DMT options. DMT, disease-modifying therapy

Therapeutic strategy recommended in the report



We recommend a therapeutic strategy based on regular monitoring that aims to maximize lifelong brain health while generating robust real-world evidence.

DMTs, disease-modifying therapies.

www.msbrainhealth.org

TO TREAT, OR NOT TO TREAT

- Treat early?
- What do we treat with first?
- What if our first treatment choice does not achieve agreed upon goals?
- What is ‘treatment optimization’?
- At what point should treatment be stopped, if ever?
- What else can or should be done for patients?

Ref 46-49

THANK YOU!

For taking the time out of your day to listen to my presentation

Special Acknowledgements:

☆ *Karen Turpin (Medical Science Liaison for Hoffman-La Roche)*

☆ *Rick Bourque (Medical Science Liaison for Biogen)*

QUESTIONS?

REFERENCES

1. U.S. Food & Drug Administration. Updated 04 Jan 2018. *The Drug Development Process*. Retrieved from: https://www.fda.gov/ForPatients/Approvals/Drugs/default.htm
2. Pacific BioLabs. n.d. *Stages of Drug Development*. Retrieved from: http://www.pacificbiolabs.com/drug_stages.asp
3. Hoffman-La Roche. n.d. *From molecule to medicine*. Retrieved from: https://www.roche.com/research_and_development/who_we_are_how_we_work/research_process/value_chain/value_chain-1.htm
4. Novartis. "Drug discovery and development process". Online video clip. YouTube. YouTube, 14 Jan 2011. Web. 23 Apr 2018.
5. U.S. Food & Drug Administration. Updated 06 Feb 2018. *What Are "Biologics" Questions and Answers*. Retrieved from: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm
6. Biotechnology Innovation Organization. n.d. *How do Drugs and Biologics Differ?* Retrieved from: https://www.bio.org/articles/how-do-drugs-and-biologics-differ
7. Bayer. n.d. *Small and large molecules*. Retrieved from: http://pharma.bayer.com/en/innovation-partnering/technologies-and-trends/small-and-large-molecules/
8. Innovative Medicines. n.d. *Specialty Medicines*. Retrieved from: http://innovativemedicines.ca/medicines/personalized-medicine-2/
9. Health Canada. Updated 03 Aug 2017. *Fact Sheet: Biosimilars*. Retrieved from: https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html
10. Innovative Medicines. n.d. *Specialty Medicines*. Retrieved from: http://innovativemedicines.ca/medicines/personalized-medicine-2/
11. Wells, KA. Winter/Spring 2014. *Biosimilars: Approval on the Horizon*. Multiple Sclerosis Association of America. Retrieved from: https://mymsaa.org/publications/motivator/winter-spring14/feature-story/
12. Nather D. 19 Feb 2016. *New drug for severe form of MS generates glimmer of hope - and tempered expectations*. STAT News. Retrieved from: https://www.statnews.com/2016/02/19/progressive-multiple-sclerosis-ocrelizumab/
13. National Multiple Sclerosis Society. Updated 9 Mar 2016. *More results released from positive phase III clinical trial of ocrelizumab in primary progressive MS*. Retrieved from: https://www.nationalmssociety.org/About-the-Society/News/More-Results-Released-from-Positive-Phase-III-Clin
14. Multiple Sclerosis Society of Canada. n.d. *Ocrelizumab*. Retrieved from: https://mssociety.ca/research-news/treatments-in-development/ocrelizumab2?_ga=2.128837324.1304022610.1521907410-318571330.1521497074
15. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, *et al*. 19 Jan 2017. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *New England Journal of Medicine*, 376:209-220.
16. Canadian Agency for Drugs and Technologies in Health (CADTH). Updated 9 May 2018. *Ocrelizumab*. Retrieved from: https://www.cadth.ca/ocrelizumab-0
17. Taylor P. 3 Nov 2017. *Smartphone monitoring shows its worth in Roche MS trial*. PMLiVE. Retrieved from: http://www.pmlive.com/pharma_news/smartphone_monitoring_shows_its_worth_in_roche_ms_trial_1210454
18. Brooks M. 02 Mar 2018. *MS Drug Daclizumab (Zinbryta) Pulled From the Market*. Medscape. Retrieved from: https://www.medscape.com/viewarticle/893352

REFERENCES

19. European Medicines Agency (EMA). 07 Mar 2018. *EMA recommends immediate suspension and recall of multiple sclerosis medicine Zinbryta.* [Press release]. Retrieved from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/03/news_detail_002920.jsp&mid=WC0b01ac058004d5c1
20. Health Canada. Updated 04 Mar 2010. *Adverse Reaction Reporting Information*. Retrieved from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/adverse-reaction-reporting-adverse-reaction-reporting-information.html
21. Health Canada. Updated 10 Oct 2017. *Adverse Reaction and Medical Device Problem Reporting*. Retrieved from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html
22. Health Canada. Updated 23 Apr 2018. *Canada Vigilance adverse reaction online database.* Retrieved from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html
23. Hoffman-La Roche. n.d. *Patient safety.* Retrieved from: https://www.roche.com/sustainability/what_we_do/for_patients/patient_safety.htm?tab_id=tab2
24. BusinessWire. 27 Oct 2017. *Alkermes Presents Data Demonstrating Safety and Gastrointestinal Tolerability Profile of ALKS 8700 for the Treatment of Multiple Sclerosis.* Retrieved from: https://www.businesswire.com/news/home/20171027005055/en/Alkermes-Presents-Data-Demonstrating-Safety-Gastrointestinal-Tolerability
25. Naismith R, Leigh-Pemberton R, Claxton A, Du Y, Hard M, von Moltke L, & Wolinsky J. 17 Apr 2017. EVOLVE-MS-1: Phase 3 Open-Label Long-Term Safety Study of ALKS 8700 in Relapsing-Remitting Multiple Sclerosis. *Neurology*, 88 (16 Supplement).
26. Naismith R. EVOLVE-MS-2: A randomized double-blind, phase 3 study of the gastrointestinal tolerability of ALKS 8700 versus dimethyl fumarate in replasing-remitting multiple sclerosis. ECTRIMS Online Library. Retrieved from: https://onlinelibrary.ectrims-congress.eu/ectrims/2017/ACTRIMS-ECTRIMS2017/200363/robert.t.naismith.evolve-ms-2.a.randomized.double-blind.phase.3.study.of.the.html
27. Kegel M. 02 May 2017. *Remyelination Candidate Opicinumab Failed in Phase 2 Trial in MS, But Biogen Won't Give Up.* Multiple Sclerosis News Today. Retrieved from: https://multiplesclerosisnewstoday.com/2017/05/02/ms-remyelination-therapy-opicinumab-fails-phase2-trial-biogen-wont-give-up/
28. Silva P. 25 Oct 2017. *#MSParis2017 - New Trial of Opicinumab, an Anti-LINGO Antibody, in MS Builds on Lessons Learned, Biogen Says.* Multiple Sclerosis News Today. Retrieved from: https://multiplesclerosisnewstoday.com/2017/10/25/msparis2017-interview-with-biogen-focused-on-opicinumab-an-anti-lingo-antibody/
29. Multiple Sclerosis Trust. Nov 2017. *Opicinumab (anti-LINGO-1).* Retrieved from: https://www.mstrust.org.uk/a-z/opicinumab-anti-lingo-1-biib033
30. Multiple Sclerosis Society of Canada. n.d. *Cladribine*. Retrieved from: https://mssociety.ca/research-news/treatments-in-development/cladribine
31. Multiple Sclerosis Society of Canada. 7 Dec 2017. *Health Canada approves oral Mavenclad for the management of relapsing-remitting MS.* Retrieved from: https://mssociety.ca/research-news/article/health-canada-approves-oral-mavenclad-for-the-management-of-relapsing-remitting-ms
32. Melão A. 6 Dec 2017. *Health Canada Approves Merck's Mavenclad to Treat RRMS. Multiple Sclerosis News Today*. Retrieved from: https://multiplesclerosisnewstoday.com/2017/12/06/health-canada-approves-mavenclad-to-treat-rrms-patients-merck-announces/
33. Holmøy T, Torkildsen Ø, & Myhr KM. 2017. An update on cladribine for relapsing-remitting multiple sclerosis. *Expert Opinion on Pharmacotherapy*, 18(15):1627-1635.
34. Wikipedia. 23 Jan 2018. *Cladribine*. Retrieved from: https://en.wikipedia.org/wiki/Cladribine

REFERENCES

35. Multiple Sclerosis Society of Canada. Updated May 2017. *Minocycline Fact Sheet.* Retrieved from:https://mssociety.ca/research-news/treatments-in-development/minocycline
36. Multiple Sclerosis Society of Canada. Updated May 2017. *Minocycline for Clinically Isolated Syndrome (CIS) FAQ*. Retrieved from: https://mssociety.ca/research-news/treatments-in-development/minocycline
37. Metz LM, Li DKB, Traboulsee AL, Duquette P, Eliasziw M, Cerchiaro G, *et al*. 01 Jun 2017. Trial of Minocycline in a Clinically Isolated Syndrome of Multiple Sclerosis. *New England Journal of Medicine*, 376:2122-2133.
38. Tobias E. 06 Jun 2017. *Jumping to Conclusions About a MS Treatment.* Multiple Sclerosis News Today. Retrieved from: https://multiplesclerosisnewstoday.com/2017/06/06/jumping-conclusion-acne-med-ms-treatment/
39. Wikipedia. 11 May 2018. *Minocycline*. Retrieved from: https://en.wikipedia.org/wiki/Minocycline
40. Americans For Safe Access. n.d. *Guide to using medical cannabis.* Retrieved from: https://www.safeaccessnow.org/using_medical_cannabis
41. Health Canada. 12 Jun 2013. *Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids.* Retrieved from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-use-marijuana/information-medical-practitioners/information-health-care-professionals-cannabis-marihuana-marijuana-cannabinoids.html#chp441
42. Cameron M, Rice J. n.d. *Cannabis for Multiple Sclerosis Symptoms.* Retrieved from: https://www.nationalmssociety.org/Treating-MS/Complementary-Alternative-Medicines/Marijuana
43. Lee K. n.d. *Medical marijuana and MS: What does the research suggest?* [Blog post]. Retrieved from: https://drkarenlee.ca/medical-marijuana-and-ms-what-does-the-research-suggest/
44. MSology. 27 Oct 2016. *Medical marijuana - the Canadian experience*. Retrieved from: http://msology.ca/medical-marijuana-the-canadian-experience
45. Butler S. Nov 2016. *Charting key to MS patient advocacy.* MS Focus. Retrieved from: https://msfocusmagazine.org/Magazine/Magazine-Items/Charting-key-to-MS-patient-advocacy
46. Freedman MS, Selchen D, Arnold DL, Prat A, Banwell B, Yeung M, Morgenthau D, & Lapierre Y. 2013. Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations. *Canadian Journal of Neurological Sciences*, 40:307-323.
47. American Academy of Neurology. Apr 2018. *Practice Guideline Recommendations Summary: Disease-Modifying Therapies for Adults with Multiple Sclerosis.* Retrieved from: https://www.aan.com/Guidelines/home/GuidelineDetail/898
48. Multiple Sclerosis Society of Canada. 07 May 2018. AAN releases practice guideline for starting, switching, and stopping disease-modifying therapies. Retrieved from: https://mssociety.ca/research-news/article/aan-releases-practice-guideline-for-starting-switching-and-stopping-disease-modifying-therapies
49. MS Brain Health. 19 Feb 2018. *Efficacy of MS drugs is linked to age.* Retrieved from: https://www.msbrainhealth.org/treatment-decisions/article/efficacy-of-ms-drugs-is-linked-to-age

Link to Health Canada Adverse Reaction reporting form: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/consumer-side-effect-reporting-form.html
Link to Health Canada's online searchable database for reported adverse reactions: http://webprod3.hc-sc.gc.ca/arquery-rechercheei/index-eng.jsp