Treating pain in autoimmune disease: concurrent use of opioids and biologic disease modifying therapy

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Epidemiology at the Brown University School of Public Health

Providence, Rhode Island

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This dissertation by Meghan Cupp Buxton is accepted in its present form by the Department of Epidemiology as satisfying the dissertation requirement for the degree of Doctor of Philosophy.

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Education

Brown University — Providence, Rhode Island
PhD Epidemiology, School of Public Health — 2020–Current

Imperial College London — London, United Kingdom
Master of Public Health — 2016–2017

- Thesis: "Neutrophil counts and cancer prognosis: an umbrella review and meta-analysis", awarded with Distinction (equivalent to GPA - 4.00)
- Master of Public Health prize for best thesis

McGill University — Montréal, Québec
BSc Nutritional Biochemistry — 2013–2016

Pre-Doctoral Fellowships

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Project Title: Treating pain in autoimmune disease: concurrent use of opioids and biologic medication

Research Experience

Brown University — Providence, Rhode Island
Research Assistant — September 2020 - June 2023

- "Safe Cardiometabolic Drug Prescribing". Research Advisor: Dr. Andrew Zullo (September 2022 - June 2023)
- Leading analysis of Medicare data to assess concurrent use of beta blockers and acetylcholinesterase inhibitors and hazardous falls in older adults
- "Pain management in older adults following hip fracture". Research Advisors: Drs. Andrew Zullo and Francesca Beaudoin (May 2021 - August 2022)
- Leading analysis of Medicare data to assess opioid prescribing in a cohort of hip fracture survivors, including 1) the role of post-acute care in opioid prescribing, 2) the safety of concurrent tramadol and SSRI use, and 3) opioid use and the risk of re-fracture
- "Sex differences in the pharmacodynamics of dexamethasone". Research Advisor: Dr. Karl Kelsey (September 2020 - May 2021)
- Conducting analysis on epigenetic changes in steroid responsive genes to build on the current understanding of sex differences in autoimmunity

University College London — London, United Kingdom
Honorary Research Associate — July 2017 - June 2019

- "Respiratory tract infection-related healthcare utilization in children with Down's Syndrome" & "Prevalence of cancerous malignancies in children with Down's Syndrome". Research Advisors: Drs. Caoimhe McKenna, Arturo Gonzalez-Izquierdo (July 2017 - June 2019)
- Assisting in analysis for two projects utilizing national linked primary-secondary care electronic health records through the Clinical research using LInked Bespoke studies and Electronic health Records (CALIBER) platform
- "Childhood Infections and Pollution (CHIP) Study". Research Advisors: Drs. Logan Manikam, Monica Lakhanpaul, Rajesh Khanna (August 2018 - June 2019)

- Hosted by the Save the Children India Rajasthan State Office for two months of field work to assist in the design and implementation of the CHIP feasibility study in Jaipur's urban slums. Field work included several site visits for selection of study geography and piloting of a household survey to establish baseline health behavior and estimate infection prevalence. Continued involvement includes developing further grant applications as a study collaborator, preparing feasibility study findings for publication and supervision of a BSc student
- "Participatory Approach for Nutrition in Children: Strengthening Health, Education, Environment and Engineering Linkages (PANChSHEEEL)". Research Advisors: Drs. Monica Lakhanpaul, Rajesh Khanna (April 2017 - June 2019)
- Assisted in developing an integrated Health, Education and Environmental (HEE) intervention to reduce malnutrition in children under five years of age in Banswara, India. Tasks included conducting an umbrella review of interventions targeting maternal and child nutrition, the development and implementation of data collection tools for community co-design and one month of field work for intervention feasibility testing. Assumed responsibility for compiling study reports and coordinating between UK and India based teams after departure of lead study coordinator

London Borough of Newham London, United Kingdom
Public Health Strategist July 2017-February 2018

- Exploring perceptions of consanguineous unions with women from an East London community: analysis of discussion groups". (August 2017 - February 2018)
- Lead researcher for a qualitative research project in partnership with London Borough of Newham. Designed the study protocol, trained facilitators, moderated focus group discussions, conducted data analysis and wrote published manuscript
- "Audit and qualitative analysis of Newham's Early Years Nutrition programme". (July 2017 - August 2017)
- Conducted a qualitative analysis of the Early Years Nutrition program in Newham through audit and qualitative analysis of local children's centers. Assisted in data analysis, preparation of report and drafting published abstract
- "Newham Universal Free School Meals: Mixed-methods evaluation". (July 2017 - August 2017)
- Led a process evaluation of Free School Meal delivery in primary schools in Newham and an assessment of progress on Newham's childhood obesity plan. Assisted in development of study protocol, data collection and drafting of final report

Work Experience

Babylon Health Partners London, United Kingdom
Epidemiologist June 2019 - July 2020

- Epidemiologist for Babylon's Healthcheck digital service, focusing on associations between risk factors and chronic disease, development of predictive models and the evaluation of suitable epidemiological evidence for product development. Additionally, supporting clinical team in provision of nutrition-related content and evaluating new models for the simulation team

Aceso Global Health Consultants Limited London, United Kingdom
Senior Research Associate July 2017 - June 2019

- Worked alongside Dr. Manikam in contract research and local authority public health practice. Held several concurrent interim and honorary positions in local public health departments, academic institutions and non-governmental organizations, alongside providing support in managing the consultancy team's portfolio of work
- Promoted to a supervisor position in January 2019, responsible for line managing and developing client relationships independently. Offered expertise in quantitative and qualitative data analysis, development of mixed-method study protocols and conduct of Joint Strategic Needs Assessments

Manuscripts in Peer Review

- **Cupp M.**, Hayes K.N., Riester M.R., Berry S.D., Beaudoin F.L., Joshi R., and A.R. Zullo, "Addressing methodologic challenges in self-controlled case series designs for medication use: opioid use after hip fracture and one-year risk of subsequent hip fracture", *Submission to PDS, 2024.*

Peer Reviewed Published Manuscripts

[1] **M. Cupp**, S. D. Berry, K. N. Hayes, L. Daiello, D. Ko, M. R. Riester, and A. Zullo, "Cholinesterase inhibitor initiation does not increase the risk of fall-related injury in older adults treated with beta-blockers: A self-controlled case series design", *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, 2024.

[2] K. N. Hayes, **M. Cupp**, R. Joshi, M. R. Riester, F. L. Beaudoin, and A. Zullo, "Differences in opioid prescriptions by race among u.s. older adults with a hip fracture transitioning to community care", *Journal of the American Geriatrics Society*, 2024.

[3] A. Zullo, M. R. Riester, K. N. Hayes, Y. Zhang, S. D. Berry, E. Belanger, **M. Cupp**, and F. L. Beaudoin, "Analgesic regimens administered to older adults receiving skilled nursing facility care following hip fracture: A proof-of-concept federated analysis", *BMC Geriatrics*, 2024.

[4] **M. Cupp**, F. L. Beaudoin, K. N. Hayes, M. R. Riester, S. D. Berry, R. Joshi, and A. R. Zullo, "Post-acute care setting after hip fracture hospitalization and subsequent opioid use in older adults", *Journal of the American Medical Directors Association*, vol. 24, no. 7, P971–977.E4, 2023.

[5] M. R. Riester, F. L. Beaudoin, R. Joshi, K. N. Hayes, **M. Cupp**, S. D. Berry, and A. Zullo, "Evaluation of post-acute care and one-year outcomes among medicare beneficiaries with hip fractures: A retrospective cohort study", *BMC medicine*, vol. 21, no. 1, pp. 1–12, 2023.

[6] S. Rutherford, M. Naman, N. Zaka, K. Michaux, **M. Cupp**, H. Hafezi, S. Sami, E. C. Alexander, M. Lakhanpaul, and L. Manikam, "Building referral mechanisms for neonatal care in humanitarian emergency settings: A systematic review", *The International Journal of Health Planning and Management*, 2023.

[7] Y. Zhang, K. N. Hayes, M. R. Riester, J. B. Silva, **M. Cupp**, Y. Lee, and A. Zullo, "Trends in covid-19-related medication use in united states nursing homes, 2018-2022", *Journal of the American Medical Directors Association*, 2023.

[8] A. Zullo, M. Riester, E. Goldberg, **M. Cupp**, S. Berry, and F. Beaudoin, "Long-term care pharmacy market shares and differences in skilled nursing facilities served", *Journal of Aging & Social Policy*, pp. 1–14, 2023.

[9] Y. Y. Boo, O.-E. Jutila, **M. Cupp**, L. Manikam, and S.-I. Cho, "The identification of established modifiable mid-life risk factors for cardiovascular disease which contribute to cognitive decline: Korean longitudinal study of aging (klosa)", *Aging Clinical and Experimental Research*, vol. 33, no. 9, pp. 2573–2586, 2021.

[10] Y. Y. Boo, K. Rai, **M. Cupp**, M. Lakhanpaul, P. Factor-Litvak, P. Parikh, R. Panda, and L. Manikam, "What are the determinants of childhood infections in india's peri-urban slums? a case study of eight cities", *Plos one*, vol. 16, no. 10, e0257797, 2021.

[11] M. Lakhanpaul, E. C. Alexander, **M. Cupp**, J. T. Owugha, A. Florschutz, A. Beckingham, V. Kisan, M. Lakhanpaul, and L. Manikam, "'birthing a better future': A mixed-methods evaluation of an exhibition on the early years of life", *Health Expectations*, vol. 24, no. 4, pp. 1270–1285, 2021.

[12] L. Manikam, M. Lakhanpaul, A. G. Schilder, P. Littlejohns, **M. Cupp**, E. C. Alexander, and A. Hayward, "Effect of antibiotics in preventing hospitalizations from respiratory tract infections in children with down syndrome", *Pediatric Pulmonology*, vol. 56, no. 1, pp. 171–178, 2021.

[13] **M. Cupp**, M. Adams, M. Heys, M. Lakhanpaul, E. C. Alexander, Y. Milner, T. Huq, M. Peachey, L. Shah, I. S. Mirza, *et al.*, "Exploring perceptions of consanguineous unions with women from an east london community: Analysis of discussion groups", *Journal of community genetics*, vol. 11, no. 2, pp. 225–234, 2020.

[14] **M. Cupp**, M. Cariolou, I. Tzoulaki, D. Aune, E. Evangelou, and A. J. Berlanga-Taylor, "Neutrophil to lymphocyte ratio and cancer prognosis: An umbrella review of systematic reviews and meta-analyses of observational studies", *BMC medicine*, vol. 18, no. 1, pp. 1–16, 2020.

[15] M. Cariolou, **M. Cupp**, E. Evangelou, I. Tzoulaki, and A. J. Berlanga-Taylor, "Importance of vitamin d in acute and critically ill children with subgroup analyses of sepsis and respiratory tract infections: A systematic review and meta-analysis", *BMJ open*, vol. 9, no. 5, e027666, 2019.

Teaching

- **Lead Teaching Assistant and SAS demonstrator** at Brown University — Fall 2022
  Applied Epidemiology (PHP 2260)
- **Lead Teaching Assistant** at Brown University — Fall 2021
  Fundamentals of Epidemiology (PHP 0850)
- **The Sheridan Teaching Seminar** at Brown University — Fall 2020
  Reflective Teaching (Certificate I)
- **Statistics demonstrator** at University College London — Spring 2019
  Statistics demonstrator for a three-part lecture series on Survival Analysis at the post-graduate level, included 3 hours of teaching

Guest Lectures

- **Guest Lecturer** at Brown University — Fall 2024
  "Coding Tutorial for Self-Controlled Case Series in R"; Methods in Pharmacoepidemiology (PHP 2490)
- **Guest Lecturer** at Brown University — Fall 2023
  "Self-Controlled Case Series and "SCOPE" designs"; Methods in Pharmacoepidemiology (PHP 2490)
- **Guest Lecturer** at Brown University — Fall 2023
  "Coding Tutorial for Self-Controlled Case Series in R"; Methods in Pharmacoepidemiology (PHP 2490)
- **Guest Lecturer** at Brown University — Fall 2022
  "Bivariable and Stratified Analyses in SAS"; Applied Epidemiology (PHP 2260)
- **Guest Lecturer** at Brown University — Fall 2021
  "Screening in Public Health"; Fundamentals of Epidemiology (PHP 0850)
- **Guest Lecturer** at University College London — Fall 2018
  7.5 hours of teaching across five sessions on topics from confounding and effect modification to advanced regression (peer reviewed performance); Basic Statistics for Medical Sciences (IEHC0046)
- **Guest Lecturer** at Farr Institute — Spring 2018
  Delivering two presentations over 4 hours on methods for utilising Electronic Health Records and the development of code lists for research; Using Primary Care Electronic Health Records for Research (FARR02)
- **Guest Lecturer** at University College London — Spring 2018
  Delivered 6 hours of teaching across two sessions on survival analysis; Advanced Statistics for Records Research (CHME0015)

Press

- **McKnight's Long-Term Care News** Clinical Daily News 19 April 2023
  "Fewer hip fracture patients receive opioids after stay in SNF than IRF: study"

Skills

- **Areas of Focus:** Pharmacoepidemiology methods, Physiologic pharmacology, Medicare policy and data structures, genetic epidemiology methods, preprocessing and analysis of blood DNA methylation data, Mendelian randomization, Analysis with Genome Wide Association Studies and Phenome-wide association studies, Advanced skills in R for epigenetic research
- **Quantitative Analysis:** R, SAS
- **Qualitative Analysis:** NVivo

Scholarships and Awards

- Harvard CausaLab Summer Course Tuition Waiver 2023
  - Full tuition coverage for the 2023 CausaLab Summer Courses
- ISPE Mid-Year Meeting 2023 Scholarship award 2023
  - Conference held in Reykjavik, Iceland, April 23-25
- ISPE Travel Scholarship Committee award for ICPE Annual Conference 2022 2022
  - Conference held in Copenhagen, Denmark, August 24-28 (declined award due to scheduling conflict)
- Induction into Brown University's Delta Omega Honorary Society in Public Health Epsilon Iota Chapter 2022
- Bailey Thomas Charitable Fund (Collaborator) 2018
  - Determining the risk of multiple malignancies in children and adults with Down Syndrome: a national linked population-based cohort study
- London Borough of Newham (Co-Investigator) 2018
  - Youth Violence: strategic understanding and preventative actions
- UCL HEIF (Co-applicant), UCL Grand Challenges (Collaborator), HKU-UCL Strategic Partnership Fund (Co-Investigator) 2018
  - Childhood Infections and Pollution (CHIP): Using citizen science to better manage and prevent infections in under 5s in Indian urban slums using a One Health approach
- International Child Health Group Winter Meeting 2018 Oral Presentation Prize (Award) 2018
  - Assessing nutritional and educational inclusion status of Nepali children screening positive for disability and variation of prevalence at different thresholds of disability screening definition
- London Borough of Newham (Co-Investigator) 2017–2018
  - A qualitative analysis exploring perceptions of consanguinity in women from an East London community
- Imperial College London Master of Public Health Prize for Best Thesis 2017
  - Neutrophil counts and cancer prognosis: an umbrella review and meta-analysis

Service to Profession

- Member of the ISPE Geriatric Pharmacoepidemiology Special Interest Group (SIG) 2022–Current
  International Society of Pharmacoepidemiology (ISPE)
- Peer Review 2023–Current
  Abstract reviewer for Society of Epidemiologic Research (SER) Annual Conference 2023

- Peer Review 2010–Current
  Article editor and peer reviewer for SAGE Open, American Journal of Preventive Medicine and Public Health, the BMJ, The Journal of Global Health, BMC Pediatrics, American Journal of Medical Genetics, and The Columbia University Journal of Global Health
- Brown University Department of Epidemiology Student Advisory Committee 2022–2023
  Third Year PhD Representative
- University College London; BSc Thesis supervisor 2020–2021
  Thesis supervisor for a BSc Population Health student assessing urinary melatonin and blood pressure from HSE 2010
- University College London; BSc Thesis supervisor 2019–2020
  Thesis supervisor for a BSc Population Health student. Thesis title: "Social determinants of Children's Health in Peri-Urban Slums in India: Focusing in Eight Cities (Delhi, Meerut, Kolkata, Indore, Mumbai, Nagpur, Hyderabad and Chennai"
- University College London; BSc Thesis co-supervisor 2018–2019
  Thesis co-supervisor for two BSc Population Health students utilizing Health Survey for England (HSE) data from 2004 to 2014"
- Public Health Data Science Hackathon Volunteer March 28th, 2019
  Developed an original data analysis task for the Public Health Data Science Hackathon using UK Data Service Teaching extracts from the Welsh Health Survey (2009 and 2010). Served as a Hackathon panel judge at the event and provided analytical support to students throughout the 5.5-hour event. Attendees included post-graduate students and Public Health England employees

Peer-reviewed Published Abstracts

1. Manikam L., **Cupp M.**, Schilder A., Hayward A., Littlejohns P., Alexander E., and M Lakhanpaul, "Respiratory Tract Infection Related Healthcare Utilisation in UK Children with Down's Syndrome", *American Journal of Respiratory and Critical Care Medicine 2018;197:A2870*

2. **Cupp M.**, Cariolou M., Tzoulaki I., Evangelos E., and A. Berlanga-Taylor, "Neutrophil counts and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies", *British Journal of Cancer Supplement. https://doi.org/10.1038/s41416-018-0299-z*

3. Jensen Y., **Cupp M.**, Osman R., Lakhanpaul M., Peachey M., Light A., Alexander E., and L. Manikam, "Audit and qualitative analysis of Newham's Early Years Nutrition programme", *https://doi.org/10.1016/S0140-6736(18)32880-0*

4. **Cupp M.**, Owugha J., Florschutz A., Beckingham A., Kisan V., Manikam L., and M. Lakhanpaul, "'Birthing a better future': A mixed-methods evaluation of a multimedia exposition conveying the significance of the first 1001 days of life", *https://doi.org/10.1016/S0140-6736(18)32191-3*

5. **Cupp M.**, Adams M., Heys M., Lakhanpaul M., Alexander E., Peachey M., and L. Manikam, "Exploring perceptions of consanguinity in women from an East London community: analysis of discussion groups", *Archives of Disease in Childhood 2018;103:A3*

6. Manikam L., **Cupp M.**, Schilder A., Hayward A., Littlejohns P., Alexander E., and M. Lakhanpaul, "Effects of Antibiotics in Preventing Hospitalisations Due to Respiratory Tract Infections in Children with Down's Syndrome", *American Journal of Respiratory and Critical Care Medicine 2018;197:A2871*

Presentations

1. **Cupp M.** *(presenting author)*, Berry S.D., Hayes K.N., Daiello L., Ko D., Riester M.R.,and A.R. Zullo, "Cholinesterase Inhibitor Initiation and Risk of Fall Related Injury in Older Adults Treated with Beta Blockers: a self-controlled case series analysis", *Abstract accepted for oral presentation at ISPE Mid-Year Meeting 2024, Orland, FL, April 2024.*

2. **Cupp M.** *(presenting author)*, Hayes K.N., Beaudoin F.L., Riester M., Berry S., Joshi R., and A.R Zullo, "Opioid use after hip fracture and one-year risk of subsequent fracture: a self-controlled case series analysis", *Abstract selected for oral presentation, Society for Epidemiological Research 2023 Annual Meeting, Portland, OR, June 2023*

3. **Cupp M.** *(presenting author)*, Beaudoin F.L., Hayes K.N., Riester M., Berry S., Joshi R., and A.R Zullo, "Post-Acute Care Setting after Hip Fracture Hospitalization and Subsequent Opioid Use in Older Adults", *Abstract selected for oral presentation, ISPE Mid-Year Meeting 2023, April, Reykjavik, Iceland*

4. Hayes K.N. *(presenting author)*, **Cupp M.**, Commey A., Joshi R., Beaudoin F.L., and A.R. Zullo, "Differences in opioid use after hip fracture by race and post-acute care use among U.S. older adults", *Oral presentation, International Conference in Pharmacoepidemiology and Therapeutic Risk Management, Aug 2022, Copenhagen, Denmark*

5. **Cupp M.** *(presenting author)*, Joshi R., Riester M.R., Hayes K.N., Beaudoin F.L., and A.R. Zullo, "One-year opioid use following discharge from post-acute care after hip fracture", *Poster presentation, Society for Epidemiological Research 2022 Annual Meeting, Chicago, June 15-17, 2022*

6. Rutherford S. *(presenting author)*, Leak K., **Cupp M.**, Lakhanpaul M., Hafezi H., and L. Manikam, "Building Referral Mechanisms for Newborn Care in Humanitarian Emergency Settings: A Systematic Review", *Poster presentation, Royal College of Paediatrics and Child Health 2020 Conference in Liverpool (29th of April)*

7. **Cupp M.** *(presenting author)*, Adams M., Heys M., Lakhanpaul M., Shah L., Peachey M., Alexander E., and L. Manikam, "Perspectives on Consanguinity in South Asian and Middle Eastern Communities within a London Borough", *Oral presentation, national Public Health Research and Science Conference 2018: Application of scientific methods to improve and protect health (20th-21st March 2018, Warwick University)*

8. Manikam L., **Cupp M.** *(presenting author)*, Schilder A., Hayward A., Littlejohns P., Alexander E., and M. Lakhanpaul, "Respiratory Tract Infection Related Healthcare Utilisation in UK Children with Down's Syndrome", *Poster presentation, 36th Annual Meeting of the European Society for Paediatric Infectious Diseases (28th May-2nd June 2018, Malmö, Sweden)*

9. Manikam M., Schilder A., Lakhanpaul M., Littlejohns P., **Cupp M.**, Alexander E. *(presenting author)*, and A. Hayward, "Effects of Antibiotics in Preventing Hospitalisations due to Respiratory Tract Infections in Children with Down's Syndrome", *Poster presentation, American Thoracic Society 2018 International Conference (18th-23rd May 2018, San Diego)*

10. Manikam M., Schilder A., Lakhanpaul M., Littlejohns P., **Cupp M.**, Alexander E. *(presenting author)*, and A. Hayward, "Respiratory Tract Infection Related Healthcare Utilisation in UK Children with Down's Syndrome", *Poster presentation, American Thoracic Society 2018 International Conference (18th-23rd May 2018, San Diego)*

11. Manikam L., **Cupp M.** *(presenting author)*, Schilder A., Hayward A., Littlejohns P., Alexander E., and M. Lakhanpaul, "Effect of Antibiotics in the Prevention of Hospitalisation due to Respiratory Tract Infections in UK Children with Down's Syndrome", *Poster presentation, World Down Syndrome Congress 2018 in Glasgow, Scotland (25th-27th July 2018)*

12. Manikam L., **Cupp M.** *(presenting author)*, Schilder A., Hayward A., Littlejohns P., Alexander E., and M. Lakhanpaul, "Healthcare Utilisation Related to Respiratory Tract Infections in UK Children with Down's Syndrome", *Poster presentation, World Down Syndrome Congress 2018 in Glasgow, Scotland (25th-27th July 2018)*

13. **Cupp M.** *(presenting author)*, Cariolou M., Tzoulaki I., Evangelos E., and A. Berlanga-Taylor, "Neutrophil counts and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies", *Oral presentation, National Cancer Research Institute conference 2018 in Glasgow, Scotland (4th-6th November 2018)*

14. **Cupp M.**, Haworth E., Costello A., Manikam L., Manandhar D., Kuper H. and M. Heys *(presenting author)*, "Assessing nutritional and educational inclusion status of Nepali children screening positive for disability and variation of prevalence at different thresholds of disability screening definition", *Oral presentation, International Child Health Group winter meeting 2018 in Liverpool, UK (20th November 2018, with award of oral presentation prize)*

15. Jensen Y., **Cupp M.** *(presenting author)*, Osman R., Lakhanpaul M., Peachey M., Light A., Alexander E., and L. Manikam, "Audit and qualitative analysis of Newham's Early Years Nutrition programme", *Poster presentation, Lancet Public Health conference in Belfast, Northern Ireland (23rd November 2018), including publication in the Lancet*

16. **Cupp M.** *(presenting author)*, Owugha J., Florschutz A., Beckingham A., Kisan V., Manikam L., and M. Lakhanpaul, "'Birthing a better future': A mixed-methods evaluation of a multimedia exposition conveying the significance of the first 1001 days of life", *Poster presentation, Lancet Public Health conference in Belfast, Northern Ireland (23rd November 2018), including publication in the Lancet*

17. **Cupp M.**, Adams M., Heys M. *(presenting author)*, Lakhanpaul M., Alexander E., Peachey M., and L. Manikam, "Exploring perceptions of consanguinity in women from an East London community: analysis of discussion groups", *Oral presentation, Great Ormond Street Hospital Conference 2018 – Continuous Care in London, UK (23rd November 2018), including publication in Archives of Disease in Childhood*

18. **Cupp M.**, Haworth E., Costello A., Manikam L., Manandhar D., Kuper H. and M. Heys *(presenting author)*, "Assessing nutritional and educational inclusion status of Nepali children screening positive for disability and variation of prevalence at different thresholds of disability screening definition", *Poster presentation, Great Ormond Street Hospital Conference 2018 – Continuous Care in London, UK (23rd November 2018)*

19. Puthucheary Z., **Cupp M.**, Manikam L. *(presenting author)*, Rocke P., Cove M., and W. Chow, "Five years of intensive care experience: epidemiology, health care costs and outcomes for communicable and non-communicable diseases in Singapore", *Poster presentation, 3rd Raffles Dialogue on the Future of Human Well-Being and Security (HWS): Towards Resilient and Empowered Societies in Singapore (27th-28th November 2018)*

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I have been fortunate to have the support of an exceptional committee who have encouraged me from the early stages of this project – Andrew Zullo, Nina Joyce, Francesca Beaudoin and Arman Oganisian. Andrew, as my dissertation chair and F31 sponsor, has been a guiding force in my pharmacoepidemiology training since my first year in the program. His mentorship has been pivotal in helping me find my path and develop the skills necessary to pursue my research interests. Nina provided invaluable methodological guidance throughout this project, and her insights were particularly critical in navigating the nuances of target trial emulation. I aspire to emulate her compassion and willingness to discuss challenges when things did not go as planned. Francesca lent essential expertise in opioid use and chronic pain management, helping to refine the research questions early on and lay the groundwork for this project. Arman contributed a fresh perspective, ensuring that the biostatistical methods were rigorously applied. I am immensely grateful to all of you for your support over the past few years.

I would also like to thank the Brown faculty outside of my committee who played integral roles in my training, including Alison Field for her insights as my academic advisor, Chanelle Howe for her excellent methods teaching, Joe Braun for his grant writing guidance, and Karl Kelsey and Steven Buka for supporting my research assistantships.

My gratitude extends to the amazing academic coordinators in the epidemiology department (Brady Moore, Brittany Leclerc, and Katie Graham), along with everyone who has assisted me with everything from grant administration to data use agreements throughout the years.

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Finally, a thank you to my family. To my parents, Jason and Patti, whose support for every goal I have ever pursued is unwavering and granted me the confidence to tackle a PhD. To my husband, Alex, who is endlessly patient and the sort of partner who moves across a literal ocean to help support my dreams. I could not have done this without all of you.

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List of abbreviations

bDMTs	biologic disease-modifying therapies
C pegol	certolizumab pegol
CCI	combined comorbidity index
CD	cluster of differentiation
CLs	confidence limits
CR	Crohn's disease
csDMTs	conventional synthetic disease-modifying therapies
DMTs	disease-modifying therapies
FDA	US Food and Drug Administration
GEE	generalized estimating equation
HCPCS	Healthcare Common Procedures Coding System
HMO	Health Maintenance Organization
IBD	inflammatory bowel disease
ICD	International Classification of Disease
IgG	immunoglobulin G
IL	interleukin
IPCW	inverse probability of censoring weights
IR	incidence rate
ITT	intention to treat
MedPAR	Medicare Provider Analysis
MME	morphine milligram equivalents
MS	multiple sclerosis

NOC	not otherwise classified
NSAIDs	prescription non-steroidal anti-inflammatory drugs
PAC	post-acute care
PP	per-protocol
PR	prevalence ratio
RA	rheumatoid arthritis
RCTs	randomized clinical trials
RHF	Residential History File
RR	risk ratio
SD	standard deviation
SLE	systemic lupus erythematosus
SMD	standardized mean difference
SNRIs	serotonin and norepinephrine reuptake inhibitors
SSRIs	selective serotonin reuptake inhibitors
UC	ulcerative colitis

INTRODUCTION

Autoimmunity in older adults

Autoimmune diseases encompass a large family of conditions in which the body is attacked by its own immune system, specifically self-reactive white blood cells.[1–3] Over 81 unique autoimmune diseases have been identified, each classified by the tissues within the body which are affected, and their estimated combined prevalence is over 8% within the United States.[4] While both genetic and environmental risk factors are hypothesized to play a role, the etiology of autoimmune diseases remains poorly understood.[5] In the past decade, substantial increases in antinuclear antibodies (a biomarker of autoimmunity) have been noted, particularly among older adults.[5] Older adults experience a higher prevalence of inflammation, pain, and autoimmune conditions compared to younger adults and this may be driven by aging-associated changes.[6–8] The ageing process is linked to the development of autoimmunity through immunosenescence, where the functioning of immune cells is compromised and accompanied by an increase in chronic inflammation and pro-inflammatory mediators like Tumor Necrosis Factor alpha (TNF-α) and interleukins 6 and 1-beta (IL-6 and IL-1β).[9] This unbalanced inflammatory response may result in an increase in infection and inflammation driven diseases, such as autoimmune disease, which are commonly diagnosed in older adults during this period of immunosenescence between 40 and 70 years of age.[6,9,10]

The most common autoimmune diseases among older adults include Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), Systemic Lupus Erythematosus (SLE) and Inflammatory Bowel Diseases (IBD; Ulcerative Colitis [UC] and Crohn's Disease [CR])[10]. Autoimmune diseases such as these are associated with chronic pain and extremely high costs in the United States, estimated at $100 billion by The National Institutes of Allergy and Infectious Diseases in 2001[11].

Disease Modifying Therapies

Several disease-modifying therapies (DMTs) are approved by the US Food and Drug Administration (FDA) for treating autoimmune diseases. These include conventional synthetic disease-modifying therapies (csDMTs) and biologic disease-modifying therapies (bDMTs). These treatments are not curative and focus on dampening the immune response to the body's own tissues. Therefore, they must be continually administered to offer effective treatment which alleviates symptoms, prevents exacerbations and slows disease progression.

csDMTs focus on an overall suppression of the immune system to reduce chronic inflammation as a first-line therapy. These csDMTs may be given orally but are usually administred by injection at intervals ranging between every other day to once per week in order to be effective in managing disease.[12] Despite the inconvenience of daily injections, these first-line therapies are relatively well tolerated.[13,14] However, they are only suitable for patients with mild to moderate disease severity as they are classified as being modestly effective therapies.[14] The use of bDMTs is often reserved for patients who do not respond to first-line therapies or have very high disease activity.[15,16] Unlike csDMTs which broadly suppress inflammation, bDMTs offer targeted treatment by focusing on the specific cellular mechanisms involved in the pathogenesis of each unique autoimmune disease.[17–21] This targeted approach helps mitigate some adverse effects associated with generalized immunosuppression, such as the generation of neutralizing antibodies that render first-line treatments ineffective.[15] Currently approved DMTs are noted in *Table 1* below.

Table 1 – US Food and Drug Administration approved conventional synthetic and biologic disease-modifying therapy exposure groups by autoimmune disease of interest.

	Rheumatoid Arthritis	Multiple Sclerosis	Systemic Lupus Erythematosus	Ulcerative Colitis	Crohn's Disease
csDMTs	hydroxychloroquine, chloroquine, sulfasalazine, methotrexate, leflunomide, azathioprine, , cyclosporine, d-penicillamine	cladribine, dimethyl fumarate, diroximel fumarate, fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1b, mitoxantrone HCl, monomethyl fumarate, ozanimod, peginterferon beta-1a, ponesimod, siponimod, teriflunomide	azathioprine, chloroquine, hydroxy-chloroquine, cyclophosphamide, cyclosporine, methotrexate, mycophenolic acid	azathioprine, cyclosporine, mercaptopurine, mesalamine, ozanimod, sulfasalazine, tacrolimus	azathioprine, mercaptopurine, mesalamine, methotrexate, sulfasalazine, tacrolimus
bDMTs	TNF inhibitors (*etanercept, adalimumab, infliximab, golimumab, certolizumab pegol*), T cell costimulatory inhibitor (*abatacept*), IL-6 receptor inhibitors (*tocilizumab, sarilumab*[*)], anti-CD20 antibody (*rituximab*)	α4-integrin antagonist (*natalizumab*), anti-CD52 antibody (*alemtuzumab*), anti-CD20 antibodies (*ocrelizumab, ofatumumab*[†] *ublituximab*[‡)]	IgG1γ antibody (*belimumab*)	TNF inhibitors (*adalimumab, golimumab, infliximab*), IL-12/IL-23 receptor inhibitors (*ustekinumab*[§)], α4-integrin antagonist (*vedolizumab*)	TNF inhibitors (*adalimumab, certolizumab pegol, infliximab*), IL-12/IL-23 receptor inhibitors (*ustekinumab*), α4-integrin antagonist (*natalizumab, vedolizumab*)

(csDMTs) conventional synthetic disease-modifying therapies; (bDMTs) biologic synthetic disease-modifying therapies; (TNF) tumor necrosis factor; (IL) interleukin; (CD) cluster of differentiation; (IgG) Immunoglobulin G;
Note: Analyses were limited to bDMTs approved by the FDA for each condition, excluding off label use.
[*] *Sarilumab was FDA approved for the treatment of rheumatoid arthritis in May 22, 2017 and is not included in analyses.*
† Ofatumumab was FDA approved for the treatment of multiple sclerosis in August 20, 2020 and is not included in analyses.
‡ Ublituximab was FDA approved for the treatment of multiple sclerosis in Dec. 28, 2022 and is not included in analyses.
§ Ustekinumab was FDA approved for the treatment of ulcerative colitis in October 21, 2019 and is not included in analyses.

Managing symptoms and pain

The current leading clinical guidelines for treatment of the most common autoimmune diseases provide detailed pathways for csDMT and bDMT use, reserving treatment with bDMTs for individuals who do not reach treatment targets on standard therapies.[22–26] The use of csDMTs and bDMTs for autoimmune disease is often guided by a treat-to-target approach, with the aim to achieve low clinical disease activity, limiting symptoms and preventing further bodily damage.[22–26] These guidelines acknowledge that full remission is not always possible even with bDMT use, and patients should seek a treatment target of low disease activity where lingering symptoms and

pain can be managed effectively. However, some symptoms, such as fatigue and pain, extend beyond the clinical markers used to gauge treatment success according to treat-to-target approaches with DMTs, and there are no clear recommendations for pain treatment beyond reducing disease activity through DMT use.[22–26]

Although pain management is indicated as a key concern by autoimmune disease research foundations and patients, clinical guidelines for treating chronic pain in autoimmune diseases remain unclear.[27–31] The Centers for Disease Control 2020 Clinical Practice Guidelines for prescribing opioids for pain recommend the initiation of disease-specific interventions for pain in autoimmune diseases, such as DMTs or glucocorticoids, before turning to opioid analgesics.[32] This guidance assumes that effective immunosuppression is sufficient for providing pain management in autoimmune disease, a notion that may not hold true across all conditions due to irreversible damage to ligaments, organs, or nerves in different conditions. The role of bDMTs in reducing pain and analgesic dependence in this vulnerable population is understudied and represents an important clinical gap.

Concurrent opioid and bDMT use

The most recent guidelines on treating chronic pain focus on carefully weighing the risks and benefits of opioid therapy, with acknowledgement of the heterogeneity of pain and underlaying conditions, and recommend alleviating pain by treating underlaying conditions whenever possible.[32] Treatment with bDMTs should help to manage symptoms and slow disease progression; however, these treatments are not curative and many individuals with autoimmune disease still require opioid analgesics for pain management.[33–39] These prescribing patterns lead to high rates of opioid use among individuals with autoimmune disease, ranging from 21% in patients with MS to 40% and 45% in patients with RA and IBD, respectively.[40–46] Adequate analgesic treatment is

vital to avoid pain which is debilitating for patients, leading to poor physical functioning and mental health.[32]

Despite the coincidence of chronic inflammation and pain in autoimmune disease, the landscape of concurrent opioid and bDMT use is poorly understood. Opioid use is higher among autoimmune disease patients treated with bDMTs compared to those who are not treated with bDMTs.[40,41,44,47–50] While bDMTs have the potential to reduce pain and inflammation, potentially influencing the need for opioids, opioid use may impact the continuation and effectiveness of bDMTs, as available evidence suggests that chronic opioid use is associated with reduced adherence to bDMTs and a reduction in their effectiveness.[51–53] This bidirectional relationship highlights the importance of understanding how opioid and bDMT use influence one another over time. These prescribing patterns have not been sufficiently investigated to date and current literature excludes a myriad of autoimmune conditions, lacks focus on outcomes related to bDMT adherence and uses methodologies unsuited to supporting causal inference. Therefore, prescribers do not have sufficient information on the relationship between opioids and bDMTs to make informed decisions about the true risks and benefits of opioid therapy for these patients. Understanding this dynamic is essential for optimizing treatment strategies, improving clinical outcomes, and minimizing potential harms associated with opioid use in vulnerable populations with autoimmune disease.

CHAPTER 1

Opioid and other analgesic use in older adults initiating a biologic disease-modifying therapy for treatment of rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis or Crohn's disease.

Abstract

Background: Autoimmune diseases cause severe pain, particularly in older adults. Despite the use of biologic disease-modifying therapies (bDMTs), opioid use remains high, and pain management guidelines are unclear for this vulnerable population.

Objective: To assess trends in analgesic use for older adults with autoimmune diseases initiating a bDMT and determine whether opioid and other analgesic use is altered following initiation.

Design: Retrospective, longitudinal descriptive study.

Participants: Community dwelling US Medicare fee-for-service beneficiaries initiating a bDMT for treatment of rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis or Crohn's disease between 2008 and 2019.

Measurements: Incidence rate of analgesic, co-analgesic adjuvant and corticosteroid use in the 12 months pre- and 24 months post-initiation of a bDMT. Risk of analgesic use in the post-initiation period, compared to the first and second year pre-initiation.

Results: Among 1,061,463 eligible individuals, 22,671 initiated bDMTs. Opioid use increased in the first and second years post-initiation in the overall cohort ($RR_{year\ 1}$ 1.04 [95% CL 1.03, 1.06];$RR_{year\ 2}$ 1.05 [95% CL 1.03, 1.07]) and only systemic lupus erythematosus patients ($RR_{year\ 1}$ 0.86 [95% CL 0.76, 0.98]; $RR_{year\ 2}$ 0.83 [95% CL 0.67, 1.04]) saw a decrease post-initiation.

Conclusions: Initiation of a bDMT did not significantly reduce analgesic use for most autoimmune conditions, underscoring the need for improved pain management strategies in older adults with autoimmune diseases.

1 Introduction

Autoimmune diseases are highly heterogenous, resulting in different manifestations depending on the tissues impacted.[1,2] Despite this heterogeneity, pathologic pain is a shared symptom across conditions.[33] Older adults in particular experience a higher prevalence of autoimmune disease compared to younger adults, complicated by more severe disease manifestations, debilitating pain and frequent use of analgesic medications.[7,8,56] Appropriate analgesic treatment is crucial in reducing the morbidity and mortality associated with these diseases. However, there are currently no clinical guidelines based on rigorous scientific evidence available to guide pain treatment in autoimmune disease.

Despite the availability and wide uptake of DMTs, individuals with autoimmune disease still report experiencing pain associated with their condition and utilize strong analgesics, such as opioids, at high rates. Paradoxically, opioid use is higher among autoimmune disease patients treated with bDMTs compared to those who are not treated with bDMTs, likely due to unmeasured confounding by disease severity.[40,41,44,47–50] A sparse body of research on RA and SLE shows no significant decrease in opioid use following bDMT initiation.[43,57,58] This research excludes individuals with other autoimmune conditions who are impacted by the same chronic pain treatment guidelines but may experience different pain trajectories after treatment. Furthermore, the current literature does not consider chronic opioid use or differentiate the patterns of acute and chronic opioid use following bDMT initiation.

Individuals living with an autoimmune disease suffer from chronic inflammation and chronic pain concurrently. Presently, there is no guidance available for analgesic therapy in patients taking bDMTs for autoimmune disease.[22,24,59] This study aims to inform providers about whether bDMT initiation is sufficient to reduce opioid use or if alternative strategies are required to reduce opioid

reliance. The first step toward safe and effective management of pain in autoimmune disease is to address the critical need for information about the relationship between bDMT use and analgesic therapy. This study describes patterns of analgesic medication use in community dwelling Medicare fee-for-service ensured adults 66 years of age and older initiating a bDMT for treatment of RA, MS, SLE, UC or CR between 2008 and 2019.

Specific objectives:

i. Calculation of the monthly cumulative incidence of analgesic, co-analgesic adjuvant and corticosteroid use, including new use of opioids, and the monthly prevalence of chronic opioid use in the year prior to bDMT initiation and in the two years following initiation, with stratification by condition.
ii. Estimation of the risk ratio (RR) of analgesic, co-analgesic adjuvant and corticosteroid use, and the prevalence ratio (PR) of chronic opioid use in the first and second year post-initiation of a bDMT, compared to the year pre-initiation, with stratification by condition.

2 Methods

2.1 Study Design

This longitudinal descriptive study utilized an open retrospective cohort of Medicare fee-for-service beneficiaries ≥ 66 years of age with a diagnosis of an autoimmune disease of interest (RA, MS, SL, UC, or CR) who initiated a bDMT for the first time between 2008 and 2019. Beneficiaries residing outside the 49 continental states or enrolled in a health maintenance organization (HMO) were excluded due to concerns about data availability and consistency. The study period spanned up to 3 years for each eligible beneficiary, including the 12 person-months prior to bDMT initiation and continuing for up to 24 person-months post-initiation, or until one of the following occurred:

death, end of the study period (31 December 2019), entry into a nursing home or hospice care, disenrollment from Medicare Parts A, B, or D, or enrollment in an HMO.

All beneficiaries were required to be community-residing and to have continuous Medicare enrollment for the 365 days prior to bDMT initiation to assess patterns of analgesic use and estimate the prevalence of analgesic use before and after bDMT initiation.

2.2 Study Population

The cohort was developed from Medicare claims data, including the Medicare Provider Analysis (MedPAR), a 20% random sample from the Carrier file, a 20% random sample from the Part D Prescription Drug Event claims, and the Residential History File (RHF). We first identified Medicare beneficiaries at least 66 years of age who had an International Classification of Disease (ICD) code for one of the five autoimmune diseases of interest in either an inpatient (MedPAR) or outpatient (Part B professional service claims for outpatient and other services) record between 2007 and 2019. Due to the study period spanning the ICD coding switch in 2012, all code lists were screened for ICD-9 and ICD-10 (*see code list in Supplementary Table 1*).

We applied a claims-based algorithm for identifying autoimmune disease diagnoses to capture individuals with varying levels of disease severity while maintaining specificity. This algorithm was adapted from a validated MS screening measure, requiring ≥3 condition related claims from any combination of: 1) inpatient claims with relevant ICD code, 2) outpatient claims with relevant ICD code, 3) claim for csDMT or bDMT indicated for condition, within a 1-year time period.[60] Although this study focused on the initiation of bDMTs, as the most advanced therapy available, csDMTs use was considered as evidence for an autoimmune disease diagnosis when refining the

eligible sample. The diagnosis date of the condition was assigned as the date on which an individual met this criteria.

Since many older adults experience their first autoimmune disease diagnosis well before the age of 66, left censoring in the data prevented the identification of first ever diagnosis dates for each condition.[56] An individual could meet the criteria for more than one autoimmune disease diagnosis over the course of follow-up.[56,61] In the case of multiple autoimmune disease diagnoses, the condition being treated with a bDMT was considered the primary diagnosis for that bDMT initiation episode, with any additional conditions considered as comorbidities. An individual with co-occurring autoimmune diseases could initiate multiple bDMTs during follow-up for one or multiple conditions, having different primary diagnoses across bDMT initiation episodes.

2.3 Exposure to Disease-Modifying Therapies

Claims from both Medicare Part D and Medicare Part B were used to identify use of csDMTs and bDMTs. Most csDMTs are self-administered and billed through Medicare Part D, while bDMTs are often administered by a healthcare provider in an outpatient setting and billed to Medicare Part B using unique Healthcare Common Procedures Coding System (HCPCS) codes, although there are exceptions to this (*see Supplementary Tables 2 and 3*). While Part D claims do not include details on the indication for each dispensing, indications for bDMTs claimed in Part D were assigned according to the most recently diagnosed autoimmune disease of interest at initiation (*as defined in 2.2 Study Population*). Other DMTs administered through infusions and injections were identified by HCPCS codes in Part B claims and required an ICD code for the relevant autoimmune disease within the same claim to define the indication. Intravenous versus subcutaneous formulations were distinguished using the 'JA' modifier for intravenous and the 'JB' modifier for

subcutaneous within the claim. When this modifier was not included for formulations with multiple routes of administration, intravenous administration was assumed.

Only FDA approved bDMTs were considered for each condition and biosimilars were excluded. Any off-label use of a bDMT for a condition not supported by FDA approved, or use before the FDA approval date, was also excluded. The approved DMTs for each condition of interest are listed in *Table 1*, with additional information on HCPCS codes and exclusions available in *Supplementary Tables 2 and 3*. Newly approved bDMTs may not be issued a unique HCPCS code until the following year. In these cases, a non-specific identifier is used until a unique code is issued, and these non-specific codes may continue to be used after the unique code is released *('J3590', 'C9399', 'Q4082', 'J9999'*). All Part B claims with a supporting ICD-9 or 10 code from the autoimmune disease code lists and a non-specific HCPCS code were evaluated to infer the medication according to an established approach. This approach incorporated the difference between the observed and expected unit price and observed dose according to the Medicare Part B Schedule for Not Otherwise Classified (NOC) Drugs and Biological Products (*see Supplementary Table 4*).[62] Any non-specific HCPCS codes which could not be identified through exact matching were treated as NOC bDMTs and included in the assessment of new bDMT use but excluded from main analyses. Any non-specific HCPCS codes without a supporting ICD code from the autoimmune disease code lists were disregarded.

Because many bDMTs are long acting medications, bDMT exposure was defined by the days with medication on hand according to the days' supply and dispensing date. Any overlapping days' supply was attributed as a single day of medication on hand.[63] For bDMTs claimed through Part D, the days' supply dispensed was provided in the claim. For bDMTs claimed through Part B, the days' supply was inferred based on the dose and number of units dispensed (see *Supplementary*

Table 2 for medication specific inferred days' supply). New use of a bDMT was established through a year of lookback free of any bDMT on hand, including any non-specific HCPCS codes with a supporting ICD code from the autoimmune disease code lists. Individuals may have more than one bDMT initiation episode for several bDMTS or conditions, as long as they are separated by at least a year with no bDMT supply on hand. Adherence to bDMTs was not required for continued eligibility in person-months after bDMT initiation.

2.4 Exposure to Analgesic Medications

Exposure to analgesic medications was assessed using a days with medication on hand approach, where person-months with drug on hand were flagged as exposed. The primary analgesic regimen of interest was opioid analgesics. Opioids with ingredients for non-pain related indications were excluded (e.g. those containing humectants or expectorants). Additionally, prescription non-steroidal anti-inflammatory drugs (NSAIDS) and co-analgesics, including antidepressants (selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], and tricyclic antidepressants) and muscle relaxers or anti-convulsant medications, were also included for their use as adjuvants in treating chronic, muscle and nerve pain.[64–66] Only analgesic medications administered in Part D were included, as those administered in an inpatient or outpatient setting are likely to reflect pain management for medical procedure prophylaxis. Non-prescription analgesics, such as over the counter NSAID use, is not captured in claims data and was not considered.

The use of glucocorticoids was also assessed, as they are commonly used to treat pain and other symptoms due to autoimmune disease flare-ups. Glucocorticoids dispensed in Part D or administered in Part B were considered. Guidelines do not recommend the use of glucocorticoids for durations over three months and they are to be used on an as needed basis.[22] This serves as an

indicator of disease activity after bDMT initiation, which may be independent of analgesic use. See *Supplementary Tables 5 and 6* for full analgesic medication inclusion and exclusion criteria.

2.5 Outcomes

The primary outcome of interest is opioid use in the first and second year post-initiation of a bDMT, compared to the year pre-initiation. Secondary outcomes include chronic opioid and non-opioid analgesic use with stratification by condition. All outcomes were dichotomized and assessed on a monthly basis, with a binary indicator for the criteria for each outcome being met in that month. Criteria for analgesic medication dispensing outcomes:

- Any analgesic use: Defined as any days with analgesic medication on hand, considering opioids, prescription NSAIDs, co-analgesic adjuvants (antidepressant, muscle relaxer/anticonvulsants) and steroids.
- Chronic opioid use: Defined as a binary indicator for meeting at least 90 days with opioids on hand, with a 30-day allowable gap in opioids on hand.

2.6 Demographics

All time-fixed demographics (age, sex and race) were measured at the time of bDMT initiation, with co-morbidities assessed through the Gagne combined comorbidity index (CCI) measured in the 12 months pre-initiation of bDMT. The chronic conditions considered in CCI were assessed through ICD codes in Part A and Part B claims. csDMT use was assessed in the 12 months pre-initiation.

2.7 Analysis

This longitudinal descriptive study was conceptualized following the guidelines laid out in the Framework for Descriptive Epidemiology checklist.[67] We assessed the monthly incidence of

analgesic use (medication on hand) across 36 person-months in new users of bDMTs. A monthly person-period data set was constructed with a row for each individual in every month of the study where eligibility criteria were met, and a binary indicator for opioid or other analgesic use in that month. For the 12 months pre- and 24 months post-initiation of a bDMT, the incidence rate of exposure to each analgesic medication was estimated. The numerator included individuals with an analgesic in each month, while the denominator included all eligible individuals in the month. The RR of analgesic medication use and the PR of chronic opioid use in the 1-12 and 13-24 months post-initiation versus the 12 month pre-initiation period was evaluated using a generalized estimating equation (GEE) model with a binomial distribution and log-link function. An autoregressive correlation matrix with a lag equal to 1 was used to account for within person correlation and the possibility of a single opioid dispensing spanning sequential months in the case of dispensings with a large days' supply. Due to the small number of individuals with unenrollment over the duration of follow-up, weights to account for censoring due to unenrollment were not applied (*see Table 2*). The alpha level for all statistical tests was 0.05 and we applied the Bonferroni correction for multiple-comparisons due to the stratification cross many analgesics and conditions.[68] We present unadjusted estimates of incidence, prevalence, RRs, and PRs, in keeping with guidance on descriptive research.[67]

2.7.1 *Subgroup analyses*

Subgroup analyses include stratification according to the autoimmune disease being treated in each initiation episode, initiation of a bDMT prior to 2015 and after 2015, and by sex. Stratification by initiation pre- and post-2015 was conducted to assess the influence of year-on-year trends in prescribing practices driven by a change in opioid use guidelines, which saw an effect in 2015.[69]

2.7.2 Stability analyses

Stability analyses included assessment of new opioid use, where new use was defined as a dispensing of an opioid after a 30-day interval with no opioids on hand, as opposed to prevalent or continued use of opioids. Once an individual experiences a gap in exposure to opioids on hand greater than 30 days, they were eligible for a subsequent episode of new opioid use.

3 Ethics

This work received Data Use Agreement approval from The Centers for Medicare & Medicaid Services and was determined as exempt from 45 CFR 46 regarding the inclusion of human participants in research by the Brown University Institutional Review Board (protocol 2022003502).

4 Results

4.1 Study Population

We assessed bDMT initiation in 1,061,463 eligible individuals with at least one autoimmune disease diagnosis of interest. Of this sample, 34,793 (3.3%) individuals were existing bDMT users with no new use episodes observed and 22,671 (2.1%) experienced an eligible new use episode during the study period (*see Figure 1*). The majority of new bDMT initiation was for the treatment of RA (21,485 initiation episodes [19,733 unique individuals]), followed by CR (1,430 initiation episodes [1,369 unique individuals]), UC (1,164 initiation episodes [1,124 unique individuals]), MS (281 initiation episodes [273 unique individuals]), and SLE (174 initiation episodes [172 unique individuals]). The majority of the sample was female (74%, N = 18,116), white (87%, N = 21,323) and initiated a bDMT prior to 2015 (54%, N = 13,312) (*see Table 2*). See supplementary

results section 1.1 for details on individuals with multiple diagnoses and initiations and supplementary results section 1.2 for information on the bDMTs initiated.

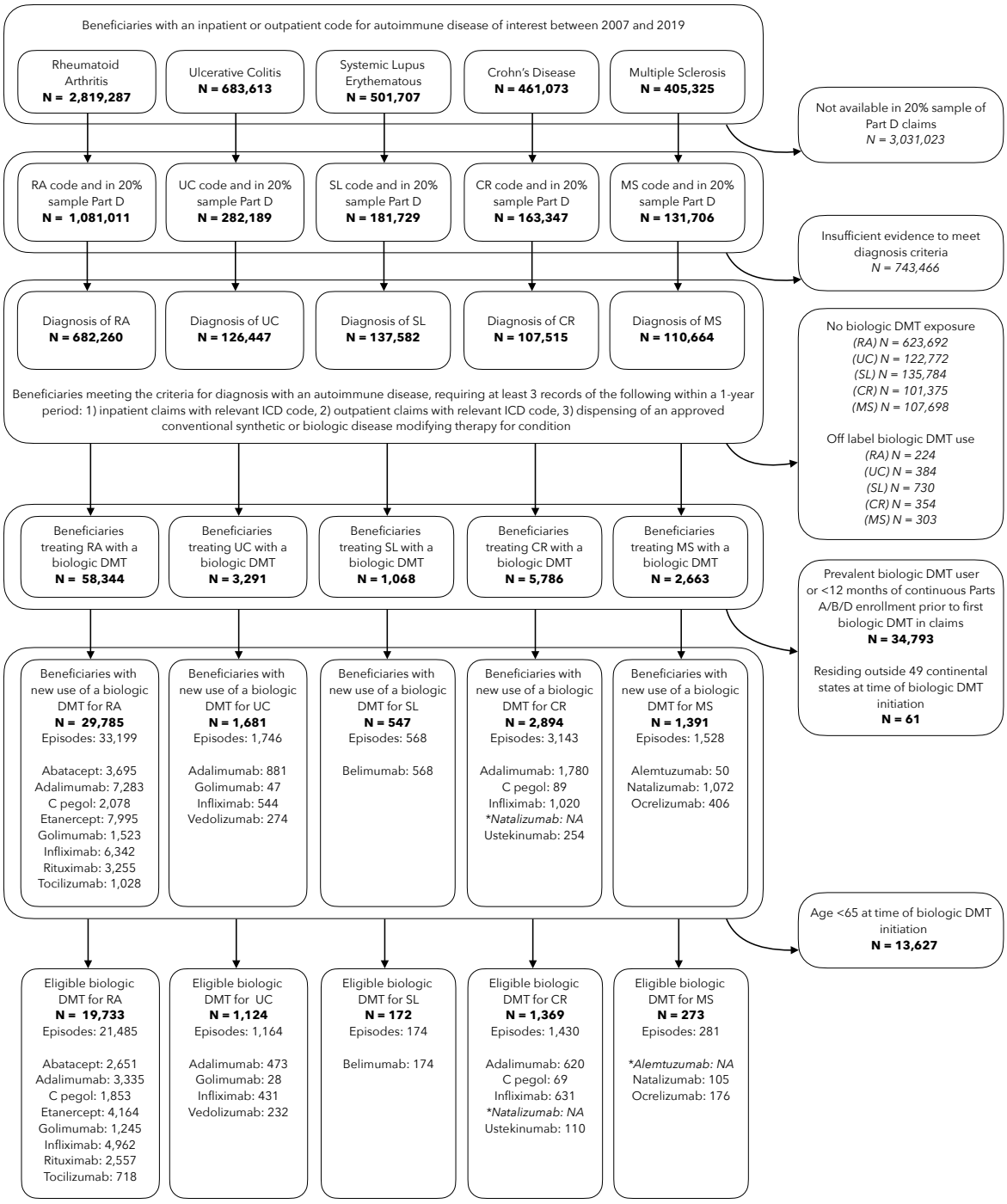

Figure 1 – Chapter 1 cohort flowchart.

(C pegol) certolizumab pegol; (RA) rheumatoid arthritis; (MS) multiple sclerosis; (UC) ulcerative colitis; (CR) Crohn's disease; (SL) systemic lupus erythematous; (DMTs) disease-modifying therapies; (ICD) International Classification of Diseases.

Table 2 – Baseline demographics for each episode of Medicare fee-for-service beneficiaries initiating a US Food and Drug Administration approved biologic disease-modifying therapy for treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, multiple sclerosis or systemic lupus erythematous between 2008 and 2019.

	Rheumatoid Arthritis, N = 21,485	**Crohn's Disease, N = 1,430**	**Ulcerative Colitis, N = 1,164**	**Multiple Sclerosis, N = 281**	**Systemic Lupus Erythematous, N = 174**
Age at bDMT initiation, years	71 (68, 76)	71 (68, 75)	71 (68, 76)	69 (67, 72)	70 (68, 75)
Sex					
Female	16,267 (76%)	860 (60%)	645 (55%)	192 (68%)	-
Male	5,218 (24%)	570 (40%)	519 (45%)	89 (32%)	-
Race					
White	18,532 (86%)	1,314 (92%)	1,068 (92%)	267 (95%)	142 (82%)
Combined Comorbidity Index	2 (1, 3)	2 (1, 4)	2 (1, 4)	2 (1, 4)	3 (1, 5)
Chronic Pain	3,493 (16%)	184 (13%)	148 (13%)	-	-
Fibromyalgia	1,315 (6.1%)	60 (4.2%)	-	-	-
Year of initiation ≤ 2015	12,171 (57%)	635 (44%)	389 (33%)	60 (21%)	57 (33%)
Region					
Midwest	3,895 (18%)	311 (22%)	285 (24%)	46 (16%)	-
Northeast	3,937 (18%)	288 (20%)	248 (21%)	50 (18%)	-
South	9,490 (44%)	595 (42%)	468 (40%)	138 (49%)	91 (52%)
West	4,163 (19%)	236 (17%)	163 (14%)	47 (17%)	-
Use of csDMT in year prior to bDMT initiation	14,321 (67%)	779 (54%)	743 (64%)	111 (40%)	146 (84%)
Antimalarial	4,199 (20%)	33 (2.3%)	37 (3.2%)	-	110 (63%)
Immunomodulator	13,400 (62%)	767 (54%)	739 (63%)	-	93 (53%)
Cause of Censoring					
None / Study end*	18,950 (88%)	1,301 (91%)	1,074 (92%)	259 (92%)	160 (92%)
Disenrollment	1,100 (5.1%)	65 (4.5%)	49 (4.2%)	-	-
Death during follow-up	1,435 (6.7%)	64 (4.5%)	41 (3.5%)	-	-
Total months of follow up after initiation	24 (18, 24)	24 (13, 24)	24 (11, 24)	10 (6, 24)	24 (8, 24)

Median (IQR); n (%)
(csDMTs) conventional synthetic disease-modifying therapies; (bDMTs) biologic synthetic disease-modifying therapies;
* *None / Study end include those with full 2 years follow-up and those who were administratively censored.*

4.3 Analgesic use patterns

In the overall cohort, the risk of all analgesic use increased significantly in both the first and second year post-initiation compared to the year pre-initiation (*see Table 3*). Opioids were the most commonly used analgesic, surpassed only by steroid use. We identified a pattern in the monthly incidence of analgesic use pre and post-initiation of a bDMT, highlighting that incidence of

analgesic use increased steadily in the 12 months prior to initiation and remained high throughout the subsequent 24 months of follow-up (*see Figure 2*).

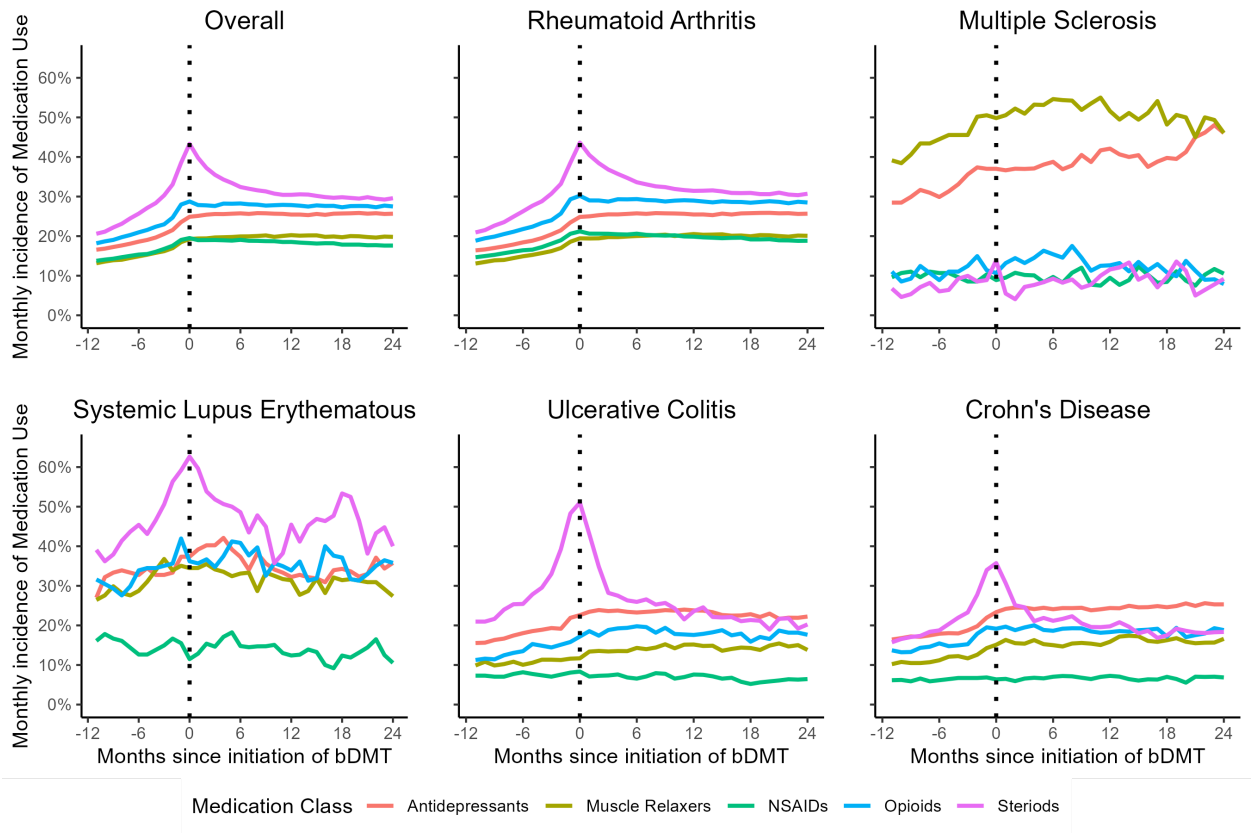

Figure 2 – Trends of analgesic medications stratified by condition.

Table 3 – Risk of analgesic use across autoimmune conditions in the first and second year period post-initiation of a biologic disease modifying therapy, compared to the one year period prior to initiation.

Sub-group	Risk period (years post-initiation)	Risk Ratio (95% CL)				
		Opioids	**NSAIDs**	**Steroids**	**Anti-depressants**	**Muscle relaxers**
Overall	Year 1	1.04 (1.03, 1.06)***	1.04 (1.02, 1.05)***	1.18 (1.16, 1.20)***	1.07 (1.06, 1.08)***	1.06 (1.04, 1.07)***
	Year 2	1.05 (1.03, 1.07)***	1.05 (1.01, 1.06)*	1.17 (1.15, 1.20)***	1.07 (1.05, 1.08)***	1.08 (1.05, 1.10)***
Crohn's Disease	Year 1	1.00 (0.91, 1.09)	0.93 (0.83, 1.06)	1.08 (1.00, 1.17)	1.07 (1.03, 1.12)*	1.07 (1.00, 1.16)
	Year 2	1.02 (0.90, 1.15)	0.98 (0.82, 1.17)	1.05 (0.95, 1.16)	1.08 (1.02, 1.15)	1.12 (1.01, 1.24)
Multiple Sclerosis	Year 1	1.00 (0.85, 1.16)	0.86 (0.71, 1.06)	1.49 (1.03, 2.15)	1.01 (0.94, 1.08)	0.99 (0.92, 1.07)
	Year 2	0.97 (0.63, 1.49)	1.08 (0.69, 1.69)	1.56 (0.97, 2.49)	0.99 (0.90, 1.08)	0.98 (0.85, 1.13)
Rheumatoid Arthritis	Year 1	1.05 (1.03, 1.07)***	1.04 (1.02, 1.06)***	1.19 (1.16, 1.21)***	1.07 (1.06, 1.08)***	1.06 (1.04, 1.08)***
	Year 2	1.05 (1.03, 1.18)***	1.04 (1.02, 1.07)**	1.18 (1.15, 1.21)***	1.07 (1.06, 1.09)***	1.08 (1.06, 1.11)***
Systemic Lupus Erythematous	Year 1	0.86 (0.68, 1.09)	0.77 (0.58, 1.01)	0.77 (0.58, 1.01)	1.01 (0.91, 1.12)	0.99 (0.87, 1.14)
	Year 2	1.00 (0.77, 1.28)	0.75 (0.54, 1.06)	0.75 (0.54, 1.06)	0.98 (0.84, 1.15)	0.97 (0.78, 1.19)
Ulcerative Colitis	Year 1	1.11 (1.00, 1.23)	1.03 (0.90, 1.17)	1.07 (0.99, 1.15)	1.04 (0.99, 1.09)	1.02 (0.94, 1.10)
	Year 2	1.10 (0.94, 1.27)	1.09 (0.92, 1.30)	1.05 (0.95, 1.15)	1.02 (0.96, 1.09)	1.05 (0.92, 1.20)

(CL) confidence limits; (NSAIDs) prescription non-steroidal anti-inflammatory drugs

RR adjusted for correlated measures through generalized estimating equation

* p-value is less than 0.05 after Bonferroni correction

** p-value is less than 0.01 after Bonferroni correction

*** p-value is less than 0.001 after Bonferroni correction

4.3.1 Overall analgesic use

The incidence rate (IR) of opioid use in the overall sample was 2.58 [95% CL 2.59, 2.57] per person-year in the pre-initiation period, 3.36 [95% CL 3.37, 3.35] per person-year in the first year post-initiation, and 3.31 [95% CL 3.37, 3.35] per person-year in the second year post-initiation. There was an increased risk of opioid use in both the first and second year post-initiation, compared to the year prior to initiation ($RR_{year\ 1}$ 1.04 [95% CL 1.03, 1.06] and $RR_{year\ 2}$ 1.05 [95% CL 1.03, 1.07], respectively), which was significant after applying the Bonferroni correction for multiple testing. Similar trends were observed for prescription NSAIDs ($RR_{year\ 1}$ 1.04 [95% CL 1.02, 1.05] and $RR_{year\ 2}$ 1.05 [95% CL 1.01, 1.06]), steroids ($RR_{year\ 1}$ 1.18 [95% CL 1.16, 1.20] and $RR_{year\ 2}$ 1.17 [95% CL 1.15, 1.20]), antidepressants ($RR_{year\ 1}$ 1.07 [95% CL 1.06, 1.08] and $RR_{year\ 2}$ 1.07 [95% CL 1.05, 1.08]), and muscle relaxers and anticonvulsants ($RR_{year\ 1}$ 1.06 [95% CL 1.04, 1.07] and $RR_{year\ 2}$ 1.08 [95% CL 1.05, 1.10]).

4.3.2 Analgesic use across subgroups

The incidence of opioid use was greatest in those initiating a bDMT for SLE (*see Supplementary Table 7*). The risk of opioid use was greater post-initiation compared to pre-initiation in all subgroups except for SLE. In the SLE subgroup, there was a reduced risk in the first year post-initiation, however confidence limits (CLs) included the null ($RR_{year\ 1}$ 0.86 [95%CLs 0.68, 1.09]).

The incidence of analgesic use tended to be greater in the female sex subgroup, although the RR did not differ meaningfully by sex (*see Supplementary Tables 7 – 11)*. Utilization patterns followed the same trends across sex aside from the incidence rate of antidepressant use, which was markedly greater in the female sex subgroup. This research must be considered in context with recent findings on the overall use of opioids in individuals with autoimmune diseases, which found a 15% annual reduction in the incidence of opioid use between 2016 and 2020[69]. However, stratification

by initiations which took place in or prior to 2015 and post-2015 did not reveal any differences for opioid use or any other analgesic assessed (*see Supplementary Tables 7 – 11).*

4.3.3 Chronic opioid use

Findings were consistent when considering chronic opioid use. The prevalence rate of chronic opioid use was 1.19 [95% CL 1.19, 1.19] per person-year in the pre-initiation period, 1.64 [95% CL 1.64, 1.65] per person-year in the first year post-initiation, and 1.73 [95% CL 1.72, 1.74] per person-year in the second year post-initiation. The increased prevalence of chronic opioid use was significant after applying the Bonferroni correction for multiple testing in both the first and second years post-initiation (prevalence ratio (PR) 1.05 [95% CL 1.04, 1.07] and 1.07 [95% CL 1.05, 1.10], respectively). The PR of chronic opioid use in the first and second year post-initiation was compatible with the null across CR, MS, SLE, and UC, and indicated a slight increase in the prevalence of chronic opioid use over time in all conditions except SLE, where there was a non-significant decrease in the first and second year post-initiation ($PR_{year\ 1}$ 0.90 [95% CL 0.78, 1.03] and $PR_{year\ 2}$ 0.83 [95% CL 0.69, 0.99]) (*see Supplementary Table 12*).

4.4 Stability analyses

Analyses which restricted the definition of incident opioid use to dispensing occurring after 30 days with no opioids on hand did not meaningfully alter overall findings (*see Supplementary Table 13*). The reduction in opioid use in the first year post-initiation of a bDMT for the SLE subgroup was not significant when considering new opioid use.

5 Discussion

In this study on the trends in analgesic use following bDMT initiation for treatment of five common autoimmune diseases in older adults insured through Medicare fee-for-service, we found a high

incidence of analgesic use both pre- and post-initiation. Although different patterns of analgesic use were observed across conditions considered, the initiation of a bDMT was not followed by any meaningful reduction in the use of analgesic medication in any subgroup.

Opioid use was common across conditions and individuals initiating a bDMT for SLE had the greatest incidence of opioid use, followed by those initiating for RA. There is limited evidence on the incidence rate of opioid use in SLE, but estimates are in line with previously published research on individuals initiating belimumab reporting a one year prevalence of 52.6%.[58] Estimates are also in line with previous work suggesting 41% of RA patients use opioids regularly and 19% are occasional users of opioids.[41] Previous research on trends in prescribing for RA found acetaminophen-hydrocodone or propoxyphene were the most common opioids between 2006 and 2014, with increases in acetaminophen-hydrocodone and tramadol following the withdrawal of propoxyphene in November 2010.[41]

Overall trends were driven by the large sample initiating a bDMT for RA, with similar trends observed in those initiating for SLE, UC, and CR. The incidence rate of prescription NSAID use was lowest for UC and CR, a finding in line with the known gastrointestinal complications associated with NSAID use.[70] While opioids are also associated with gastrointestinal complications, clinicians report recognizing the utility of opioids in treating flares from IBD.[27] Trends in those initiating for MS were unique, with a lower incidence of both steroid and opioid use and a high incidence of muscle relaxer and anticonvulsant use. These findings are in line with previous research on analgesic use in MS, where anticonvulsants are common to alleviate neuropathic pain due to the implication of nerve damage in MS etiology.[71]

In terms of analgesic changes after bDMT initiation, previous studies report a modest decrease in opioid use after initiating TNF-inhibiting bDMTs, including etanercept, and significantly lower odds of opioid use in TNF inhibiting bDMTs and a non-significant association in non-TNF inhibiting bDMTs.[43,57,72] These findings are discordant with the present study and are likely limited by unmeasured confounding due to the comparison of bDMT users to non-bDMT users without following the same individuals over time.[72] When compared to the larger body of literature suggesting a reduction of steroid use following initiation of a bDMT, the present study also presents discordant results.[57,73–75] The unadjusted incidence rate of steroid use was greater post-initiation across conditions and this increased risk persisted after accounting for correlated measures. It is possible these differences arise due to the use of prevalence to report analgesic use in previous literature, rather than incidence which takes repeated outcomes into account. This study is the first to assess changes in the incidence of analgesic use pre and post-initiation of a bDMT for MS, CR and UC and the first to include the assessment of chronic opioid use. This inclusion of chronic opioid use is particularly relevant, as long-term opioid use has not been linked with improved pain control in rheumatic disease and is complicated by the known risks of opioid use.[76,77]

Our study has several limitations to consider. Firstly, some subgroup analyses are limited by small sample sizes and a lack of generalizability to all individuals treating autoimmune disease. Due to the small sample size of individuals with conditions other than RA initiating a bDMT for the first time, overall findings are heavily weighted by this subgroup. This work also excluded the use of bDMTs for conditions which they are not FDA approved and excluded the use of biosimilars. For example, rituximab is often prescribed off label for the treatment of MS and SLE but was not included in this work. Initiations for bDMTs treating MS and SLE were uncommon in the

population of interest, as the majority of initiations occurred in individuals under the age of 66 and were excluded. Therefore, these findings are not generalizable to individuals initiating an off-label bDMT or those initiating at a younger age.

Second, there is a risk of exposure misclassification when assessing bDMT initiation in claims data. It is possible that the first initiation observed in Medicare claims does not reflect an individual's first ever exposure to a bDMT for their condition. Since most autoimmune conditions have an age of onset well before the age of Medicare eligibility (65 years), there is a high likelihood of left censoring in our data. While we cannot ensure that the first observed initiation is truly new use, this was mitigated with the inclusion of a one year pre-initiation period free of any bDMT exposure. This is a particular concern for newly approved bDMTs which do not have a specific HCPCS code for a long period of time. For example, Natalizumab was originally FDA approved for MS in 2004 but shortly removed due to safety concerns and did not have a specific HCPCs code for a two year duration until it was reintroduced in 2006. We also did not account for adherence in this analysis, as it is unclear how opioid use itself may influence bDMT adherence.

Third, there is a possibility of outcome misclassification. As with all pharmacoepidemiology studies, we are unable to know if dispensed medication is ingested as directed. We also only include medications which are billed through Medicare fee-for-service, and cannot observe over the counter analgesics not billed through Part D. This likely impacts the incidence rate of NSAID use, as all non-prescription use is excluded. Regarding the definition of chronic opioid use, there are multiple ways this exposure can be defined, and estimates may change with different exposure thresholds. However, we have selected a definition commonly used across the literature. We also do not consider dose of analgesic medications in the present study, and there may be changes in

dose which reflect an altered utilization of analgesics post-initiation of a bDMT which is not captured here.

Fourth, we are not able to make inferences about the appropriateness of analgesic use in this population, as Medicare claims data do not offer information about disease or pain severity among community-dwelling beneficiaries. For example, there is a high prevalence of concomitant fibromyalgia in RA, which was also found in the current study and may reflect a need for analgesics outside of pain caused by the autoimmune condition.[78] We also do not include information on the use of non-pharmacologic pain management strategies, such as physical therapy, which may play an important role in autoimmune disease pre- and post-initiation.

6 Conclusions

The initiation of a bDMT was not followed by the withdrawal of analgesic medication in Medicare insured older adults treating RA, MS, SL, UC and CR. This study is the first to describe analgesic use patterns pre- and post-initiation of a bDMT across several autoimmune conditions. Management of symptoms and reduction of pain are vital targets when treating autoimmune disease and initiating a bDMT alone does not appear to alter analgesic use. This indicates that clinicians must also employ additional strategies for deprescribing and pain management to reduce the use of potentially risky analgesic medications, such as opioids.

CHAPTER 2

Effect of initiating biologic disease modifying therapy versus leflunomide on the risk of opioid use discontinuation in older adults with rheumatoid arthritis

Abstract

Background: Little is known about how the transition from conventional disease modifying therapy (csDMT) use to biologic disease modifying therapy (bDMT) use impacts opioid use in older adults with rheumatoid arthritis (RA).

Objective: This study aims to make causal inference about the effect of bDMT initiation on opioid use discontinuation among prevalent opioid users.

Participants: Community dwelling US Medicare fee-for-service beneficiaries initiating leflunomide or a bDMT for treatment of RA from 2008–2019.

Measurements: 12-month risk of opioid use discontinuation in individuals who initiate a bDMT rather than leflunomide following methotrexate mono-therapy for the treatment of RA.

Results: There was no difference in the risk of opioid use discontinuation between individuals initiating leflunomide or a bDMT for prevalent and chronic opioid users (RR: 1.00 [95%CLs 0.98, 1.04] and 0.99 [95%CLs 0.88, 1.12], respectively). Findings were robust to different definitions of opioid use discontinuation (30, 60 and 90 days with no use).

Conclusions: The initiation of bDMTs in older adults with RA does not alter opioid discontinuation in prevalent or chronic opioid users. Achieving successful pain management for RA patients is more than a function of treating the underlaying condition. Rheumatologists must consider pain management in addition to disease management and coordinate care with specialist clinicians.

1 Introduction

Effective management of RA with DMTs involves not only on improving functional outcomes but also addressing pain, a critical and often persistent symptom.[77] Most treatment targets for RA center on biomarkers, functionality and disease activity scores to guide the use of DMTs, with little guidance available on pain management.[79] Pain in RA is often managed through the use of analgesics, including opioids, alongside DMTs.[77] Long-term opioid use is associated with poor disease outcomes, reduced quality of life, and increased risk of cognitive impairment, falls, fractures, and opioid use disorder.[76,77,80] Therefore, the high prevalence of opioid use in RA patients presents a substantial concern and underscores the need for effective DMTs that not only control RA symptoms but also mitigate reliance on opioids.

bDMTs are the most advanced treatments available for RA, yet their impact on opioid use remains poorly understood. The limited research on bDMT initiation and opioid use lacks appropriate controls, with descriptive studies reporting increased prevalence of opioid use among individuals using bDMTs, likely reflecting confounding by disease severity.[40,41,43,44,47–50,72] Yet, it remains unknown how initiation of bDMTs influences sustained opioid use among individuals using opioids to manage their pain. This uncertainty underscores the need to better understand the impact of RA treatments on pain management and opioid dependency.

Initial management of RA typically begins with csDMTs, advancing to a more aggressive approach with biologic bDMTs if an individual fails to achieve treatment targets on csDMTs.[22–26,79,81] In individuals with moderate to severe disease activity who are bDMT-naive, monotherapy with oral methotrexate is recommended as first-line treatment due to its well-established safety and efficacy.[22,79,82,83] However, methotrexate intolerance or failure is common, often driven by

advancing disease, inadequate response, or side effects such as gastrointestinal distress and hepatotoxicity.[82] Other csDMTs, such as hydroxychloroquine, sulfasalazine, azathioprine and leflunomide are common second-line options for treating RA, either as monotherapy or in combination with other csDMTs (i.e. dual or triple therapy).[22,79] The decision to initiate a second-line csDMT or a bDMT after methotrexate failure depends on an individual's disease severity and treatment targets, but is often up to the treating clinician's judgement.[22,79,84]

Leflunomide is the second-line csDMT most often initiated for individuals who fail to meet their treatment targets with methotrexate therapy.[85–88] Evidence from randomized clinical trials (RCTs) suggests that leflunomide elicits effects on biomarkers of RA severity which are comparable to low-dose rituximab, a biologic DMT targeting B cells via monoclonal anti-CD20 antibodies.[89] This suggests initiation of either csDMTs or bDMTs may have similar effects on disease activity, at least in early treatment. However, the impact of initiating a bDMT versus a csDMT, such as leflunomide, on pain and analgesic use is unknown, with no research to date focusing on opioid use.[90] A RCT to address this gap is unlikely due to the costs associated with bDMT use and ethical concerns about withholding available therapies for a progressive disease like RA. However, we can emulate an RCT with an augmentation design to inform decision making around therapy initiation and analgesic use.

We use a target trial emulation approach to assesses the impact of bDMT initiation on opioid use discontinuation, compared to initiation of leflunomide, in community dwelling Medicare fee-for-service beneficiaries age 65 years or older who were previously using methotrexate for the treatment of RA. This study aims to provide evidence to inform treatment strategies that optimize RA control while reducing opioid dependency.

Specific objectives:

i. Estimate the 3, 6 and 12-month risk of opioid use discontinuation in individuals who initiate a bDMT rather than leflunomide following methotrexate mono-therapy for the treatment of RA.
ii. Estimate the 6 and 12-month risk of opioid use discontinuation in individuals who initiate and remain adherent to bDMT rather than leflunomide following methotrexate mono-therapy for the treatment of RA.

2 Methods

2.1 Study Design and Data Sources

This target trial emulation study utilized an open retrospective cohort of Medicare fee-for-service beneficiaries over 65 years of age with a diagnosis of RA who initiated either a bDMT or leflunomide following methotrexate use for the first time between 2008 and 2019.

Details on the data sources involved in the creation of a person-month level dataset can be found in Chapter 1. The cohort's bDMT exposure arm was derived from the larger dataset described in Chapter 1 and restricted to individuals initiating a bDMT specifically for an RA diagnosis (*ICD-9: 714.0, 714.1, 714.2, 714.8; ICD-10: M05.X, M06.X).* An unexposed treatment strategy group consisting of individuals initiating leflunomide was included to serve as a clinical alternative for bDMT initiation.[91] The study included all bDMTs approved by the FDA for RA treatment during the study period, specifically: TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitors (abatacept), IL-6 receptor inhibitors (tocilizumab), and anti-CD20 antibodies (rituximab). Details on the code lists and inclusion criteria for bDMT administration and dispensing covered by Medicare Part D pharmaceutical drug claims

and Part B professional service claims for outpatient and other services are available in Chapter 1 (see *Section 2.4 Exposure to biologic disease-modifying therapy* and *Chapter 1: Supplementary Table 2*). The creation of the leflunomide arm followed a parallel process but screened exclusively for dispensing in Medicare Part D claims due to leflunomide's oral route of administration and singular billing through Part D. Only the first observed initiation of either bDMT or leflunomide was considered.

2.2 Specification of the target trial

We used a target trial emulation framework to assess opioid discontinuation in the year following initiation of a bDMT or leflunomide. Specifying a hypothetical RCT, often called the "target trial," and then emulating that trial using observational data has helped researchers to elucidate and overcome the challenges of using observational data to answer causal questions.[92,93] In other words, we first conceive of and describe the protocol of our the ideal hypothetical target trial we would have conducted. We then emulate this target trial in our observational data, hewing as closely as possible to the protocol.

The casual question of interest for the target trial was: *"Among older Medicare fee-for-service beneficiaries with RA and prevalent use of opioid analgesics, does the initiation of a bDMT alter the risk of opioid use discontinuation, compared to those who were eligible to initiate a bDMT, but instead initiate leflunomide as a second-line csDMT?"*. The elements of this target trial are detailed in the summary of the protocol of the target trial in *Chapter 2: Supplementary Table 1*.

2.2.1 Eligibility Criteria

Individuals with new use of leflunomide or bDMT for the treatment of RA between 2008 and 2019 were considered for eligibility. In both arms, individuals were required to have exposure to

methotrexate in the 6 months before initiation of therapy and were permitted to initiate either therapy concurrently with methotrexate due to the regularity of dual therapy with methotrexate (code lists for methotrexate are available in *Chapter 1: Supplementary Table 3*). Both oral and subcutaneous methotrexate were considered as first-line therapy, as the subcutaneous injection was historically a second-line therapy but is often adopted without prior oral therapy to limit gastrointestinal complications.[82] Eligible individuals were also required to complete self-report for pain severity at baseline and in each month of follow-up to account for possible time varying confounding due to adherence to therapy. Additional eligibility criteria include: continuous enrollment in Medicare fee-for-service (Medicare Parts A, B and D) for the 12 months prior to study start, age ≥ 66 years at time of leflunomide or bDMT initiation, and prevalent use of opioids at the time of therapy initiation. Only opioids administered in Medicare Part D claims were included (the code lists and exclusion criteria for opioid analgesics are available in *Chapter 1: Supplementary Table 5*); Medicare Part B covers methadone, buprenorphine, and naltrexone for opioid use disorder treatment, but these opioid administrations were not of interest since we were focused on the use of opioids for pain management.

2.2.2 Treatment strategies

For each eligible individual seeking a second-line treatment following methotrexate use, one of two treatments is randomly assigned: 1) initiate a bDMT, either as a monotherapy or a dual therapy with methotrexate or 2) initiate leflunomide, either as a monotherapy or a dual therapy with methotrexate. Under both treatment strategies, the decision to discontinue or initiate any additional therapies other than bDMT or leflunomide is left to the patient and their healthcare professionals' discretion. Blinding is not possible due to the differences in administration of each therapy and the risk associated with the use of immunomodulating drugs.

2.2.3 Assignment Procedures

Eligible individuals are randomized to one of the two treatment strategies without blinding.

2.2.4 Follow-up

Eligible individuals were followed from assigned therapy initiation until the first occurrence of the outcome of interest (opioid use discontinuation), the end of the 1-year follow up period, death, disenrollment from Medicare Part A, B or D, enrollment in a HMO (i.e., Medicare Advantage), entering into institutional post-acute care (PAC; e.g., in a skilled nursing facility), or the end of study period (December 31, 2019).

2.3.5 Outcomes

The primary outcome of interest opioid use discontinuation at 3-months, 6-months and 12-months post-initiation of assigned therapy. We defined opioid use discontinuation as the first occurrence of a 30-day period with no opioid exposure according to a days with medication on hand approach.[63] Most literature on chronic opioid use applies a definition of 90 days of continuous opioid use, with a 30-day allowable gap in opioid exposure. We used this allowance for a 30-day gap in exposure as a definition for opioid use discontinuation, since such a gap would qualify as the end of a chronic opioid use episode.

2.3.6 Causal contrasts of interest

We estimate the intention to treat (ITT) estimand and a per-protocol (PP) estimand.

2.3.7 Analysis Plan

For the ITT effect, a pooled logistic regression model is used to estimate the risk of opioid use discontinuation across one-year of follow-up according to the initiation of bDMT rather than

leflunomide. Our PP effect assesses sustained treatment with these treatments, as individuals are artificially censored when they become non-adherent to assigned therapy, defined as a 90-day period with no exposure to assigned therapy. Inverse probability of censoring weights (IPCW) will account for losses to follow-up.

2.3 Emulation of the target trial

2.3.1 Eligibility Criteria

The eligibility criteria when emulating the target trial are the same as the hypothetical target trial, aside from the necessity to use proxies from claims in place of primary data collection on pain severity.

2.3.2 Treatment strategies

The treatment strategies are the same as for target trial, except we will assess treatment at monthly intervals according to the days' supply of medications dispensed in Medicare Part D and B. Any overlapping days' supply was attributed as a single day of medication on hand.[63] We have no information on clinical outcomes in Medicare claims, so the initiation of a second-line csDMT or bDMT following methotrexate us is a proxy for treatment failure. The treatment strategies for the emulation are ascertained from Medicare Part D claims and Part B claims rather than being randomly assigned. Individuals in each treatment group were assumed to be exchangeable conditional on measured baseline covariates (*see section 2.3.4 Measurement of covariates*).

- Treatment strategy 1 (ITT): initiate bDMT following methotrexate use. Methotrexate may be administered orally or subcutaneously and at any therapeutic dose.
- Treatment strategy 1 (PP): initiate bDMT following methotrexate use and remain adherent to bDMT. Methotrexate may be administered orally or subcutaneously and at any therapeutic

dose. Individuals initiate a bDMT and sustain the treatment strategy. Individuals must remain adherent according to the 90-day definition for treatment discontinuation. Individuals cannot discontinue bDMT use (defined as a 90-day gap in days' supply) or initiate leflunomide (defined as dispensing of leflunomide) at any point during follow-up.

- Treatment strategy 2 (ITT): initiate leflunomide following methotrexate use. Methotrexate may be administered orally or subcutaneously and at any therapeutic dose.
- Treatment strategy 2 (PP): initiate leflunomide following methotrexate use and remain adherent to leflunomide. Methotrexate may be administered orally or subcutaneously and at any therapeutic dose. Individuals initiate leflunomide and sustain the treatment strategy. Individuals must remain adherent according to the 90-day definition for treatment discontinuation. Individuals cannot discontinue leflunomide use (defined as a 90-day gap in days' supply) or initiate a bDMT (defined as dispensing of a bDMT) at any point during follow-up.

2.3.3 Follow-up, outcomes and causal contrasts of interest

The follow-up period and outcomes assessed are the same as the target trial. The ITT and observational analog of the PP effect are the causal contrasts of interest.

The initiation of an eligible therapy marks the start of follow-up ('Time 0') in the emulated trial. Treatment compliance was defined through Medicare Part D and B claims for dispensing or administration of a bDMT or leflunomide in monthly intervals, where any person-months in compliance with our definition of adherence were flagged as adherent. Non-adherence to therapy was defined as a period of more than 90 days with no exposure to therapy according to a days with medication on hand approach. This definition has been widely used in the DMT adherence literature to indicate discontinuation of therapy.[94,95] By this definition, an individual could have up

to a 3-month break in their exposure to treatment before they were artificially censored for treatment non-adherence. Switching of therapy was the dispensing or administration of the comparator medication to an individual in either arm (e.g. dispensing of leflunomide in bDMT arm or dispensing of bDMT in leflunomide arm).

2.3.4 Measurement of covariates

All relevant baseline covariates were assessed relative to the date of therapy initiation for each individual, including age, sex, race, and region of residence. The use of methotrexate prior to therapy initiation was assessed to determine the duration of time since methotrexate discontinuation, whether methotrexate was administered orally or through injection in the past six months and the count of months with corticosteroid use in the past year. Opioid use prior to therapy initiation was classified as high or low dose according to a threshold of ≥ 50 daily morphine milligram equivalents (MME).[23–25] Comorbidities were measured in the 12 months prior to therapy initiation from MedPAR and Medicare Part B claims, including the Gagne CCI, history of chronic opioid use, and diagnosis of chronic pain, fibromyalgia, SLE, and opioid use disorder. Diagnosed comorbidities were assessed through ICD-9 and ICD-10 codes in MedPAR and Medicare Part B claims (see code list in Chapter 1: *Supplementary Table 15*).

Time-varying covariates were assessed at the start of each person-month contributed by an eligible individual. Healthcare encounters in the 30 days prior to the start of each person-month were assessed, including the count of hospitalizations, claims for corticosteroids in Part B or Part D (including: cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone) and the number of unique medications dispensed in Part D. The count of medications dispensed were coarsened into a polypharmacy indicator variable to classify those with less than 5, ≥5 and < 10, or ≥10 medications dispensed.[96,97]

2.3.5 Statistical analyses

We estimated the observational analogues of the ITT effect (initiation of either therapy) and a PP effect (sustained use of either therapy). The 3, 6 and 12-month RR of opioid use discontinuation was estimated using inverse probability of treatment weights (IPTWs) in discrete time marginal structural models with covariates, exposure and outcome assessed at the start of each month.[98] We estimated stabilized weights using logistic regression, including: 1) baseline IPTWs to achieve a reasonable approximation of exchangeability at baseline and 2) time-varying IPTWs to account for selection bias induced by artificial censoring.

For the ITT analysis, models were adjusted only for baseline characteristics (*see Supplementary Figures 1-2*). For the PP analysis, the model was adjusted for baseline characteristics and treatment adherence, with any person-months post-discontinuation of therapy being artificially censored. The use of IPCW was considered to account for censoring due to switching therapy, death, disenrollment or entering into PAC in both analyses. However, a very small incidence of these censoring events were observed across eligible person-months and IPCWs were not employed due to the risk of large and unstable weights. Although 400 individuals experienced either switching therapy, death, disenrollment or entering into PAC before the end of 1-year of follow-up, only 34 individuals experienced one of these events before the outcome of interest when using the most conservative definition for opioid use discontinuation (90 days with no exposure).

The baseline covariates incorporated in modeling probability of treatment for the baseline IPTW include: individual demographics (age, sex, race, region of residence, year of therapy initiation), comorbidities (CCI, SLE, fibromyalgia, chronic pain, opioid use disorder), and pre-initiation medication use (time since methotrexate failure, methotrexate by injection, count of months with

corticosteroid use in past year, high dose opioid use at initiation, chronic opioid use at initiation). For the modeling of IPTWs, the time-varying covariates for treatment adherence include: 30-day healthcare utilization (hospitalizations, polypharmacy score) and proxies for pain severity (daily MME, corticosteroid exposure).

Overall stabilized IPTWs were calculated as the product of baseline IPTWs and the time-varying IPTWs. Stabilized baseline IPTWs were calculated as follows using only a subset of the data from Time 0 for both ITT and PP approaches:

$$W_{t=0} = \frac{\Pr\left(A(t=0)=a\right.}{\Pr\left(A(t=0)=a|L(t=0)\right.}$$

Where:

t = Person-month

A(*t=0*) = Exposure for at baseline (person-month *t=0)*

L(*t=0*) = Vector of baseline (individual demographics including age, comorbidities, pre-initiation medication use) and covariates at baseline (person-month *t=0)*

Stabilized time-varying IPTWs were calculated as the ratio of the cumulative probability of receiving the observed treatment, conditional on person-month (number of months post-initiation), age, and having received treatment in all prior person-months (i.e. the numerator) and the cumulative probability of receiving the observed treatment, conditional on having received treatment in all prior person-months and all baseline and time-varying covariates from the prior person-month (i.e. the denominator).[99] The outcome of treatment non-adherence can only be observed after month 3 post-initiation due to our requirement for a 90-day period of being unexposed to treatment. Therefore, we modeled the time-varying treatment weights from month 4

onwards and observations before month 4 were assigned a weight of 1 for probability of treatment. Weights were calculated as follows:

$$\text{SW}_t = \prod_{t \leq T} \frac{\Pr\left(A(t)=a_t | A(t-1), age, T \geq t\right)}{\Pr\left(A(t)=a_t | A(t-1), L(t), T \geq t\right)}$$

Where:

t = Person-month

T = Person-month of event

A(*t*) = Exposure for person-month *t*

A(*t - 1*) = Exposure for person-month prior to person-month *t*

L(*t*) = Vector of baseline (individual demographics including age, comorbidities, pre-initiation medication use) and time-varying (30 day healthcare utilization, proxies for pain severity) covariates at person-month *t*

For months 0 - 4 post-initiation, overall stabilized IPTWs were truncated at the 99.5th percentile, month 5 at the 99th, months 6 - 7 at the 98.5th percentile, months 8-9 at the 98th and months 10 - 12 at the 97th percentile according to the observed distribution within each person-month to account for extreme weights in later person-months when few individuals remained adherent to assigned therapy (*see Supplementary Tables 16 – 17*).[99,100]

The risk of opioid use discontinuation at 3, 6 and 12 months was modeled in a discrete time model with logistic regression. The model included interactions between exposure and time, including a cubic term for time to allow for flexibility in the model. Individuals were followed from therapy initiation up to 1 year or until the outcome of opioid use discontinuation, censoring or treatment

discontinuation (PP analysis only). The 95% CLs were estimated using non-parametric bootstrapping with 500 replicates.

2.3.6 Subgroup analysis

A subgroup analysis was conducted for chronic opioid users, as treatment with bDMT or leflunomide may have a different relationship with discontinuation of chronic opioid use in cases of chronic opioid use. Weights for baseline covariates and treatment adherence were modeled separately for the chronic opioid use sub analysis, excluding chronic opioid use at initiation.

2.3.7 Stability analysis

We aimed to conduct stability analysis with 3 different definitions for opioid use discontinuation across analyses, requiring a 30-day, 60-day and 90-day gap in opioid exposure according to days with medication on hand. Weights for baseline covariates from primary analyses were applied for the ITT and PP stability analyses. For the treatment time-varying treatment weights in PP analysis, the models were fit separately in the resulting data sets for all three definitions of opioid use discontinuation. This was done because the use of a longer duration of opioid discontinuation to qualify as discontinuation resulted in longer follow-up times with more opportunities for non-adherence, resulting in more extreme weights and therefore increasing the likelihood of findings being compromised due to selection bias (*see Supplementary Tables 18, 21, and 23*). Truncation of extreme weights were conducted as described for primary analyses.

3 Ethics

This work received Data Use Agreement approval from The Centers for Medicare & Medicaid Services and was determined as exempt from 45 CFR 46 regarding the inclusion of human

participants in research by the Brown University Institutional Review Board (protocol 2022003502).

4 Results

4.1 Study Population

Of 682,260 eligible individuals meeting the diagnosis criteria for RA, 53,835 (7.89%) were treated with leflunomide and 58,344 (8.55%) were treated with a bDMT between 2008 and 2019. Of those initiating leflunomide, 3,803 (7.06%) met the criteria for new use following treatment with methotrexate and 1,198 (31.50%) were prevalent users of opioids at the time of initiation. Of those initiating a bDMT, 8,732 (14.96%) met the criteria for new use following treatment with methotrexate and 2,769 (31.71%) were prevalent users of opioids at the time of initiation. The final cohort consisted of 3,967 eligible individuals (*see Figure 3*). Measured baseline covariates were generally well balanced between bDMT and leflunomide initiators according to standardized mean differences (SMD) <0.10.[101] Initiators of bDMTs were slightly younger than leflunomide initiators and were more likely to initiate a bDMT as a concurrent therapy with methotrexate, compared to leflunomide initiators (*see Table 4*).

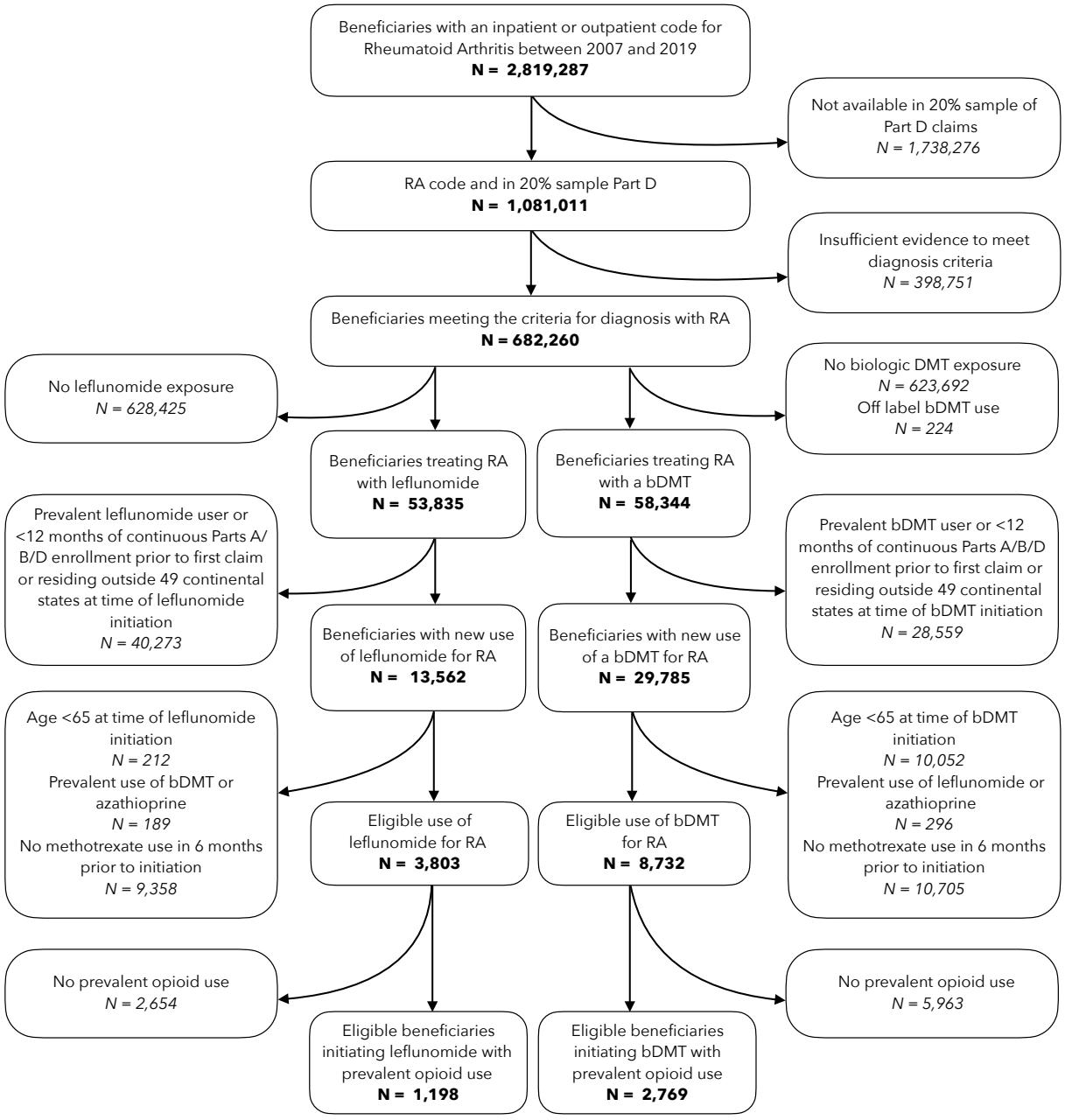

Figure 3 – Chapter 2 Study inclusion flow chart.

Table 4 – Demographics of Medicare beneficiaries initiating biologic disease modifying therapy or leflunomide for treatment of RA following methotrexate use, 2008-2019.

	Overall N = 3,967	Leflunomide N = 1,198	bDMT N = 2,769	SMD*
Age	71.0 (68.0, 76.0)	72.0 (69.0, 77.0)	71.0 (68.0, 76.0)	0.16
Sex				0.01
Female	3,158 (80%)	957 (80%)	2,201 (79%)	
Male	809 (20%)	241 (20%)	568 (21%)	
Race				0.11
White	3,270 (82%)	982 (82%)	2,288 (83%)	
Black	299 (7.5%)	111 (9.3%)	188 (6.8%)	
Hispanic	279 (7.0%)	71 (5.9%)	208 (7.5%)	
Asian/Pacific Islander/American Indian/Alaska Native/Other/Unknown	119 (3.0%)	34 (2.8%)	85 (3.1%)	
Region				0.18
Midwest	822 (21%)	309 (26%)	513 (19%)	
Northeast	521 (13%)	135 (11%)	386 (14%)	
South	1,923 (48%)	544 (45%)	1,379 (50%)	
West	701 (18%)	210 (18%)	491 (18%)	
Year				0.23
2008	240 (6.0%)	52 (4.3%)	188 (6.8%)	
2009	202 (5.1%)	62 (5.2%)	140 (5.1%)	
2010	180 (4.5%)	47 (3.9%)	133 (4.8%)	
2011	209 (5.3%)	55 (4.6%)	154 (5.6%)	
2012	288 (7.3%)	78 (6.5%)	210 (7.6%)	
2013	345 (8.7%)	117 (9.8%)	228 (8.2%)	
2014	395 (10.0%)	108 (9.0%)	287 (10%)	
2015	400 (10%)	105 (8.8%)	295 (11%)	
2016	486 (12%)	187 (16%)	299 (11%)	
2017	439 (11%)	138 (12%)	301 (11%)	
2018	408 (10%)	147 (12%)	261 (9.4%)	
2019	375 (9.5%)	102 (8.5%)	273 (9.9%)	
CCI	1.00 (0.00, 3.00)	1.00 (1.00, 3.00)	1.00 (0.00, 3.00)	0.07
Comorbidities				
SLE	366 (9.2%)	115 (9.6%)	251 (9.1%)	0.02
Fibromyalgia	415 (10%)	123 (10%)	292 (11%)	-0.01
Chronic pain	1,046 (26%)	339 (28%)	707 (26%)	0.06
Opioid Use Disorder	189 (4.8%)	63 (5.3%)	126 (4.6%)	0.03
Time since methotrexate failure				0.52
Initiated as dual therapy	3,032 (76%)	706 (59%)	2,326 (84%)	
1 - 3 months since methotrexate failure	661 (17%)	356 (30%)	305 (11%)	
> 3 months since methotrexate failure	274 (6.9%)	136 (11%)	138 (5.0%)	
Methotrexate by injection†	833 (21%)	234 (20%)	599 (22%)	-0.05
High dose opioid use at initiation‡	763 (19%)	238 (20%)	525 (19%)	0.02
Chronic Opioid Use	1,595 (40%)	506 (42%)	1,089 (39%)	0.06

(CCI) combined comorbidity index; (SLE) Systemic Lupus Erythematosus; (bDMT) biologic disease modifying therapy; (SMD) standardized mean difference; (MME) morphine milligram equivalents

* Standardized Mean Difference.[102,103]

† At least one dose of methotrexate administered by injection in the 6 months before initiation of therapy.

‡ High dose defined as over 50 MME per day.[23–25]

4.2 Opioid use discontinuation among all individuals with prevalent use

When we required a 30-day period to define opioid use discontinuation, the mean time to discontinuation was 1.68 months (standard deviation [SD]: 2.03); 1.64 months (SD: 1.97) in leflunomide initiators and 1.69 months (SD: 2.05) in bDMT initiators. The ITT showed no effect of bDMT initiation on the risk of opioid discontinuation across the year of follow-up, with RRs at the null for months 3, 6 and 9 and indistinguishable cumulative incidence curves (*see Table 5 and Figure 4*).

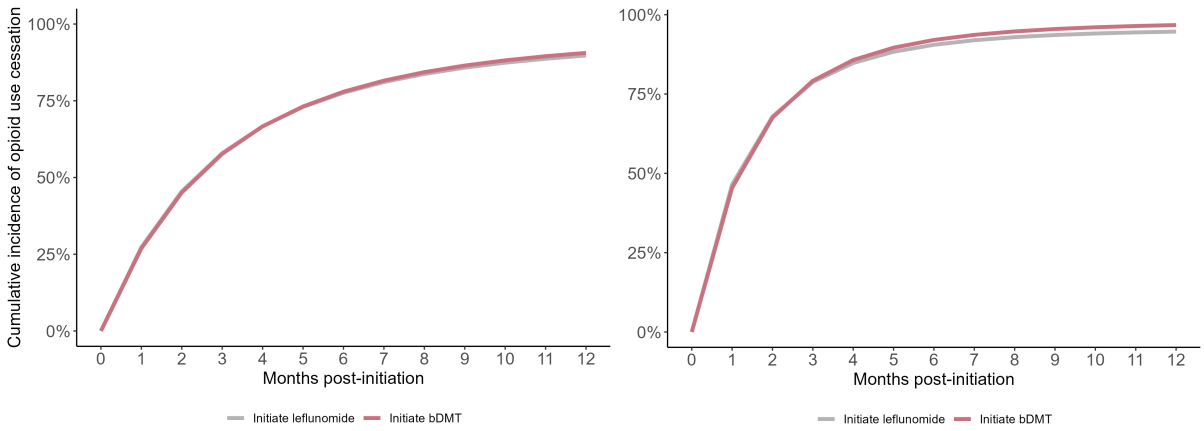

Figure 4 – Cumulative incidence curves for opioid use discontinuation among all individuals with prevalent opioid use (left: ITT effect; right: PP effect)

The PP effect showed a greater risk of discontinuation, but the 6-month and 12-month RR of discontinuation also showed no effect at RR: 1.02 [95%CLs: 0.98, 1.06] and RR: 1.02 [95%CLs: 0.99, 1.09], respectively.

Table 5 – Risk of opioid use discontinuation among all Medicare beneficiaries treating RA with a bDMT versus leflunomide, 2008-2019.

	Risk in Treatment 0: leflunomide (95%CLs)	Risk in Treatment 1: bDMT (95%CLs)	Risk Difference, per 1,000 person-trials (95%CLs)	Risk Ratio (95%CLs)
ITT effect				
3-month Discontinuation	57.94% (54.36, 61.05)	57.71 (55.54, 59.77)	-2.33 (-44.29, 40.05)	1.00 (0.93, 1.07)
6-month Discontinuation	77.62% (74.67, 80.10)	77.95% (76.17, 79.52)	3.34 (-29.39, 38.78)	1.00 (0.96, 1.05)
12-month Discontinuation	89.74% (87.35, 91.76	90.61% (89.03, 91.91)	8.73 (-18.42, 34,47)	1.00 (0.98, 1.04)
PP effect				
6-month Discontinuation	90.51% (86.89, 93.43)	92.04% (90.58, 93.97)	15.30 (-15.00, 54.33)	1.02 (0.98, 1.06)
12-month Discontinuation	94.67% (89.74, 97.35)	96.74% (94.80, 99.01)	20.64 (-9.42, 7785)	1.02 (0.99, 1.09)

(ITT) intention to treat; (PP) per-protocol

4.2 Opioid use discontinuation among individuals with chronic opioid use

Among individuals with chronic opioid use prior to initiation of therapy, the mean time to experiencing opioid use discontinuation was 1.83 months (standard deviation [SD]: 2.21). Among those initiating a bDMT, the mean time was 1.81 months (SD: 2.20) and among those initiating leflunomide the mean time was 1.84 months (SD: 2.22). In analyses for the ITT effect among those with chronic opioid use, the risk for discontinuation by month 3 was low for both unexposed and exposed at 28.58% and 25.88%, respectively. The RR of discontinuation was below the null at months 3 (0.91 [95%CLs 0.69, 1.24]) and 6 (0.94 [95%CLs 0.78, 1.15]), and settled at the null by month 12 (*see Table 6*).

Table 6 – Risk of chronic opioid use discontinuation among all Medicare beneficiaries treating RA with a bDMT versus leflunomide, 2008-2019.

	Risk in Treatment 0: leflunomide (95%CLs)	Risk in Treatment 1: bDMT (95%CLs)	Risk Difference, per 1,000 person-trials (95%CLs)	Risk Ratio (95%CLs)
ITT effect				
3-month Discontinuation	28.58% (21.73, 35.27)	25.88% (21.94, 30.12)	-27.05 (-105.87, 51.53)	0.91 (0.69, 1.24)
6-month Discontinuation	49.06% (40.60, 56.43)	46.09% (40.62, 51.19)	-29.73 (-123.06, 60.86)	0.94 (0.78, 1.15)
12-month Discontinuation	74.19% (66.24, 79.74)	73.17% (67.38, 78.52)	-10.11 (-92.05, 83.26)	0.99 (0.88, 1.12)
PP effect				
6-month Discontinuation	93.10% (88.03, 97.55)	92.38% (81.64, 100)	-7.21 (-122.91, 76.84)	0.99 (0.87, 1.09)
12-month Discontinuation	94.49% (90.63, 99.00)	95.91% (83.56, 100)	14.23 (-132.09, 78.75)	1.02 (0.86, 1.09)

(ITT) intention to treat; (PP) per-protocol

4.3 Stability analyses of varying the definition for opioid use discontinuation

Stability analyses of the ITT approach utilizing an opioid use discontinuation definition of 60-days unexposed to opioids similarly found bDMT initiation had no effect on opioid use discontinuation among individuals with prevalent opioid use (*see Supplementary Table 18*). Among those with chronic opioid use, the RR for opioid use discontinuation was increased for the 3-month and 6-month RRs of discontinuation at 1.42 [95%CLs 0.91, 2.65] and 1.28 [95%CLs 0.91, 1.98], respectively. However, estimates remained non-significant and leveled off to a RR of 1.06 [95%Cls 0.87, 1.32] by month 12 (*see Table 6*). The use of a discontinuation definition of 90-days unexposed to opioids further attenuated effect estimates, though estimates remained non-significant (*see Supplementary Tables 19 – 23*).

5 Discussion

Findings suggest the initiation of a bDMT for the treatment of RA among individuals with prevalent opioid use has no effect on opioid use discontinuation, compared to the initiation of leflunomide. This is the first work to assess bDMT initiation and opioid use discontinuation using a target trial design and an appropriate clinical alternative for a head-to-head comparison. We applied a target trial emulation approach to assess initiation of a bDMT versus initiation of leflunomide as a clinical alternative. The clinical alternative group consisted of individuals who would have been eligible to initiate a bDMT but instead initiated leflunomide as a second-line csDMT. By requiring use of methotrexate therapy prior to new use of either bDMTs or leflunomide, we aligned the exposed and unexposed at a similar clinical treatment point in their RA management trajectory to reduce confounding. The use of leflunomide as a clinical alternative also allowed the unexposed group to be bound by the same requirements for adherence and revealed no significant effect of bDMT use, even under our definition of adherence to treatment.

A 2023 paper by Sood et al. also assessed the effect of the initiation of DMTs on prevalent opioid use in the Medicare ensured population with RA, finding significantly reduced odds of opioid use following initiation of csDMTs and TNF-inhibiting bDMTs (*adalimumab, certolizumab, etanercept, golimumab, infliximab*).[72] However, the reduction observed with initiation of non-TNF bDMTs (*abatacept, rituximab, sarilumab, tocilizumab, baricitinib, tofacitinib, upadacitinib*) was not significant.[72] This work compared the odds of post-DMT opioid dispensing in DMT users to non-DMT users, increasing likelihood for unmeasured confounding, and did not account for adherence to therapy or changes to therapy over follow-up. It is possible that bDMT initiation may confer different effects on treatment adherence, pain and opioid use according to molecular target.[104–106] Further subgroup analysis by specific bDMT initiated or molecular target may reveal different risks for opioid use discontinuation. However, small sample sizes limited our ability to run further subgroup analyses. This analysis also did not consider whether a bDMT was initiated after triple therapy, which may confer different effects than bDMT monotherapy or dual therapy with methotrexate.[107] A previous RCT suggested that initiation of triple therapy (methotrexate alongside sulfasalazine and hydroxychloroquine) reduced biomarkers for RA disease activity over bDMT (*infliximab*) initiation but it is unknown how this translates to functional outcomes, such as reliance on analgesics.[107] A 2019 paper by Black et al. found that bDMT use was associated with a decrease in opioid initiation and a decreased probability of opioid use discontinuation in prevalent opioid users.[108] However, this finding relied on within-individual comparisons and did not consider adherence to therapy. Across all analyses, the PP effect showed higher risk of discontinuation of opioids compared to the ITT effect in both the exposed and unexposed. This finding aligns with prior research on the benefits of good bDMT adherence on RA functional outcomes and opioid use.[49]

This work has several limitations to consider. First, this analysis does not offer insights on the risk of recurrence of opioid use or chronic opioid use after discontinuation. These findings offer short term insights on analgesic use post-initiation of therapy but do not account for the longer term effects of bDMT initiation on opioid use among prevalent users of opioids. Second, adherence to DMTs for RA is known to be poor even among individuals with Medicare coverage.[104,109] This results in challenges when requiring adherence for a PP estimate. We applied a commonly used definition for adherence to DMTs which allows for large gaps in use before non-adherence is defined and still faced challenges with low adherence. We used truncation liberally to achieve reasonable variance in exchange for bias reduction, particularly for later observations (*see Supplementary Figures 3 – 4*). This truncation of weights likely resulted in the re-introduction of selection bias from administrative censoring.[99] There are also unanswered questions around the impact of analgesic use on bDMT adherence itself (*see Chapter 3*). Third, adherence to assigned therapy may be driven by different mechanisms between bDMTs and leflunomide which are not captured in the binomial model used to estimate IPTWs. The use of bDMTs often involves self-injection or administration by a health care provider, increasing the burden of receiving treatment, while leflunomide is taken orally. Furthermore, the use of bDMTs is often cost prohibitive and treatment access restrictions (e.g. requirements for prior authorization and high out-of-pocket costs) are associated with lower adherence.[110–114] It is unknown how individual Part D plan tiering for Medicare beneficiaries may influence adherence and this analysis does not account for out of pocket expenditure as a barrier to bDMT adherence. The use of two marginal models to predict adherence to bDMT or leflunomide separately may account for these differences in adherence for future work. Forth, while leflunomide was the most commonly used second-line csDMT in this population, it is not the only csDMT available. Individuals may be escalated to triple therapy after

methotrexate failure, but it is challenging to identify the initiation of triple therapy in claims data because additional DMTs are often introduced in stages. Initiation of azathioprine could be used in a stability analysis, but it is more commonly used as a third-line treatment for RA and may reflect cases where both methotrexate and leflunomide have failed but an individual is not able to initiate a biologic, limiting exchangeability. Finally, our study is limited by both exposure and outcome misclassification due to the reliance on claims data from medication dispensing to classify adherence to treatment and the outcome of opioid use discontinuation. It is possible an individual does not take their therapy as directed or does not use opioid analgesics after they are dispensed, resulting in an overestimation of both adherence to therapy (exposure) and time to discontinuation of opioids (outcome).

6 Conclusions

The initiation of bDMTs in older adults with RA does not alter opioid use in prevalent or chronic users. Effective pain management in patients with RA requires more than simply controlling disease activity with bDMTs. Analgesic use in RA is persistent despite the widespread use of bDMTs and underscores the need for a more comprehensive approach. Pharmacologic strategies and non-pharmacologic interventions must be integrated into treatment plans to ensure optimal care. Future research should focus on refining and personalizing pain management strategies to improve outcomes for this patient population.

CHAPTER 3

Opioid versus prescription NSAID use and discontinuation and switching of biologic disease modifying therapy in older adults with rheumatoid arthritis

Abstract

Background: Effective management of rheumatoid arthritis (RA) involves balancing biologic disease-modifying therapies (bDMTs) with pain control strategies. While opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used analgesics, the impact of these treatments on bDMT adherence remains underexplored.

Objective: This study evaluates the comparative effects of opioid versus NSAID use on bDMT discontinuation and switching in Medicare fee-for-service beneficiaries aged 66 years and older initiating bDMT for RA from 2008–2019.

Participants: Community dwelling US Medicare fee-for-service beneficiaries treating RA with a bDMT and initiating opioids or NSAIDS.

Measurements: Risk of bDMT discontinuation and switching in the 12 months post-initiation of a dDMT.

Methods: We conducted a target trial emulation study using the clone censor weight approach to assess two regimens for pain treatment in older adults treating RA with bDMT therapy: initiate opioid therapy within 3 months of bDMT initiation and sustain treatment and initiate NSAID therapy within 3 months of bDMT initiation and sustain treatment.

Results: Sustained opioid use was associated with a higher risk of bDMT discontinuation at 12 months (RR: 1.51, 95% CI: 1.05–2.96) compared to NSAID use, though the risk of therapy switching was similar between groups. Sensitivity analyses supported these findings, emphasizing the potential role of confounders such as pain severity.

Conclusions: Pain management strategies significantly influence bDMT adherence in older adults with RA. These findings highlight the need for integrated care approaches that balance effective pain control with sustained bDMT use.

1 Introduction

Effective management of RA often requires a multifaceted approach, including the use of DMTs and various analgesics to manage disease activity and pain. bDMTs are highly effective in targeting specific components of the immune system to control autoimmunity and chronic inflammation in severe cases of RA.[22] However, since treatment with bDMTs is not curative, their effectiveness in preventing exacerbations and slowing disease progression relies on good adherence to therapy and the continuity of treatment.[94] A reduction in bDMT adherence is a poor outcome for patients, as it is linked to disease progression, treatment failure, and increased medical care expenditure.[115,116]

One of the primary therapeutic goals of bDMTs is to control symptoms which interrupt daily life, with severe joint pain being a major symptom in RA. However, breakthrough pain is still common in older adults with RA and there is a high prevalence of opioid use among bDMT users.[40,41,44,47–50] Continued reliance on opioids during bDMT use may present significant challenges, as literature suggests opioid use can negatively impact adherence to other medications for chronic disease management.[53,117] Opioid use is also thought to reduce the effectiveness of bDMTs and is associated with a reduction in time to starting targeted treatments among patients with RA.[51,118,119] While some factors associated with good bDMT adherence are widely researched, the impact of opioid use is understudied[41–44,52,108]. Available evidence links chronic opioid use with reduced adherence to bDMTs in patients with CR but excludes other common diagnoses such as RA.[51–53]

Pharmacologic pain management is a necessity for many individuals living with RA and it is unclear which analgesics offer the best safety outcomes in this population. The comparative safety between opioids and NSAIDs is of particular interest in light of RCT evidence suggesting that opioids and NSAIDs confer equivalent control of osteoarthritis pain after 12 months of use.[120]

Findings on the effects of opioid and NSAID use on bDMT adherence could inform clinical guidelines and support healthcare providers in optimizing treatment strategies for older adults with RA, aiming to enhance both their physical function and overall quality of life. Given the complexities of polypharmacy and the unique challenges faced by older adults, it is essential to assess how analgesic use may affect adherence to bDMTs. In this vulnerable population with high rates of analgesic use, it is concerning if the treatment of pain interferes with adherence to necessary therapeutics for underlaying conditions.

This study emulates a target trial to evaluate the impact of opioid use, compared to prescription NSAID use, on the discontinuation and switching of bDMT therapy in older adults with RA. The cohort includes community dwelling Medicare fee-for-service beneficiaries aged 66 years and older who initiated bDMT for the treatment of RA between 2008 and 2019.

Specific objectives:

iii. Estimation of the 12-month risk of bDMT discontinuation in individuals who begin treatment with opioid analgesics rather than prescription NSAIDs within 3 months of bDMT initiation and sustain their analgesic treatment strategy.

iv. Estimation of the 12-month risk of bDMT switching in individuals who begin treatment with opioid analgesics rather than prescription NSAIDs within 3 months of bDMT initiation and sustain their analgesic treatment strategy.

2 Methods

2.1 Data Source

This study utilized a retrospective open cohort of Medicare fee-for-service beneficiaries ≥ 66 years of age with a diagnosis of RA who initiated a bDMT for the first time between 2008 and 2019. This cohort is a subset of the larger dataset compiled in *Chapter 1*, limited to those initiating a bDMT for an RA diagnosis (*ICD-9: 714.0, 714.1, 714.2, 714.8; ICD-10: M05.X, M06.X*). Exposure to bDMTs was assessed through Medicare Part D and Part B claims, depending on whether the bDMT was self-administered or administered by a healthcare professional, respectively. Claims for a bDMT with FDA approval to treat RA were considered, including the following: TNF inhibitors (*etanercept, adalimumab, infliximab, golimumab, certolizumab pegol*), T cell costimulatory inhibitors (*abatacept*), IL-6 receptor inhibitors (*tocilizumab*), and anti-CD20 antibodies (*rituximab*). Specific criteria for valid HCPCS codes and FDA approval dates are detailed in *Chapter 1* and its supplementary materials. Individuals were required to be bDMT-naïve for 365 days to qualify as new users.

2.2 Specification of the target trial

We adopted a target trial emulation framework to estimate the 12-month risk of bDMT discontinuation following initiation of a bDMT for the treatment of RA. This approach mirrors the design of the RCT we would theoretically conduct using observational data to minimize the biases which often limit observational studies.[92,93]

Due to the known hazards of opioid use, we emulated a pragmatic trial where individuals are randomized to receive analgesic medication to take as needed. The casual question of interest was: *"Among Medicare fee-for-service beneficiaries initiating a bDMT for the treatment of RA, does*

the initiation of a sustained analgesic treatment strategy with opioids in the first 3 months of new use of a bDMT increase the risk of bDMT discontinuation within 12 months, compared to the initiation of a sustained analgesic treatment strategy with prescription NSAIDs?". The elements of this target trial are detailed in the target trial emulation framework in *Supplementary Table 1*.

2.2.1 Eligibility Criteria

The target trial includes new users of bDMTs for treatment of RA to ensure initiation reflects first exposure without prior therapy adjustments due to adverse events. Eligibility criteria include: initiation of a bDMT with RA approval for the treatment of RA, self-reported moderate to severe pain which requires analgesic therapy, age ≥ 66 years, continuous enrollment in Medicare fee-for-service (Medicare Parts A, B and D) for the 12 months prior to study start, no HMO membership, no history of contraindications to treatment with opioids (including: opioid use disorder, substance use disorder), no history of contraindications to treatment with NSAIDs (including: history of gastric bleeding or diagnosis with UC or CR), and no prevalent use of opioids or prescription NSAIDs in the 30 days prior to bDMT initiation. Only first observed initiations were considered.

2.2.2 Treatment strategies

Individuals with self-reported moderate to severe pain were assigned to one of the two treatment strategies: 1) initiation of sustained opioid therapy within three months of bDMT initiation or 2) initiation of sustained prescription NSAID therapy within three months of bDMT initiation. An eligible individual can be randomized to either treatment strategy, but blinding is not possible due to the known risks associated with opioid use.

2.2.3 Follow-up

Each eligible individual is followed from bDMT initiation until the first occurrence of discontinuation, switching, end of the 12-month follow up period, death, unenrollment from Medicare Part A, B or D, enrollment in an HMO, or the end of study period (December 31, 2019).

2.3.4 Outcomes

The primary outcome of interest is the 12-month risk of bDMT discontinuation, defined as a 90-day gap in exposure to a bDMT. Poor adherence may lead to early treatment failure and increase therapeutic cycling, so switching therapies was also considered. The secondary outcome of interest is the 12-month risk of switching to a new bDMT, defined as dispensing of a different bDMT before the end of current bDMT days' supply or within 90 days of the end of the previous bDMT days' supply. Switching of bDMT was not considered discontinuation if the new bDMT was initiated within 90 days of the prior days' supply ending. A 90-day window of treatment interruption was selected in keeping with previously published literature on bDMT adherence and discontinuation.[94,95,121] Once a discontinuation or switching occurred, that beneficiary was not able to contribute further person-time for either analysis.

2.3.5 Causal contrasts of interest

The analgesic treatment strategies are compared by estimating a PP effect. The intention-to-treat effect was estimated in stability analyses.

2.3.6 Analysis Plan

A pooled logistic regression model is used to estimate the 12-month risk of bDMT discontinuation and bDMT switching. IPCWs will account for losses to follow-up.

2.3 Emulation of the target trial

2.3.1 Eligibility Criteria

The eligibility criteria when emulating the target trial are the same as the hypothetical target trial, aside from the requirement for self-report of moderate to severe pain. Since Medicare claims do not supply information on pain severity, we are unable to assess if eligible individuals are experiencing moderate to severe pain in our emulated trial.

2.3.2 Treatment strategies

The treatment strategies deviate from the target trial, since the medication exposures for the emulation are ascertained from Medicare Part D pharmaceutical drug claims rather than being randomly assigned. The code lists and exclusion criteria for opioid analgesics and prescription NSAIDs are available in *Chapter 1: Supplementary Table 5*. We used a 3 month grace period to ascertain which individuals were initiating treatment with either opioids or prescription NSAIDs after bDMT initiation. Treatment assignment was assumed to be exchangeable conditional on measured baseline and select time-varying covariates (*see section 2.3.4 Measurement of covariates*).[122,123]

- Treatment strategy 1: initiate analgesic therapy with opioids in the 3 months post-bDMT initiation and sustain use of opioids. Individuals cannot discontinue opioids (defined as a 30-day gap in days' supply) or initiate concurrent analgesic therapy (defined as dispensing of a prescription NSAID) at any point during follow-up.

- Treatment strategy 2: initiate analgesic therapy with prescription NSAIDs in the 3 months post-bDMT initiation and sustain use of prescription NSAIDs. Individuals cannot discontinue

prescription NSAIDs (defined as a 30-day gap in days‘ supply) or initiate concurrent analgesic therapy (defined as dispensing of an opioid) at any point during follow up.

2.3.3 Follow-up, outcomes and causal contrasts of interest

The follow-up period and outcomes assessed are the same as the target trial. The observational analog of the PP effect is the causal contrast of interest since we are assessing a sustained treatment strategy. An ITT effect is estimated in stability analyses.

2.3.4 Measurement of covariates

All relevant baseline covariates were assessed relative to the date of bDMT initiation for each individual, including age, sex, race, and region of residence. Comorbidities were measured in the 12 months prior to baseline, including the Gagne CCI, diagnosis of chronic pain and diagnosis of fibromyalgia. Diagnosis of chronic pain and fibromyalgia were assessed through ICD-9 and ICD-10 codes in MedPAR and Medicare Part B claims (see code list in *Supplementary Table 15*).

Time-varying confounders were assessed within each person-month contributed by an eligible individual. Healthcare encounters in the 30 days prior to the start of each person-month were assessed, including the count of hospitalizations, claims for corticosteroids in Part B or Part D (including: cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone) and the number of unique medications dispensed in Part D. The count of medications dispensed were coarsened into a polypharmacy indicator variable to classify those with less than 5, ≥5 and < 10, or ≥ 10 medications dispensed.[96,97]

2.3.5 Statistical analyses

Details on the creation of a person-month level dataset spanning the year pre and post bDMT initiation can be found in *Chapter 1*. The initiation of a bDMT marks ‘Time 0’ in the emulated

trial. Compliance with each treatment strategy was assessed in a 3-month grace period post bDMT initiation for each eligible individual. Treatment compliance was defined through Medicare Part D claims for dispensing of opioids or prescription NSAIDS in monthly intervals, where any person-months with opioids or prescription NSAIDS on hand were flagged. Individuals dispensed an opioid or prescription NSAID in the month prior to bDMT initiation were considered prevalent users and were excluded.

The clone-censor-weight approach was used to account for the misalignment between start of follow-up at bDMT initiation and ascertainment of compliance with each treatment strategy after the 3-month grace period.

2.3.5.1 Cloning

In the cloning step, all eligible individuals with no opioid or prescription NSAID exposure in the month prior to bDMT initiation were assigned to both treatment strategies at bMDT initiation, effectively cloning the eligible sample and ensuring exchangeability in both treatment arms as the treatment arms differ only in their treatment assignment.[124–127] This cloning step eliminates the immortal time bias which would otherwise arise due to a misalignment between Time 0 and the ascertainment of treatment compliance at the end of the 3-month grace period.[126]

2.3.5.2 Censoring

Clones were censored when their observed exposures deviated from the assigned strategy for that treatment arm. After the 3-month grace period, all individuals in compliance with either of the two treatment strategies have been identified, so no duplicated individuals are retained.

Under the opioid treatment strategy, clones were artificially censored if the first analgesic exposure observed within the grace period was an NSAID dispensing. Under the NSAID treatment strategy,

clones were artificially censored if the first analgesic exposure observed within the grace period was an opioid dispensing. Individuals with initiation of both NSAIDs and opioids within the same person-month were censored in both treatment arms, as they were considered compliant with neither treatment strategy. Any individuals who did not initiate either strategy by the end of the grace period (i.e. by the end of month 3 post-bDMT initiation) were artificially censored for treatment non-compliance (*see Figure 5*). The censoring of clones is this step creates selection bias so we must then apply weights to account for this informative censoring based on an individual's probability of remaining uncensored at each time point.[126]

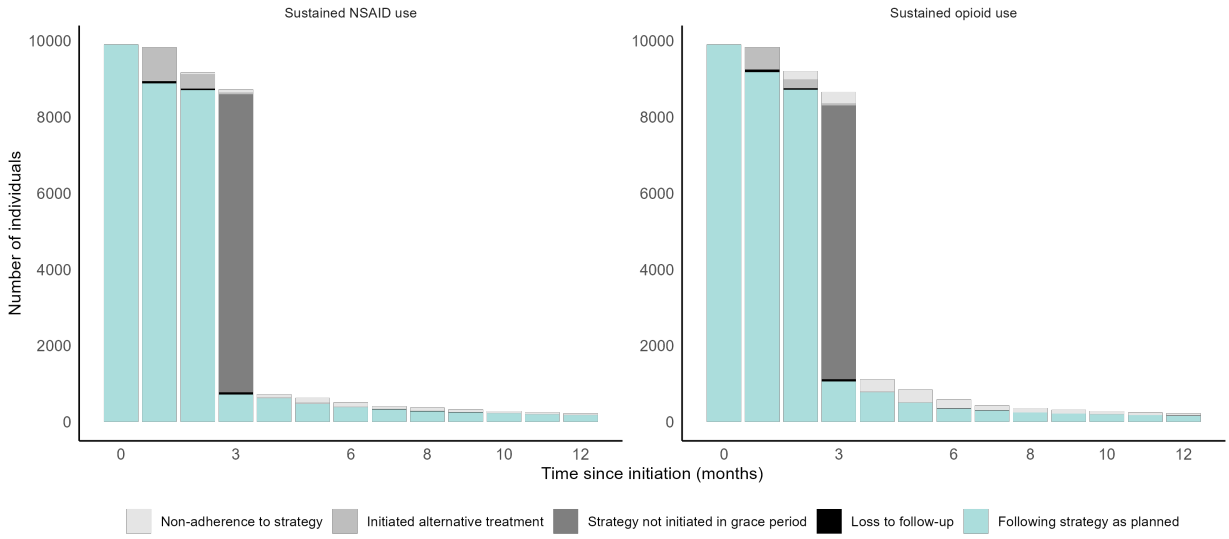

Figure 5 – Clones following assignment treatment strategy in each treatment arm across follow-up time (sustained exposure).

2.3.5.3 Weighting

To account for the resulting selection bias from censoring due to non-compliance, we generated IPCWs to re-balance the sample and upweight treatment compliant individuals who best represent those who were censored for non-compliance.[124] These treatment compliant individuals are those

who complied with their assigned treatment strategy in the last observed interval of time within the grace period (i.e. those who complied in month 3).

We modeled treatment initiation through a multinomial regression in a subset of the un-cloned dataset which was restricted to observations from months 1 through 3 with no prior history of initiating either treatment strategy to predict the probability of initiating either opioids, prescription NSAIDs, both prescription NSAIDs and opioids, or neither strategy in each person-month within the grace period. This model was fit with flexible terms for time (month) as a function of the covariates listed in the *Assignment Procedure* section of the TTE Framework in *Supplementary Table 24* and *section 2.3.4 Measurement of covariates*.

After modeling the probability of treatment initiation for every person-month in the grace period, each uncensored individual in the cloned dataset was assigned a time-varying weight reflecting the estimated cumulative probability of being uncensored in each person-month according to their baseline covariates, time-varying covariates and treatment history. In months 1 and 2, individuals could only be censored for initiating the alternative treatment strategy to what they were assigned and so any uncensored individuals were weighted by the probability of receiving either the assigned treatment or initiating no treatment within the same person-month. For month 3, the last interval of time within the grace period, individuals who initiated their assigned treatment strategy where weighted according to their probability of initiating this strategy. Stabilized IPCW were then estimated using these predicted probabilities (*see formulas for weight calculations in Table 7*). Initiation of either treatment strategy in month 0 (Time 0) was not possible due to the new user

design, so all observations in month 0 were assigned a weight of 1. All observations after an individual initiated their assigned strategy were also assigned a weight of 1.

Stabilized IPCWs were also calculated for censoring due to: 1) initiation of concurrent analgesic therapy (i.e. use of NSAIDs after initiating opioid treatment strategy and vice versa), 2) cessation of assigned therapy (i.e. a gap of 30 days in exposure to assigned therapy), and 3) loss to follow up due to disenrollment or entering into PAC.[128,129] Weights for censoring due to initiation of concurrent analgesic therapy were estimated separately in each treatment arm with restriction to person-months where individuals had already initiated their assigned therapy. Person-months prior to initiation of the assigned strategy were assigned a weight of 1, since concurrent therapy is not possible until one treatment is initiated. Weights for cessation of assigned therapy and loss to follow-up were modeled together in both treatment arms. The competing event of death was not considered as censoring criteria due to the small number of deaths observed over the one year of follow-up (N = 169, 1.62%) and our intention to estimate the total effect of treatment, rather than the direct effect.[130] The final weights were the product of the clone-censor weights, IPCWs for initiation of concurrent analgesic therapy, IPCWs for cessation of therapy and IPCWs for loss to follow-up. The resulting weights were truncated at the 99.5% percentile (*see Supplementary Table 25 for distribution of weights*).

Table 7 – Summary of time-specific contributions to the stabilized inverse probability of treatment weights (clone-censoring weights).

Month post-initiation of bDMT (t)	**Contribution to stabilized clone-censoring weights in month *t***		**Explanation**
	Prescription NSAID Arm Weight	**Opioid Arm Weight**	
Month 0	1	1	No censoring at baseline.
Month 1	$\frac{\Pr(A_t \in \{0,1\} \mid A_{(t-1)} = 0)}{\Pr(A_t \in \{0,1\} \mid A_{(t-1)} = 0, L_t)}$	$\frac{\Pr(A_t \in \{0,2\} \mid A_{(t-1)} = 0)}{\Pr(A_t \in \{0,2\} \mid A_{(t-1)} = 0, L_t)}$	Censoring occurs for initiating the alternative strategy, including dispensing of both treatments in the same person-month.
Month 2	$\frac{\Pr(A_t \in \{0,1\} \mid A_{(t-1)} = 0)}{\Pr(A_t \in \{0,1\} \mid A_{(t-1)} = 0, L_t)}$	$\frac{\Pr(A_t \in \{0,2\} \mid A_{(t-1)} = 0)}{\Pr(A_t \in \{0,2\} \mid A_{(t-1)} = 0, L_t)}$	Same as Month 1; censoring for the alternative strategy.
Month 3	$\frac{\Pr(A_t = 1 \mid A_{(t-1)} = 0)}{\Pr(A_t = 1 \mid A_{(t-1)} = 0, L_t)}$	$\frac{\Pr(A_t = 2 \mid A_{(t-1)} = 0)}{\Pr(A_t = 2 \mid A_{(t-1)} = 0, L_t)}$	Censoring reflects failure to initiate the assigned treatment.
Month 4+	1	1	No more censoring of clones; grace period ends.

t = month of follow-up post-initiation of bDMT.
A_t = the treatment initiated by month t, where:
0 = no treatment initiated
1 = prescription NSAIDs initiated
2 = opioids initiated
3 = both prescription NSAIDs and opioids initiated
$A_{(t-1)}$ = the treatment initiation history in the month prior to t
L_t = A vector of covariates, including baseline and time-varying covariates observed up to time t.
Note: individuals who are censored receive a weight of 0 from the point of censoring onwards.

The risk of bDMT discontinuation and bDMT switching were estimated using discrete-time models, predicting the binary outcome by each person-month of follow-up, conditional on treatment strategy, month of follow-up and product terms between treatment strategy and month of follow-up. The weights applied were the product of the IPCWs for each individual. The cumulative product of the predicted probability of discontinuation for each person-month was used to estimate the 12-month risk of bDMT discontinuation and bDMT switching. The 95% CLs were estimated using the sandwich estimator for robust variance.[131]

2.3.6 Stability analyses

We conducted stability analyses to evaluate alternative treatment strategies where individuals were not required to be continuously exposed to the assigned treatment strategy in order to remain uncensored. We removed the weights for treatment adherence and concurrent therapy initiation to generate estimates reflecting an ITT effect (*see Figure 6*).

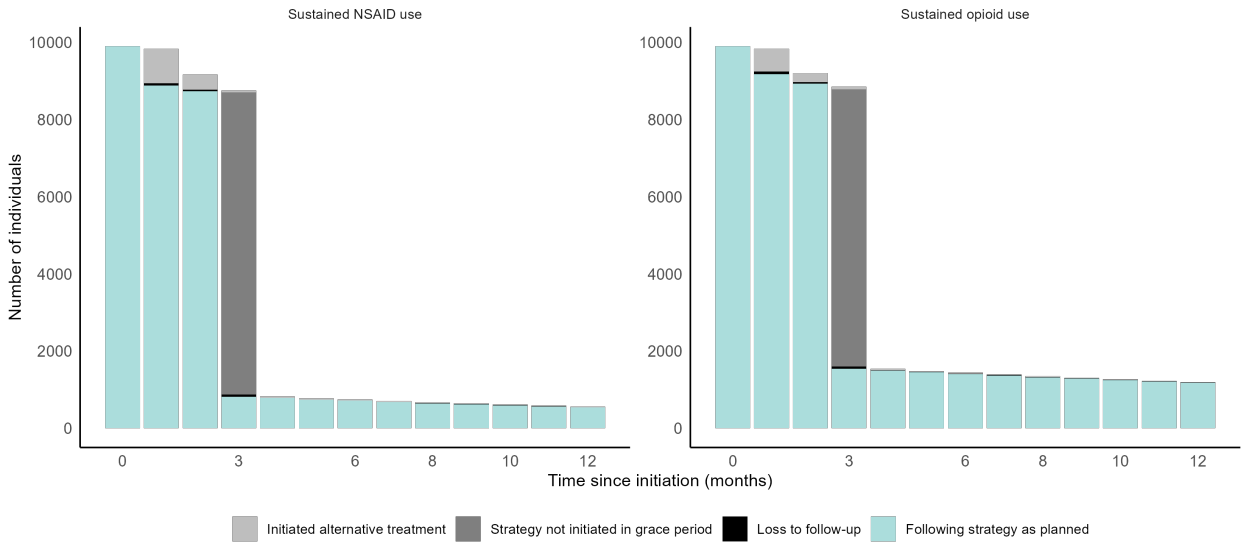

Figure 6 – Clones following assignment treatment strategy in each treatment arm across follow-up time (*Initiation only* – intention-to-treat effect).

2.3.7 Sensitivity analyses

Due to concerns over unmeasured confounding by pain and disease severity between opioid and NSAID users, the potential impact of residual confounding was assessed through the array method.[132] The prevalence of the unmeasured confounder and the strength of the relationship between the confounding and the outcome were varied to model the impact on the observed effect of the exposure and outcome.[132] We theorized an unmeasured continuous confounder "pain severity" as 0 – 10 point scale and assessed the imbalance between the exposed and unexposed which would alter the observed RR. A mean pain severity of 5 was used for the unexposed, and this value was varied for the exposed to visualize the impact on the RR.

2.3.9 Software

Data management was performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). Analyses were performed using R statistical software version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

3 Ethics

This work received Data Use Agreement approval from The Centers for Medicare & Medicaid Services and was determined as exempt from 45 CFR 46 regarding the inclusion of human participants in research by the Brown University Institutional Review Board (protocol 2022003502).

4 Results

4.1 Study population

We included 10,437 eligible individuals, with 871 (8.3%) compatible with the initiate NSAIDs strategy and 1,732 (16.6%) compatible with the initiate opioids strategy (*see Figure 7*). Of the

7,834 (75%) individuals who were ineligible for either strategy, 131 (1.3%) initiated both NSAIDs and opioids in the same person-month and contributed no person-time to either strategy, the remainder initiated neither NSAIDs nor opioids by the end of month 3 post-initiation of a bDMT. There were 266 (2.5%) individuals who initiated both NSAIDS and opioids within the grace period and were classified as compliant with the strategy they initiated first; the initiation of the alternative strategy was cause for artificial censoring within the grace period. On average, individuals under treatment with opioids were slightly older, had a higher CCI, experienced more polypharmacy and were less likely to initiate a TNF-inhibiting bDMT (*see Table 8*).

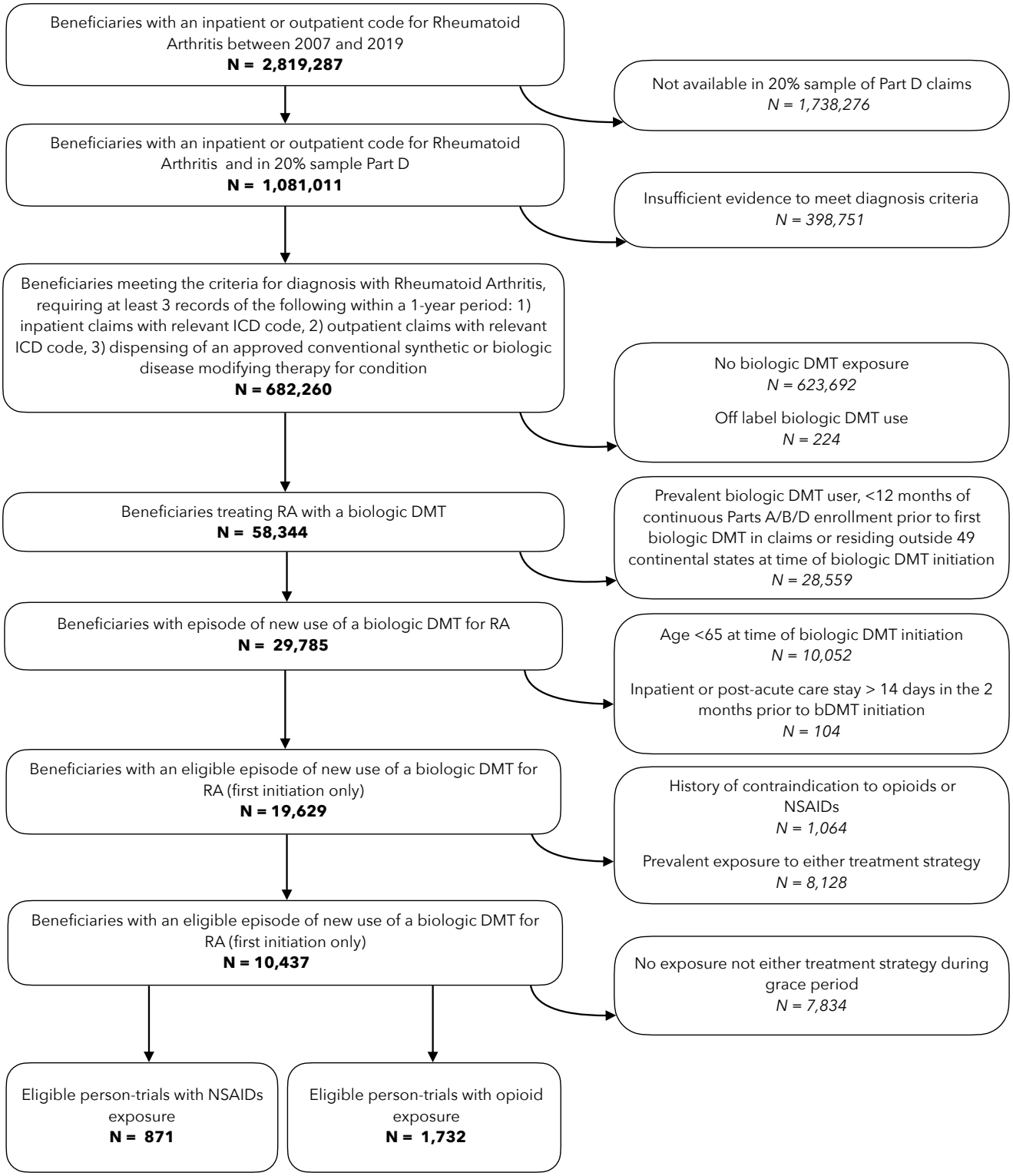

Figure 7 – Chapter 3 Study sample flow chart.

Table 8 – Characteristics at baseline and under each analgesic regimen observed in 3 month grace period, Medicare beneficiaries initiating a bDMT for treatment of RA 2008 – 2019.

		Exposure in 3 month grace period			
	Baseline N = 10,437	**Ineligible for either strategy N = 7,834**	**NSAID strategy N = 871**	**Opioid strategy N = 1,732**	**SMD**
Age	71.0 (68.0, 76.0)	71.0 (68.0, 77.0)	69.0 (67.0, 74.0)	71.0 (68.0, 76.0)	-0.30
Sex					0.03
Female	7,649 (73%)	5,698 (73%)	660 (76%)	1,291 (75%)	
Male	2,788 (27%)	2,136 (27%)	211 (24%)	441 (25%)	
Race					0.20
White	8,654 (83%)	6,552 (84%)	668 (77%)	1,434 (83%)	
Black	599 (5.7%)	451 (5.8%)	47 (5.4%)	101 (5.8%)	
Hispanic	632 (6.1%)	415 (5.3%)	86 (9.9%)	131 (7.6%)	
Asian/Pacific Islander/American Indian/Alaska Native/Other/Unknown	552 (5.3%)	416 (5.3%)	70 (8.0%)	66 (3.8%)	
CCI	1.00 (1.00, 3.00)	1.00 (1.00, 3.00)	1.00 (0.00, 2.00)	2.00 (1.00, 4.00)	-0.40
Comorbidities					
Chronic Pain	996 (9.5%)	647 (8.3%)	70 (8.0%)	279 (16%)	-0.25
Fibromyalgia	404 (3.9%)	247 (3.2%)	44 (5.1%)	113 (6.5%)	-0.06
Atrial Fibrillation	2,302 (22%)	1,662 (21%)	159 (18%)	481 (28%)	-0.23
Alzheimer's	382 (3.7%)	279 (3.6%)	30 (3.4%)	73 (4.2%)	-0.04
Asthma	956 (9.2%)	664 (8.5%)	85 (9.8%)	207 (12%)	-0.07
Chronic Kidney Disease	2,078 (20%)	1,505 (19%)	136 (16%)	437 (25%)	-0.24
Mood Disorder	1,772 (17%)	1,204 (15%)	156 (18%)	412 (24%)	-0.15
Chronic Obstructive Pulmonary Disease	2,035 (19%)	1,451 (19%)	155 (18%)	429 (25%)	-0.17
Hypertension	5,199 (50%)	3,729 (48%)	467 (54%)	1,003 (58%)	-0.09
Use of a csDMT at bDMT initiation	5,692 (55%)	4,266 (54%)	476 (55%)	950 (55%)	0.00
bDMT administered orally	5,300 (51%)	3,968 (51%)	453 (52%)	879 (51%)	0.03
bDMT name					0.37
abatacept	1,113 (11%)	845 (11%)	63 (7.2%)	205 (12%)	
adalimumab	1,658 (16%)	1,233 (16%)	173 (20%)	252 (15%)	
certolizumab	881 (8.4%)	680 (8.7%)	62 (7.1%)	139 (8.0%)	
etanercept	2,105 (20%)	1,499 (19%)	252 (29%)	354 (20%)	
golimumab	600 (5.7%)	459 (5.9%)	50 (5.7%)	91 (5.3%)	
infliximab	2,505 (24%)	1,915 (24%)	197 (23%)	393 (23%)	
rituximab	1,271 (12%)	971 (12%)	54 (6.2%)	246 (14%)	
tocilizumab	304 (2.9%)	232 (3.0%)	20 (2.3%)	52 (3.0%)	
TNF-inhibitor initiated	7,749 (74%)	5,786 (74%)	734 (84%)	1,229 (71%)	0.32
Initiation pre-2015	5,010 (48%)	3,672 (47%)	464 (53%)	874 (50%)	0.06

(SMD) Standardized Mean Difference in NSAIDs versus opioids, (CCI) Combined Comorbidity Index, (bDMT) biologic disease modifying therapy.

4.2 Biologic disease modifying therapy discontinuation

Among individuals under the treatment strategy to initiate and remain exposed to analgesic therapy with NSAIDs, 243 (cumulative risk: 19%) discontinued their bDMT within one year of follow-up and the mean time to discontinuation in the was 5.42 months (SD: 2.60 months). Among individuals under the treatment strategy to initiate and remain exposed to analgesic therapy with opioids, 493 (cumulative risk: 29%) discontinued their bDMT within one year of follow-up and the mean time to discontinuation in the was 6.23 months (SD: 2.69 months). By month 6, the risk of discontinuation was similar between the two treatment strategies, with an absolute difference of 8.269 discontinuations per 1,000 eligible individuals. However, by one year of follow-up this absolute difference jumped to 97.164 per 1,000 eligible individuals and the 12-month RR of bDMT discontinuation was 1.51 [95%CLs 1.05, 2.96] (*see Table 9*). The cumulative incidences for discontinuation of bDMT therapy by initiation of either treatment strategy are shown in *Figure 8*.

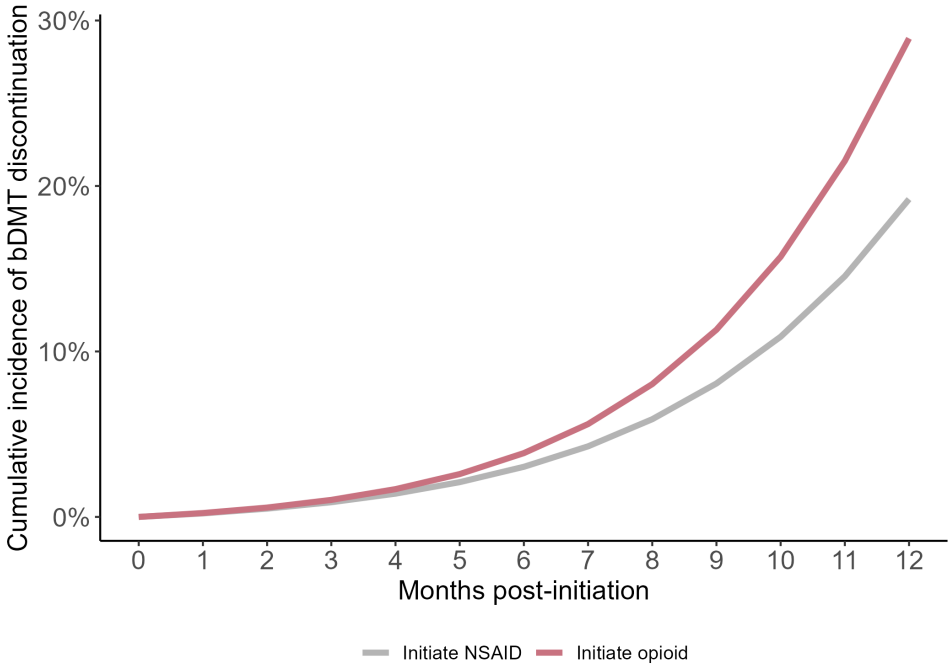

Figure 8 – Cumulative incidence of bDMT discontinuation by analgesic treatment initiated.

Table 9 – Risk of bDMT discontinuation and switching according to analgesic strategy among Medicare beneficiaries initiating a bDMT for initiation of RA, 2008-2019.

	Risk in Treatment 0: NSAID strategy	Risk in Treatment 1: Opioid strategy	Risk Difference (per 1,000 person-months; 95%CLs)	Risk Ratio (95%CLs)
bDMT Discontinuation				
6-month Discontinuation	3%	4%	8.27 (-259.09, 275.63)	1.27 (0.00, 10.32)
12-month Discontinuation	19%	29%	97.16 (-170.20, 364.53)	1.51 (1.05, 2.96)
bDMT Switching				
6-month Switching	7%	7%	3.62 (-309.30, 316.53)	1.06 (0.02, 5.92)
12-month Switching	8%	9%	12.07 (-300.85, 324.98)	1.15 (0.06, 5.17)

4.3 Biologic disease modifying therapy switching

Among individuals under the treatment strategy to initiate and remain exposed to analgesic therapy with NSAIDs, 542 (cumulative risk: 8%) switched their bDMT within one year of follow-up and the mean time to the first observed therapy switch in the was 1.61 months (SD: 2.38 months). Among individuals under the treatment strategy to initiate and remain exposed to analgesic therapy with opioids, 611 (cumulative risk: 9%) switched their bDMT within one year of follow-up and the mean time to discontinuation in the was 2.31 months (SD: 3.10 months). The risk of bDMT switching was nearly indistinguishable between the two treatment strategies by month 6, with an absolute difference of only 3.62 discontinuations per 1,000 eligible individuals. The risks diverged slightly after one year of follow-up, but the RR remained compatible with the null (RR: 1.15 [95%CL 0.06, 5.17]), indicating no significant difference in the 12-month risk of bDMT switching between treatment groups (*see Figure 9*).

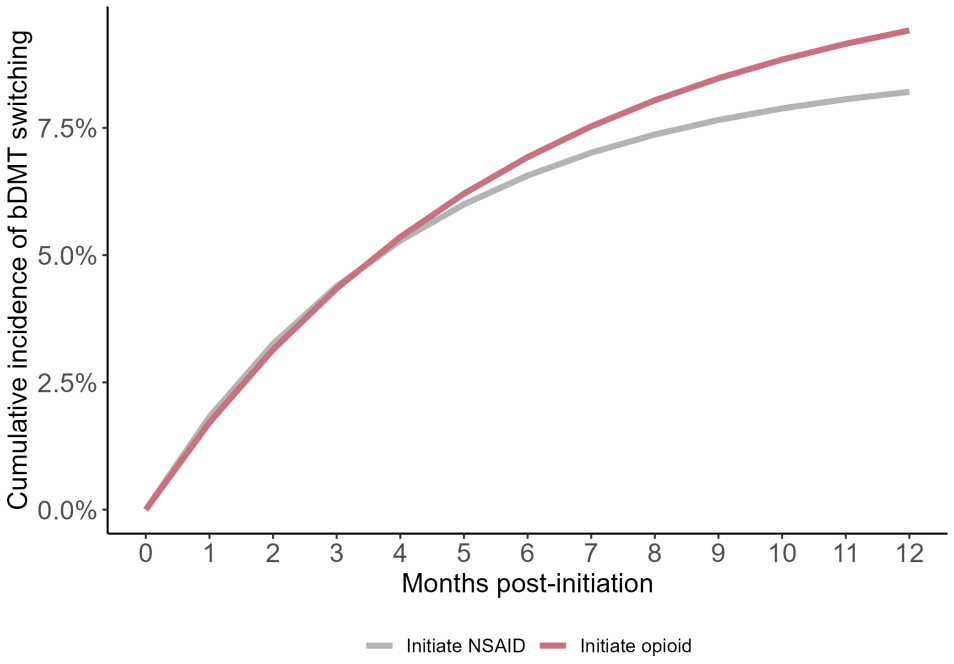

Figure 9 – Cumulative incidence of bDMT switching by analgesic treatment initiated.

4.4 Stability analyses

The stability analysis removing the requirement for sustained treatment did not meaningfully alter findings. The trend for an increased risk of both discontinuation and switching of bDMTs persists, although the CLs include the null for risk at 6 months and 12 months (*see Table 10*).

Table 10 – Results of stability analysis for risk of bDMT discontinuation and switching according to analgesic strategy among Medicare beneficiaries initiating a bDMT for initiation of RA, 2008-2019.

	Risk in Treatment 0: NSAID strategy	**Risk in Treatment 1: Opioid strategy**	**Risk Difference (per 1,000 person-months; 95%CLs)**	**Risk Ratio (95%CLs)**
bDMT Discontinuation				
6-month Discontinuation	3%	5%	12.12 (-217.14, 241.38)	1.35 (0.00, 8.09)
12-month Discontinuation	18%	22%	41.48 (-187.78, 270.74)	1.23 (0.95 2.50)
bDMT Switching				
6-month Switching	7%	8%	3.09 (-213.22, 219.40)	1.04 (0.14, 4.04)
12-month Switching	11%	13%	13.93 (-202.38, 230.24)	1.13 (0.44, 3.13)

4.5 Sensitivity analyses

Sensitivity analysis of the 12-month RR for bDMT discontinuation suggests that a potential confounder "pain severity" with a mean of 5 among those under the NSAID treatment strategy would need to have a mean of 8 among those under the opioid treatment strategy and increase the risk of the outcome by 10% for each 1 point increase to fully explain the increase in risk of discontinuation observed for the opioid strategy (*see Figure 10*).

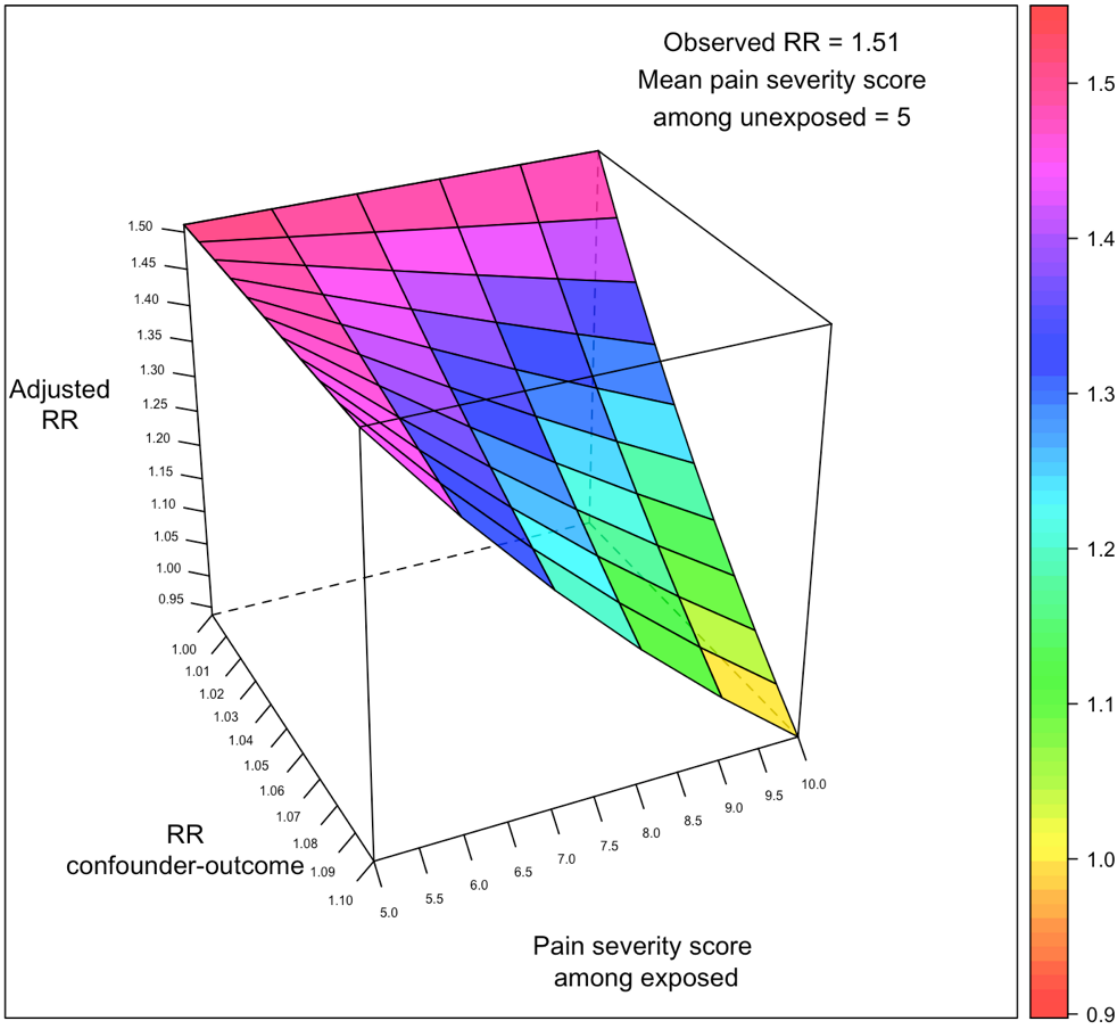

Figure 10 – Array method for the adjusted risk ratio as a function of confounder-disease relationship and pain severity score.

5 Discussion

This is the first study to assess strategies for pharmacologic pain management in RA and outcomes related to bDMT adherence using a design informed by a TTE framework. The estimated absolute risk differences of bDMT discontinuation and switching between individuals treated with sustained opioid versus sustained NSAID therapy were small in the first 6 months of follow-up post-bDMT initiation. The estimated 12-month risk of bDMT discontinuation yielded CLs which excluded the null by a narrow margin and suggest that sustained opioid use over time leads to a 51% greater risk of discontinuing bDMT therapy, compared to sustained NSAID use. Although the estimated risk of bDMT switching increased with sustained opioid use compared to sustained NSAID use over follow-up, the findings remained compatible with the null hypothesis after 12 months.

Stability analyses assessed the initiation of initiation of either opioid or NSAID therapy within 3 months of bDMT initiation and removed the requirement for adherence to the assigned therapy. This approach approximates the ITT effect and allows the assigned analgesic to be used on an "as needed basis" rather than to be continuously used as a sustained exposure. This may be a more realistic approximation of how pain medication is used, since both opioids and NSAIDs should not be taken without an indication of pain, which may vary over time. The estimates for the ITT effect were slightly attenuated when compared with those emulating a PP effect from sustained treatment. The initiation of opioids still conferred an increase in risk of both discontinuation and bDMT switching, although all 95% CLs included the null.

While opioid use has been linked with lower rates of DMT use and delays in DMT initiation among RA patients, this is the first study to link opioid use with reduced bDMT adherence in RA.[111] A 2021 paper by Rhudy et al. reached similar conclusions regarding chronic opioid use and the

increased risk of early bDMT discontinuation in individuals with IBD.[53] Previous research on analgesic use and bDMT adherence is limited across all autoimmune diseases and it is unknown how these findings translate to bDMT adherence outside of the context of RA. Autoimmune diseases with a relapsing remitting course, such as MS, CR or UC, are especially prone to bDMT switching and may be differentially impacted by long-term opioid use. It is also unclear how different opioid use trajectories, such as discontinuation of opioid use, may influence bDMT adherence since opioid tapering has been tied to reduced medication adherence and increased emergency room visits.[133]

This work has several important limitations to consider. First, the use of the clone-censor-weight approach ensures that all baseline confounders are perfectly balanced at baseline, but selection bias still arises due to artificial censoring when individuals deviate from treatment assignment. The models for censoring weights must be well specified in order to account for this informative censoring and rebalance potential confounders at each study timepoint. Second, there is concern about reverse causation when assessing how pain treatment impacts adherence to a therapy which manages a painful condition. Discontinuation can only be observed after 90 days without bDMT exposure and poor adherence in the interim may exacerbate pain and increase analgesic use, making opioid exposure a response to an early manifestation of bDMT discontinuation. The use of NSAIDs an active comparator limits this risk of bias due to reverse causation. Third, Medicare claims carry no information about pain or disease severity and there is risk of residual confounding by pain severity between individuals treated with opioids and NSAIDs. While opioids and NSAIDs share an indication for pain management, opioids are often reserved for treating severe pain while NSAIDs are used more widely and have been used as an active comparator for weak opioids in RCTs.[120] We conducted sensitivity analyses to assess the possible influence of pain severity as an

unmeasured confounder and determined that the strength of this confounder would need to be greater than reasonably expected to account for results. Fourth, there is a known risk for misclassification in claims data. When determining the days' supply for each bDMT from Part B claims, intravenous versus subcutaneous formulations were distinguished using the 'JA' modifier for intravenous and the 'JB' modifier for subcutaneous. When this modifier was not included for formulations with multiple routes of administration, intravenous administration was assumed. Since intravenous administration of bDMTs leads to a longer day's supply in most cases, the risk of discontinuation may be an underestimation. Off label use of bDMTs was also not considered, so switching to an off label bDMT would appear as a discontinuation. It is also challenging to determine adherence with bDMTs which are billed through Part D and self-administered. For example, etanercept subcutaneous injections are required on a weekly dosing schedule and an individual may receive several syringes to cover doses for several weeks when self-injecting, while those having their injections administered by a healthcare professional must appear weekly to receive it. Discontinuation can only be observed in Part D when the time covered by the total number of doses dispensed has past, while in Part B discontinuation may be observed within a single week when an individual fail to appear for their next dose administration. Finally, sample sizes were not substantial enough to conduct subgroup analyses by bDMT type. Adherence may vary according to which bDMT is initiated as a first or second-line therapy, with tocilizumab, tofacitinib and abatacept associated with improved retention times compared to other bDMTs (*including: etanercept, infliximab, adalimumab, and golimumab*).[104] While the selection of first and second-line bDMTs is largely left up to the prescribing clinician in treatment guidelines, there are potential confounding factors associated with initiation of different bDMTs.[84,134] We also had an insufficient sample to limit prescription NSAIDs to high dose only, possibly reducing

confounding by pain severity between groups. It is not possible to include dose in the propensity score model as a proxy for pain severity, as there is no established equivalency between opioids and NSAIDs.

6 Conclusions

Adherence to bDMTs is crucial for achieving optimal disease control and improving patient outcomes in RA. This study demonstrates that sustained opioid use is associated with a significantly higher risk of bDMT discontinuation compared to NSAID use, highlighting the potential for pain management strategies to influence bDMT adherence. Understanding these dynamics provides insights into developing comprehensive disease management plans that address both pain control and disease activity. Our findings emphasize the need for integrated care approaches that consider the relationship between effective pain management and good adherence to bDMTs.

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SUPPLEMENTARY RESULTS

1.1 Sample with multiple diagnoses and bDMT initiations

We found several occurrences of overlapping diagnoses, where UC and CR were the most commonly co-occurring diagnoses (N = 18,550 [1.7%]), followed by RA and CR (N = 7,040 [0.7%]). However, the occurrence of bDMT initiation for more than one condition during follow-up was uncommon. While 1,754 (7.7%) individuals experienced more than one initiation episode, 756 (3.3%) individuals initiated the same bDMT for a single condition, 932 (4.1%) initiated multiple bDMTs for a single condition, and 66 (<1%) initiated bDMTs for two different conditions.

1.2 Biologic disease modifying therapies initiated

Infliximab (N = 4,962, 23.1%), etanercept (N = 4,164, 19.4%), and adalimumab (N = 3,335, 15.5%) were the most frequently initiated bDMTs for RA. The remaining 42% of initiations comprised abatacept (N = 2,651), rituximab (N = 2,557), certolizumab pegol (N = 1,853), golimumab (N = 1,245), and tocilizumab (N = 718). For both UC and CR, adalimumab and infliximab made up the majority of initiations, accounting for 77.6% (adalimumab N = 473; infliximab N = 431) and 91% (adalimumab N = 620; infliximab N = 631) of all initiations, respectively. Other initiations for UC included golimumab (N = 28) and vedolizumab (N = 232), while for CR, certolizumab pegol (N = 69) and ustekinumab (N = 110) were initiated; natalizumab initiations were excluded due to low counts (<20). Belimumab is the sole bDMT approved for SL, with all 174 initiations attributed to it. For MS, ocrelizumab (N = 176; 63%) was the most common, followed by natalizumab (N = 105; 37%); alemtuzumab initiations were excluded due to low counts (<20).

1.3 Most common analgesic regimens

Acetaminophen-hydrocodone and tramadol were the leading opioids dispensed for all conditions. For prescription NSAIDs, meloxicam and celecoxib were the top choices. Prednisone stood out as the most frequently prescribed steroid by a significant margin. Gabapentin was the preferred muscle relaxer/anticonvulsant in most conditions, except for MS, where baclofen was more commonly dispensed. Among antidepressants, sertraline (an SSRI) and duloxetine (an SNRI) were the most frequently prescribed across various conditions.

SUPPLEMENTARY TABLES

Supplementary Table 1 – International Classification of Diseases-9 and -10 code lists for autoimmune diseases of interest.

Condition	ICD-9	ICD-10
Multiple Sclerosis	340	G35
Rheumatoid Arthritis	714.0, 714.1, 714.2, 714.8	M05.X, M06.X
Systemic Lupus Erythematosus	710.0	M32.X
Ulcerative Colitis	556.X	K51.X
Crohn's Disease	555.X	K50.X

(ICD) International Classification of Diseases;

Supplementary Table 2 – Code list for identifying biologic disease-modifying therapy exposure from Medicare Part D and B claims, including HCPCS codes and inferred days' supply.

Name	FDA approval Date (M/D/YYYY)	Interval between approval and HCPCS code availability	Recommended Dose	Identification in Medicare Part B				Expected Dosing Frequency	Inferred Days' Supply
				HCPCS Code	HCPCS modifier for route of administration	Dose (billing unit)	Date code active (M/D/YYYY)		
abatacept	RA: 12/23/2005	Code active prior to study start	500 - 1,000 mg 125 mg	J0129	IV: 'JA' SC: 'JB'	10 mg	1/1/2007 - current	Every 4 weeks Once weekly	28 7
adalimumab	RA: 1/2/2003 CR: 12/31/2002 UC: 9/28/2012	Code active prior to study start	40 mg	J0135	*SC only*	20 mg	1/1/2005 - current	Every other week	14
alemtuzumab	MS: 11/14/2014	Code active prior to study start	36 mg	J9010 Q9979 J0202	*IV only*	10 mg 1 mg 1 mg	1/1/2003 - 21/31/2015 10/1/2015 - 12/31/2015 1/1/2016 - current	12 months	365
belimumab	SL: 3/9/2011	SL: 114 days	10 mg/kg 200 mg	Q2044 J0490	IV: 'JA' SC: 'JB'	10 mg 10 mg	7/1/2011 - 12/31/2011 1/1/2012 - current	Every 4 weeks Weekly	28 7
certolizumab pegol	CR: 4/22/2008 RA: 5/13/2009	CR: 344 days RA: Code active prior to approval	200 - 400 mg	C9249 J0718 J0717	*SC only*	1 mg 1 mg 1 mg	4/1/2009 - 1/1/2010 1/1/2010 - 1/1/2014 1/1/2014 - current	Every 4 weeks Every other week	28 14
etanercept	RA: 11/2/1998	Code active prior to study start	50 mg	J1438	*SC only*	25 mg	1/1/2000 - current	Once weekly	7
golimumab	RA: 7/18/2013 UC: 5/15/2013	RA: 167 days UC: 231 days	2 mg/kg	J1602	IV: 'JA' SC: 'JB'	1 mg	1/1/2014 - current	Every 8 weeks	56
infliximab	RA: 11/10/1999 CR: 8/24/1998 UC: 9/15/2005	Code active prior to study start	5 mg/kg 120 mg	J1745	IV: 'JA' SC: 'JB'	10 mg	1/1/2000 - current	Every 8 weeks Every 2 weeks	56 14
natalizumab	MS: 11/23/2004 CR: 1/14/2008	MS: 39 days CR: Code active prior to FDA approval	30 - 300 mg	Q4079 J2323	*IV only*	1 mg 1 mg	1/1/2005 - 12/31/2007 1/1/2008 - current	Every 4 weeks	28
ocrelizumab	MS: 3/28/2017	MS: 187 days	600 mg	C9494 J2350	*IV only*	1 mg 1 mg	10/1/2017 - 12/31/2017 1/1/2018 - current	Every 6 months	182
rituximab	RA: 2/28/2006	Code active prior to study start	1000 mg	J9310 J9312	*IV only*	100 mg 10 mg	1/1/1999 - 12/31/2018 1/1/2019 - current	Every 24 weeks	168
tocilizumab	RA: 1/11/2010	RA: 355 days	4 mg/kg	J3262	*IV only*	1 mg	1/1/2011 - current	Every 4 weeks	28

vedolizumab	UC: 5/20/2014 CR: 4/18/2024*	UC: 591 CR: Code active prior to approval	300 mg	J3380	*IV only*	1 mg	1/1/2016 - current	Every 8 weeks	56
ustekinumab	CR: 9/26/2016 UC: 10/21/2019*	Code active prior to study start	260 - 520 mg	C9487		1 mg	4/1/2017 - 6/30/2017	Single dose (switch to SC)	56
			260 - 520 mg	Q9989	IV: 'JA'	1 mg	7/1/2017 - 12/31/2017	Single dose (switch to SC)	56
			260 - 520 mg	J3358		1 mg	1/1/2018 - current	Single dose (switch to SC)	56
			90 mg	J3357	SC: 'JB'	1 mg	1/1/2011 - current	every 8 weeks (after IV initiation)	56
sarilumab*	RA: 5/22/2017	NA	200 mg	*NA*	*NA*	*NA*	*NA*	Every 2 weeks	14
ofatumumab*	MS: 8/20/2020	Code active prior to study start	20 mg	J9302	*NA*	10 mg	1/1/2011 - current	every 4 weeks	28
ublituximab*	MS: 12/28/2022	MS: 185 days	450 mg	J2329	*NA*	1 mg	7/1/2023 - current	Every 24 weeks	168

(FDA) US Food and Drug Administration; (HCPCS) Healthcare Common Procedures Coding System; (mg) milligram; (kg) kilogram; (RA) rheumatoid arthritis; (MS) multiple sclerosis; (UC) ulcerative colitis; (CR) Crohn's disease; (SL) systemic lupus erythematous; (IV) intravenous; (SC) subcutaneous

**Excluded from consideration due to FDA approval or unique HCPCS availability occurring after study end.*

Supplementary Table 3 – Code list for identifying conventional synthetic disease-modifying therapy exposure from Medicare Part D and B claims, including HCPCS codes and inferred days' supply.

Name	Classification	Conditions	Route of Administration	Identification in Medicare Part B		
				HCPCS Code	Dose (billing unit)	Date code active (MM/DD/YYYY)
hydroxychloroquine	Anti-malarial	RA, SL	oral		*Part D only*	
chloroquine	Anti-malarial	RA, SL	oral		*Part D only*	
azathioprine	Immunosuppressant	RA, SL, UC, CR	oral	J7500	50 mg	1/1/88
cladribine	Immunosuppressant	MS	oral		*Part D only*	
cyclophosphamide	Immunosuppressant	RA, SL	oral IV	J8530 J9070	25 mg 100 mg	1/1/95 1/1/84
cyclosporine	Immunosuppressant	RA, SL, UC	oral IV	J7515 J7516	25 mg 250 mg	1/1/00 1/1/00
d-penicillamine	Immunosuppressant	RA	oral		*Part D only*	
dimethyl fumarate	Immunosuppressant	MS	oral		*Part D only*	
diroximel fumarate	Immunosuppressant	MS	oral		*Part D only*	
fingolimod	Immunosuppressant	MS	oral		*Part D only*	
glatiramer acetate	Immunosuppressant	MS	SC	J1595	20 mg	1/1/04
interferon beta-1a	Immunosuppressant	MS	IM SC	J1826 Q3027	30 mcg 1 mcg	1/1/11 1/1/14
interferon beta-1b	Immunosuppressant	MS	SC	J1830	0.25 mg	1/1/82
leflunomide	Immunosuppressant	RA	oral		*Part D only*	
mercaptopurine	Immunosuppressant	UC, CR	oral	S0108	50 mg	4/1/02
mesalamine	Immunosuppressant	UC, CR	oral transdermal		*Part D only*	
methotrexate	Immunosuppressant	RA, SL, CR	oral IM, SC	J8610 J9250	2.5 mg 5 mg	1/1/95 1/1/94
minocycline hydrochloride	Immunosuppressant	RA	oral		*Part D only*	
mitoxantrone HCl	Immunosuppressant	MS	IV	J9293	5 mg	1/1/90
monomethyl fumarate	Immunosuppressant	MS	oral		*Part D only*	
mycophenolate mofetil / mycophenolic acid	Immunosuppressant	RA, SL	oral	J7517	250 mg	1/1/00
ozanimod	Immunosuppressant	MS, UC	oral		*Part D only*	
peginterferon beta 1-a	Immunosuppressant	MS	IM, SC		*Part D only*	
ponesimod	Immunosuppressant	MS	oral		*Part D only*	
siponimod	Immunosuppressant	MS	oral		*Part D only*	
sulfasalazine	Immunosuppressant	RA, UC, CR	oral		*Part D only*	
tacrolimus, extended release	Immunosuppressant	UC, CR	oral	J7508	0.1 mg	1/1/14
teriflunomide	Immunosuppressant	MS	oral		*Part D only*	

(HCPCS) Healthcare Common Procedures Coding System; (mg) milligram; (RA) rheumatoid arthritis; (MS) multiple sclerosis; (UC) ulcerative colitis; (CR) Crohn's disease; (SL) systemic lupus erythematous; (IV) intravenous; (SC) subcutaneous; (IM) intramuscular

Supplementary Table 4 – Identification of Not Otherwise Classified drug and biologicals with non-specific HCPCS codes through exact matching by codes from The Centers for Medicare & Medicaid Services Part B Drug Average Sale Price records.

Name	*ICD code*	*Earliest FDA approval date*	*Code Created*	*Possible years with non-specific code used*	*Unit cost by year*	*Unit*
certolizumab pegol	*RA/CR*	*April 22, 2008*	*January 1, 2010*	***Jan-Mar 2008 (NOC)***	*NA*	*NA*
				Apr-Jun 2008 (NOC)	*NA*	*NA*
				Jul-Sep 2008 (NOC)	*NA*	*NA*
				Oct-Dec 2008 (NOC)	*NA*	*NA*
				Jan-Mar 2009 (NOC)	*3.417*	*1 mg*
				Apr-Jun 2009 (NOC)	*3.515*	*1 mg*
				Jul-Sep 2009 (NOC)	*3.584*	*1 mg*
				Oct-Dec 2009 (NOC)	*3.800*	*1 mg*
				Jan-Mar 2010	*3.723*	*1 mg*
				Apr-Jun 2010	*3.782*	*1 mg*
				Jul-Sep 2010	*3.792*	*1 mg*
				Oct-Dec 2010	*3.963*	*1 mg*
tocilizumab	*RA*	*January 8, 2010*	*January 1, 2011*	***Jan-Mar 2010 (NOC)***	*NA*	*NA*
				Apr-Jun 2010 (NOC)	*NA*	*NA*
				Jul-Sep 2010 (NOC)	*3.519*	*1 mg*
				Oct-Dec 2010 (NOC)	*3.477*	*1 mg*
				Jan-Mar 2011	*3.475*	*1 mg*
				Apr-Jun 2011	*3.473*	*1 mg*
				Jul-Sep 2011	*3.474*	*1 mg*
				Oct-Dec 2011	*3.474*	*1 mg*

(FDA) US Food and Drug Administration; (HCPCS) Healthcare Common Procedures Coding System; (NOC) Not Otherwise Classified; (mg) milligram; (RA) rheumatoid arthritis; (CR) Crohn's disease;
Note: Golimumab, ocrelizumab, belimumab, vedolizumab not included in NOC lists and could not be identified
Unit cost by year from: https://www.cms.gov/medicare/payment/part-b-drugs/asp-pricing-files

Supplementary Table 5 – Analgesic medication inclusion criteria from Medicare Part D and B claims.

Medication class	Part D Claims		Part B Claims	
	Ingredients included in Part D	**Exclusions**	**HCPCS code**	**HCPCS code description**
Non-steroidal anti-inflammatory drugs	aspirin celecoxib rofecoxib valdecoxib acetylsalicylic ibuprofen naproxen meloxicam etodolac nabumetone diclofenac ketorolac sulindac indomethacin piroxicam diflunisal fenoprofen flurbiprofen ketoprofen meclofenamate mefenamic oxaprozin salsalate	*Only medications with an oral route of administration were included. All formulations with component ingredients from the non-pain related indications, opioid or muscle relaxer code list were also excluded.*		
Opioids	oxycodone hydrocodone fentanyl codeine meperidine morphine hydromorphone oxymorphone pentazocine propoxyphene tramadol tapentadol levorphanol dihydrocodeine methadone	*All formulations with an opioid antagonist component ingredient (naloxone, naltrexone, or methylnaltrexone) or non-pain related indications were excluded. Remifentanil was excluded due to primary use as surgical prophylaxis.*		

Steroids	prednisone	*Only medications with an oral or injection route of administration were included. Formulations containing formoterol were excluded due to indication for treating asthma. All steroids exclude route of inhalation through inhalation due to indication for treating asthma.*	J7512	Prednisone, immediate release or delayed release, oral, 1 mg
	prednisolone		J2650	Injection, prednisolone acetate, up to 1 ml
			J7510	Prednisolone oral, per 5 mg
			J1010	Injection, methylprednisolone acetate, 1 mg
	methylprednisolone		J7509	Methylprednisolone oral, per 4 mg
			J2919	Injection, methylprednisolone sodium succinate, 5 mg
	budesonide			
			J1094	Injection, dexamethasone acetate, 1 mg
			J1100	Injection, dexamethasone sodium phosphate, 1 mg
	dexamethasone		J8540	Dexamethasone, oral, 0.25 mg
			J7312	Injection, dexamethasone, intravitreal implant, 0.1 mg
			J1700	Injection, hydrocortisone acetate, up to 25 mg
	hydrocortisone		J1710	Injection, hydrocortisone sodium phosphate, up to 50 mg
			J1720	Injection, hydrocortisone sodium succinate, up to 100 mg
	betamethasone		J0702	Injection, betamethasone acetate 3 mg and betamethasone sodium phosphate 3 mg
			J3304	Injection, triamcinolone acetonide, preservative-free, extended-release, microsphere formulation, 1 mg
			J3303	Injection, triamcinolone hexacetonide, per 5 mg
			J3302	Injection, triamcinolone diacetate, per 5 mg
	triamcinolone		J3301	Injection, triamcinolone acetonide, not otherwise specified, 10 mg
			J3300	Injection, triamcinolone acetonide, preservative free, 1 mg
			J3299	Injection, triamcinolone acetonide (xipere), 1 mg
	cortisone			
Muscle Relaxers	tizanidine baclofen dantrolene carisoprodol chlorzoxazone cyclobenzaprine orphenadrine methocarbamol metaxalone	*Only medications with an oral route of administration were included. All formulations with component ingredients from the opioid code list were also excluded. Benzodiazepines were excluded.*		
Anticonvulsants	benzodiazepine diazepam Valproic acid carbamazepine oxcarbazepine fosphenytoin phenytoin	*Only medications with an oral route of administration were included.*		

	tiagabine levetiracetam primidone ezogabine lacosamide topiramate zonisamide gabapentin lamotrigine ethosuximide felbamate mephobarbital rufinamide pregabalin	
Selective serotonin reuptake inhibitors	citalopram escitalopram fluoxetine fluvoxamine paroxetine sertraline	*Only medications with an oral route of administration were included.*
Serotonin–norepinephrine reuptake inhibitors	desvenlafaxine duloxetine levomilnacipran milnacipran venlafaxine	*Only medications with an oral route of administration were included.*
Tricyclic antidepressants	amitriptyline amoxapine clomipramine desipramine doxepin imipramine maprotiline nortriptyline protriptyline trimipramine	*Only medications with an oral route of administration were included.*

(HCPCS) Healthcare Common Procedures Coding System; (mg) milligram;

Supplementary Table 6 – Analgesic medication exclusion criteria.

Exclusion group	Ingredients excluded	Exclusions for indications outside pain relief
Medications with non-pain related indications	dipyridamole	Indicated as a blood thinner
	diphenhydramine	Indicated for allergy relief
	phenylephrine	Indicated for allergy relief
	pseudoephedrine	Indicated for allergy relief
	pyrilamine	Indicated for allergy relief
	chlorpheniramine	Indicated for allergy relief
	carbinoxamine	Indicated for allergy relief
	brompheniramine	Indicated for allergy relief
	potassium guaiacolsulfonate	Indicated for allergy relief
	homatropine	Indicated for allergy relief
	promethazine	Indicated for allergy relief
	guaifenesin	Indicated for cough relief
	butalbital	Indicated for migraine
	sumatriptan	Indicated for migraine
	meprobamate	Indicated for anxiety
	naltrexone	Indicated for AUD and OUD
	omeprazole	Indicated for treatment of ulcer and gastric reflux
	esomeprazole	Indicated for treatment of ulcer and gastric reflux
	sodium bicarbonate	Indicated for treatment of ulcer and gastric reflux

(AUD) alcohol use disorder; (OUD) opioid use disorder;

Supplementary Table 7 – Risk of opioid use across autoimmune conditions in the first and second year period post-initiation of a biologic disease modifying therapy, compared to the one year period prior to initiation.

		Count with opioid use (N)	Person-months (N)	Incidence per 12 person-months (95% CL)	Risk Ratio (95% CL)	P-value	Adjusted P- value*
Overall	Pre-initiation	58,011	269,819	2.58 (2.57, 2.59)	*reference*		
	1 year post-initiation	75,316	269,051	3.36 (3.35, 3.37)	1.04 (1.03, 1.06)	< 0.001	< 0.001
	2 years post-initiation	64,779	234,826	3.31 (3.30, 3.32)	1.05 (1.03, 1.07)	< 0.001	< 0.001
Female	Pre-initiation	45,515	199,221	2.74 (2.73, 2.75)	*reference*		
	1 year post-initiation	58,617	198,940	3.54 (3.52, 3.55)	1.05 (1.03, 1.07)	< 0.001	< 0.001
	2 years post-initiation	50,966	174,338	3.51 (3.49, 3.52)	1.05 (1.02, 1.08)	< 0.001	0.001
Male	Pre-initiation	12,496	70,598	2.12 (2.11, 2.14)	*reference*		
	1 year post-initiation	16,699	70,111	2.86 (2.84, 2.88)	1.03 (0.99, 1.07)	0.091	0.911
	2 years post-initiation	13,813	60,488	2.74 (2.72, 2.76)	1.04 (0.99, 1.10)	0.100	1.000
Pre-2015	Pre-initiation	32,214	161,264	2.40 (2.39, 2.41)	*reference*		
	1 year post-initiation	40,555	143,061	3.40 (3.38, 3.42)	1.06 (1.04, 1.09)	< 0.001	< 0.001
	2 years post-initiation	32,281	115,524	3.35 (3.33, 3.37)	1.08 (1.04, 1.11)	< 0.001	< 0.001
Post-2015	Pre-initiation	25,797	108,555	2.85 (2.83, 2.87)	*reference*		
	1 year post-initiation	34,761	125,990	3.31 (3.29, 3.33)	1.03 (1.01, 1.05)	0.016	0.156
	2 years post-initiation	32,498	119,302	3.27 (3.25, 3.29)	1.02 (0.99, 1.06)	0.120	1.199
CR	Pre-initiation	2,388	15,730	1.82 (1.79, 1.85)	*reference*		
	1 year post-initiation	2,924	15,320	2.29 (2.25, 2.33)	1.00 (0.91, 1.09)	0.922	1.000
	2 years post-initiation	2,339	12,702	2.21 (2.17, 2.25)	1.02 (0.90, 1.15)	0.804	1.000
MS	Pre-initiation	342	3,091	1.33 (1.28, 1.38)	*reference*		
	1 year post-initiation	364	2,601	1.68 (1.62, 1.75)	1.00 (0.85, 1.16)	0.962	1.000
	2 years post-initiation	123	1,091	1.35 (1.27, 1.44)	0.97 (0.63, 1.49)	0.878	1.000
RA	Pre-initiation	52,915	236,280	2.69 (2.68, 2.70)	*reference*		
	1 year post-initiation	69,096	237,084	3.50 (3.48, 3.51)	1.05 (1.03, 1.07)	< 0.001	< 0.001
	2 years post-initiation	60,110	209,864	3.44 (3.42, 3.45)	1.05 (1.03, 1.18)	< 0.001	< 0.001
SL	Pre-initiation	634	1,914	3.97 (3.80, 4.16)	*reference*		
	1 year post-initiation	652	1,765	4.43 (4.23, 4.64)	0.86 (0.68, 1.09)	0.221	1.000
	2 years post-initiation	478	1,375	4.17 (3.96, 4.40)	1.00 (0.77, 1.28)	0.976	1.000
UC	Pre-initiation	1,732	12,804	1.62 (1.60, 1.65)	*reference*		
	1 year post-initiation	2,280	12,281	2.23 (2.19, 2.27)	1.11 (1.00, 1.23)	0.044	0.438
	2 years post-initiation	1,729	9,794	2.12 (2.08, 2.16)	1.10 (0.94, 1.27)	0.225	1.000

Supplementary Table 8 – Risk of NSAID use across autoimmune conditions in the first and second year period post-initiation of a biologic disease modifying therapy, compared to the one year period prior to initiation.

		Count with NSAID use (N)	Person-months (N)	Incidence per 12 person-months (95% CL)	Risk Ratio (95% CL)	P-value	Adjusted P- value*
Overall	Pre-initiation	42,207	269,819	1.88 (1.87, 1.88)	*reference*		
	1 year post-initiation	50,913	269,051	2.27 (2.26, 2.28)	1.04 (1.02, 1.05)	< 0.001	< 0.001
	2 years post-initiation	42,286	234,826	2.16 (2.15, 2.17)	1.05 (1.01, 1.06)	0.002	0.020
Female	Pre-initiation	32,722	199,221	1.97 (1.96, 1.98)	*reference*		
	1 year post-initiation	39,162	198,940	2.36 (2.35, 2.37)	1.04 (1.02, 1.06)	0.001	0.005
	2 years post-initiation	32,690	174,338	2.25 (2.24, 2.26)	1.04 (1.01, 1.06)	0.010	0.097
Male	Pre-initiation	9,485	70,598	1.61 (1.60, 1.62)	*reference*		
	1 year post-initiation	11,751	70,111	2.01 (2.00, 2.03)	1.04 (1.00, 1.08)	0.071	0.713
	2 years post-initiation	9,596	60,488	1.90 (1.89, 1.92)	1.05 (1.00, 1.10)	0.059	0.588
Pre-2015	Pre-initiation	25,244	161,264	1.88 (1.87, 1.89)	*reference*		
	1 year post-initiation	29,661	143,061	2.49 (2.48, 2.50)	1.06 (1.03, 1.08)	< 0.001	< 0.001
	2 years post-initiation	22,932	115,524	2.38 (2.37, 2.40)	1.06 (1.03, 1.09)	< 0.001	0.004
Post-2015	Pre-initiation	16,963	108,555	1.88 (1.86, 1.89)	*reference*		
	1 year post-initiation	21,252	125,990	2.02 (2.01, 2.04)	1.01 (0.99, 1.04)	0.290	1.000
	2 years post-initiation	19,354	119,302	1.95 (1.94, 1.96)	1.02 (0.98, 1.05)	0.283	1.000
CR	Pre-initiation	1,005	15,730	0.77 (0.75, 0.78)	*reference*		
	1 year post-initiation	1,023	15,320	0.80 (0.79, 0.81)	0.93 (0.83, 1.06)	0.282	1.000
	2 years post-initiation	845	12,702	0.80 (0.78, 0.81)	0.98 (0.82, 1.17)	0.806	1.000
MS	Pre-initiation	310	3,091	1.20 (1.16, 1.25)	*reference*		
	1 year post-initiation	249	2,601	1.15 (1.11, 1.19)	0.86 (0.71, 1.06)	0.159	1.000
	2 years post-initiation	105	1,091	1.15 (1.09, 1.23)	1.08 (0.69, 1.69)	0.732	1.000
RA	Pre-initiation	39,642	236,280	2.01 (2.01, 2.02)	*reference*		
	1 year post-initiation	48,488	237,084	2.45 (2.44, 2.46)	1.04 (1.02, 1.06)	< 0.001	< 0.001
	2 years post-initiation	40,537	209,864	2.32 (2.31, 2.33)	1.04 (1.02, 1.07)	0.001	0.009
SL	Pre-initiation	291	1,914	1.82 (1.74, 1.91)	*reference*		
	1 year post-initiation	256	1,765	1.74 (1.66, 1.82)	0.77 (0.58, 1.01)	0.056	0.564
	2 years post-initiation	172	1,375	1.50 (1.42, 1.58)	0.75 (0.54, 1.06)	0.102	1.000
UC	Pre-initiation	959	12,804	0.90 (0.88, 0.91)	*reference*		
	1 year post-initiation	897	12,281	0.88 (0.86, 0.89)	1.03 (0.90, 1.17)	0.703	1.000
	2 years post-initiation	627	9,794	0.77 (0.75, 0.78)	1.09 (0.92, 1.30)	0.323	1.000

Supplementary Table 9 – Risk of steroid use across autoimmune conditions in the first and second year period post-initiation of a biologic disease modifying therapy, compared to the one year period prior to initiation.

		Count with steroid use (N)	Person-months (N)	Incidence per 12 person-months (95% CL)	Risk Ratio (95% CL)	P-value	Adjusted P- value*
Overall	Pre-initiation	72,261	269,819	3.21 (3.20, 3.23)	*reference*		
	1 year post-initiation	92,918	269,051	4.14 (4.13, 4.16)	1.18 (1.16, 1.20)	< 0.001	< 0.001
	2 years post-initiation	70,209	234,826	3.59 (3.57, 3.60)	1.17(1.15, 1.20)	< 0.001	< 0.001
Female	Pre-initiation	54,414	199,221	3.28 (3.26, 3.29)	*reference*		
	1 year post-initiation	69,571	198,940	4.20 (4.18, 4.21)	1.17 (1.14, 1.19)	< 0.001	< 0.001
	2 years post-initiation	53,586	174,338	3.69 (3.67, 3.71)	1.17 (1.14, 1.20)	< 0.001	< 0.001
Male	Pre-initiation	17,847	70,598	3.03 (3.01, 3.06)	*reference*		
	1 year post-initiation	23,347	70,111	4.00 (3.97, 4.03)	1.21 (1.16, 1.25)	< 0.001	< 0.001
	2 years post-initiation	16,623	60,488	3.30 (3.27, 3.32)	1.18 (1.13, 1.24)	< 0.001	< 0.001
Pre-2015	Pre-initiation	39,594	161,264	2.95 (2.93, 2.96)	*reference*		
	1 year post-initiation	49,485	143,061	4.15 (4.13, 4.17)	1.23 (1.20, 1.27)	< 0.001	< 0.001
	2 years post-initiation	35,063	115,524	3.64 (3.62, 3.66)	1.24 (1.21, 1.28)	< 0.001	< 0.001
Post-2015	Pre-initiation	32,667	108,555	3.61 (3.59, 3.63)	*reference*		
	1 year post-initiation	43,433	125,990	4.14 (4.11, 4.16)	1.11 (1.08, 1.14)	< 0.001	< 0.001
	2 years post-initiation	35,146	119,302	3.54 (3.52, 3.56)	1.09 (1.06, 1.12)	< 0.001	< 0.001
CR	Pre-initiation	3,306	15,730	2.52 (2.48, 2.56)	*reference*		
	1 year post-initiation	3,666	15,320	2.87 (2.83, 2.92)	1.08 (1.00, 1.17)	0.060	0.595
	2 years post-initiation	2,368	12,702	2.24 (2.20, 2.28)	1.05 (0.95, 1.16)	0.388	1.000
MS	Pre-initiation	228	3,091	0.89 (0.85, 0.92)	*reference*		
	1 year post-initiation	211	2,601	0.97 (0.94, 1.01)	1.49 (1.03, 2.15)	0.034	0.337
	2 years post-initiation	107	1,091	1.18 (1.11, 1.25)	1.56 (0.97, 2.49)	0.065	0.647
RA	Pre-initiation	64,177	236,280	3.26 (3.25, 3.27)	*reference*		
	1 year post-initiation	84,404	237,084	4.27 (4.25, 4.29)	1.19 (1.16, 1.21)	< 0.001	< 0.001
	2 years post-initiation	64,990	209,864	3.72 (3.70, 3.73)	1.18 (1.15, 1.21)	< 0.001	< 0.001
SL	Pre-initiation	869	1,914	5.45 (5.21, 5.70)	*reference*		
	1 year post-initiation	880	1,765	5.98 (5.71, 6.27)	0.77 (0.58, 1.01)	0.057	0.567
	2 years post-initiation	627	1,375	5.47 (5.19, 5.77)	0.75 (0.54, 1.06)	0.103	1.000
UC	Pre-initiation	3,681	12,804	3.45 (3.39, 3.51)	*reference*		
	1 year post-initiation	3,757	12,281	3.67 (3.61, 3.74)	1.07 (0.99, 1.15)	0.093	0.931
	2 years post-initiation	2,117	9,794	2.59 (2.54, 2.65)	1.05 (0.95, 1.15)	0.338	1.000

Supplementary Table 10 – Risk of antidepressant use across autoimmune conditions in the first and second year period post-initiation of a biologic disease modifying therapy, compared to the one year period prior to initiation.

		Count with antidepressant use (N)	Person-months (N)	Incidence per 12 person-months (95% CL)	Risk Ratio (95% CL)	P-value	Adjusted P- value*
Overall	Pre-initiation	51,348	269,819	2.28 (2.28, 2.29)	*reference*		
	1 year post-initiation	68,639	269,051	3.06 (3.05, 3.07)	1.07 (1.06, 1.08)	< 0.001	< 0.001
	2 years post-initiation	60,118	234,826	3.07 (3.06, 3.08)	1.07 (1.05, 1.08)	< 0.001	< 0.001
Female	Pre-initiation	43,742	199,221	2.63 (2.62, 2.65)	*reference*		
	1 year post-initiation	57,750	198,940	3.48 (3.47, 3.50)	1.06 (1.05, 1.08)	< 0.001	< 0.001
	2 years post-initiation	50,492	174,338	3.48 (3.46, 3.49)	1.06 (1.05, 1.08)	< 0.001	< 0.001
Male	Pre-initiation	7,606	70,598	1.29 (1.28, 1.30)	*reference*		
	1 year post-initiation	10,889	70,111	1.86 (1.85, 1.88)	1.09 (1.06, 1.12)	< 0.001	< 0.001
	2 years post-initiation	9,626	60,488	1.91 (1.89, 1.92)	1.09 (1.05, 1.14)	< 0.001	< 0.001
Pre-2015	Pre-initiation	25,853	161,264	1.92 (1.91, 1.93)	*reference*		
	1 year post-initiation	33,425	143,061	2.80 (2.79, 2.82)	1.09 (1.07, 1.11)	< 0.001	< 0.001
	2 years post-initiation	27,581	115,524	2.86 (2.85, 2.88)	1.09 (1.07, 1.12)	< 0.001	< 0.001
Post-2015	Pre-initiation	25,495	108,555	2.82 (2.80, 2.84)	*reference*		
	1 year post-initiation	35,214	125,990	3.35 (3.34, 3.37)	1.04 (1.03, 1.06)	< 0.001	< 0.001
	2 years post-initiation	32,537	119,302	3.27 (3.25, 3.29)	1.04 (1.02, 1.06)	< 0.001	< 0.001
CR	Pre-initiation	2,852	15,730	2.18 (2.14, 2.21)	*reference*		
	1 year post-initiation	3,701	15,320	2.90 (2.85, 2.95)	1.07 (1.03, 1.12)	0.002	0.019
	2 years post-initiation	3,156	12,702	2.98 (2.93, 3.03)	1.08 (1.02, 1.15)	0.012	0.117
MS	Pre-initiation	994	3,091	3.86 (3.73, 4.00)	*reference*		
	1 year post-initiation	984	2,601	4.54 (4.37, 4.72)	1.01 (0.94, 1.08)	0.854	1.000
	2 years post-initiation	455	1,091	5.00 (4.72, 5.31)	0.99 (0.90, 1.08)	0.784	1.000
RA	Pre-initiation	44,571	236,280	2.26 (2.25, 2.27)	*reference*		
	1 year post-initiation	60,400	237,084	3.06 (3.04, 3.07)	1.07 (1.06, 1.08)	< 0.001	< 0.001
	2 years post-initiation	53,830	209,864	3.08 (3.06, 3.09)	1.07 (1.06, 1.09)	< 0.001	< 0.001
SL	Pre-initiation	632	1,914	3.96 (3.79, 4.14)	*reference*		
	1 year post-initiation	665	1,765	4.52 (4.32, 4.74)	1.00 (0.91, 1.12)	0.923	1.000
	2 years post-initiation	459	1,375	4.01 (3.80, 4.22)	0.98 (0.84, 1.15)	0.833	1.000
UC	Pre-initiation	2,299	12,804	2.15 (2.12, 2.19)	*reference*		
	1 year post-initiation	2,889	12,281	2.82 (2.77, 2.87)	1.04 (0.99, 1.09)	0.103	1.000
	2 years post-initiation	2,218	9,794	2.72 (2.66, 2.77)	1.02 (0.96, 1.09)	0.517	1.000

Supplementary Table 11 – Risk of muscle relaxer and anticonvulsant use across autoimmune conditions in the first and second year period post-initiation of a biologic disease modifying therapy, compared to the one year period prior to initiation.

		Count with muscle relaxer use (N)	Person-months (N)	Incidence per 12 person-months (95% CL)	Risk Ratio (95% CL)	P-value	Adjusted P- value*
Overall	Pre-initiation	40,918	269,819	1.82 (1.83, 1.81)	*reference*		
	1 year post-initiation	53,122	269,051	2.37 (2.38, 2.36)	1.06 (1.04, 1.07)	< 0.001	< 0.001
	2 years post-initiation	46,830	234,826	2.39 (2.4, 2.38)	1.08 (1.05, 1.10)	< 0.001	< 0.001
Female	Pre-initiation	32,893	199,221	1.98 (1.99, 1.97)	*reference*		
	1 year post-initiation	42,599	198,940	2.57 (2.58, 2.56)	1.06 (1.04, 1.08)	< 0.001	< 0.001
	2 years post-initiation	37,421	174,338	2.58 (2.59, 2.56)	1.07 (1.05, 1.10)	< 0.001	< 0.001
Male	Pre-initiation	8,025	70,598	1.36 (1.37, 1.35)	*reference*		
	1 year post-initiation	10,523	70,111	1.8 (1.81, 1.79)	1.05 (1.01, 1.08)	0.012	0.120
	2 years post-initiation	9,409	60,488	1.87 (1.88, 1.85)	1.09 (1.04, 1.14)	< 0.001	0.007
Pre-2015	Pre-initiation	19,584	161,264	1.46 (1.46, 1.45)	*reference*		
	1 year post-initiation	24,198	143,061	2.03 (2.04, 2.02)	1.07 (1.05, 1.10)	< 0.001	< 0.001
	2 years post-initiation	19,829	115,524	2.06 (2.07, 2.05)	1.10 (1.06, 1.14)	< 0.001	< 0.001
Post-2015	Pre-initiation	21,334	108,555	2.36 (2.37, 2.34)	*reference*		
	1 year post-initiation	28,924	125,990	2.75 (2.77, 2.74)	1.04 (1.02, 1.06)	< 0.001	< 0.001
	2 years post-initiation	27,001	119,302	2.72 (2.73, 2.7)	1.06 (1.03, 1.09)	< 0.001	0.001
CR	Pre-initiation	1,812	15,730	1.38 (1.4, 1.36)	*reference*		
	1 year post-initiation	2,360	15,320	1.85 (1.88, 1.82)	1.07 (1.00, 1.16)	0.062	0.619
	2 years post-initiation	2,071	12,702	1.96 (1.99, 1.92)	1.12 (1.01, 1.24)	0.034	0.343
MS	Pre-initiation	1,368	3,091	5.31 (5.5, 5.13)	*reference*		
	1 year post-initiation	1,369	2,601	6.32 (6.56, 6.08)	0.99 (0.92, 1.07)	0.865	1.000
	2 years post-initiation	542	1,091	5.96 (6.33, 5.62)	0.98 (0.85, 1.12)	0.730	1.000
RA	Pre-initiation	35,777	236,280	1.82 (1.82, 1.81)	*reference*		
	1 year post-initiation	47,115	237,084	2.38 (2.39, 2.38)	1.06 (1.04, 1.08)	< 0.001	< 0.001
	2 years post-initiation	42,378	209,864	2.42 (2.43, 2.41)	1.08 (1.06, 1.11)	< 0.001	< 0.001
SL	Pre-initiation	590	1,914	3.7 (3.87, 3.54)	*reference*		
	1 year post-initiation	586	1,765	3.98 (4.17, 3.8)	0.99 (0.87, 1.14)	0.899	1.000
	2 years post-initiation	416	1,375	3.63 (3.83, 3.44)	0.97 (0.78, 1.19)	0.741	1.000
UC	Pre-initiation	1,371	12,804	1.28 (1.31, 1.26)	*reference*		
	1 year post-initiation	1,692	12,281	1.65 (1.68, 1.62)	1.02 (0.94, 1.10)	0.668	1.000
	2 years post-initiation	1,423	9,794	1.74 (1.78, 1.71)	1.05 (0.92, 1.20)	0.469	1.000

Supplementary Table 12 – Risk of chronic opioid use across autoimmune conditions in the first and second year period post-initiation of a biologic disease modifying therapy, compared to the one year period prior to initiation.

		Count with chronic opioid use (N)	Person-months	Prevalence per 12 person-months (95% CL)	Prevalence Ratio (from GEE)	P-value	Adjusted P- value*
Overall	Pre-initiation	26,766	269,819	1.19 (1.19, 1.19)	reference		
	1 year post-initiation	36,854	269,051	1.64 (1.64, 1.65)	1.05 (1.04, 1.07)	< 0.001	< 0.001
	2 years post-initiation	33,889	234,826	1.73 (1.72, 1.74)	1.07 (1.05, 1.10)	< 0.001	< 0.001
CR	Pre-initiation	930	15,730	0.71 (0.70, 0.72)	reference		
	1 year post-initiation	1,176	15,320	0.92 (0.91, 0.94)	1.07 (0.99, 1.16)	0.081	0.489
	2 years post-initiation	985	12,702	0.93 (0.91, 0.95)	1.06 (0.94, 1.19)	0.377	1.000
MS	Pre-initiation	123	3,091	0.48 (0.46, 0.49)	reference		
	1 year post-initiation	168	2,601	0.78 (0.75, 0.81)	1.27 (1.02, 1.58)	0.035	0.208
	2 years post-initiation	59	1,091	0.65 (0.61, 0.69)	1.24 (0.99, 1.56)	0.060	0.606
RA	Pre-initiation	24,773	236,280	1.26 (1.25, 1.26)	reference		
	1 year post-initiation	34,327	237,084	1.74 (1.73, 1.74)	1.05 (1.04, 1.07)	< 0.001	< 0.001
	2 years post-initiation	31,862	209,864	1.82 (1.81, 1.83)	1.08 (1.06, 1.10)	< 0.001	< 0.001
SL	Pre-initiation	320	1,914	2.01 (1.92, 2.10)	reference		
	1 year post-initiation	375	1,765	2.55 (2.43, 2.67)	0.90 (0.78, 1.03)	0.135	0.792
	2 years post-initiation	266	1,375	2.32 (2.20, 2.45)	0.83 (0.69, 0.99)	0.042	0.251
UC	Pre-initiation	620	12,804	0.58 (0.57, 0.59)	reference		
	1 year post-initiation	808	12,281	0.79 (0.78, 0.80)	1.01 (0.94, 1.10)	0.725	1.000
	2 years post-initiation	717	9,794	0.88 (0.86, 0.90)	1.06 (0.94, 1.20)	0.357	1.000

* P-values adjusted for multiple testing with Bonferroni correction.

Supplementary Table 13 – Risk of new opioid use across autoimmune conditions in the first and second year period post-initiation of a biologic disease modifying therapy, compared to the one year period prior to initiation.

		Count with acute opioid use (N)	Person-months	Incidence per 12 person-months (95% CL)	Risk Ratio (from GEE)	P-value	Adjusted P- value*
Overall	Pre-initiation	15326	227134	0.81 (0.81, 0.81)	reference		
	1 year post-initiation	17392	211127	0.99 (0.98, 0.99)	1.16 (1.13, 1.18)	< 0.001	< 0.001
	2 years post-initiation	14625	184672	0.95 (0.95, 0.95)	1.11 (1.09, 1.15)	< 0.001	< 0.001
CR	Pre-initiation	930	15,730	0.71 (0.70, 0.72)	reference		
	1 year post-initiation	1,176	15,320	0.92 (0.91, 0.94)	1.19 (1.07, 1.31)	0.001	0.004
	2 years post-initiation	985	12,702	0.93 (0.91, 0.95)	1.15 (1.03, 1.28)	0.014	0.084
MS	Pre-initiation	123	3,091	0.48 (0.46, 0.49)	reference		
	1 year post-initiation	168	2,601	0.78 (0.75, 0.81)	1.10 (0.85, 1.41)	0.467	1.000
	2 years post-initiation	59	1,091	0.65 (0.61, 0.69)	0.94 (0.64, 1.38)	0.746	1.000
RA	Pre-initiation	24,773	236,280	1.26 (1.25, 1.26)	reference		
	1 year post-initiation	34,327	237,084	1.74 (1.73, 1.74)	1.15 (1.13, 1.18)	< 0.001	< 0.001
	2 years post-initiation	31,862	209,864	1.82 (1.81, 1.83)	1.11 (1.08, 1.14)	< 0.001	< 0.001
SL	Pre-initiation	320	1,914	2.01 (1.92, 2.10)	reference		
	1 year post-initiation	375	1,765	2.55 (2.43, 2.67)	0.86 (0.68, 1.09)	0.220	1.000
	2 years post-initiation	266	1,375	2.32 (2.20, 2.45)	1.00 (0.77, 1.28)	0.976	1.000
UC	Pre-initiation	620	12,804	0.58 (0.57, 0.59)	reference		
	1 year post-initiation	808	12,281	0.79 (0.78, 0.80)	1.29 (1.16, 1.43)	< 0.001	< 0.001
	2 years post-initiation	717	9,794	0.88 (0.86, 0.90)	1.15 (1.02, 1.30)	0.024	0.146

* P-values adjusted for multiple testing with Bonferroni correction.

Supplementary Table 14 – Chapter 2: Target Trial Emulation Framework.

Protocol component	Target trial	Emulation study of hypothetic target trial
Eligibility criteria	• Enrolled in Medicare fee-for-service, with continuous enrollment in Medicare Parts A, B and D for at least one year prior to trial start. • Not a member of an HMO currently or in year prior to trial start. • Age >= 65 as of January 1, 2008. • Prevalent user of opioids, defined as days' supply of medication on hand in the 30 days prior to study start. • Treatment failure with methotrexate within 6 months of study start. • New users of a bDMT with FDA approval for the treatment of RA, initiated between January 1, 2008 and December 31, 2019. • An existing diagnosis of rheumatoid arthritis. • No history of contraindications to treatment with opioids: opioid use disorder, substance use disorder, or alcohol use disorder. • No history of contraindications to treatment with DMTs: cancer, HIV, otherwise compromised immune system.	Same as for target trial, except discontinuation of methotrexate will be indicated by advancing to a second-line csDMT or initiating a bDMT. We have no information on clinical outcomes in Medicare claims, so discontinuation is a proxy for treatment failure.
Treatment strategies	Because RA is a progressive disease which could worsen if treatment were delayed, an augmentation design is required. The control group will receive a standard of care rather than no therapy. 1. Initiate a bDMT for treatment of RA after failure of methotrexate. 2. Initiate leflunomide as a second line csDMT for treatment of RA after failure of methotrexate.	Same as for target trial, except we will assess treatment at monthly intervals according to the days' supply of medications dispensed in Medicare Part D and B.
Assignment procedures	Participants with a need for RA treatment escalation are randomly assigned to a treatment group and are aware of their assigned strategy due to the known risks of DMT use and differences in the routes of administration for leflunomide and bDMTs.	Participants are assigned to a treatment strategy based on medication use observed in Part D and B Medicare Claims. Assume that individuals are randomly assigned to either treatment within levels of observed confounders.

Follow-up period	Starts at assigned therapy initiation and ends after 1-year of follow up or until one of the following: 1. Cessation of opioid use 2. Death 3. Unenrollment from Medicare Part A, B or D or enrollment in an HMO 4. End of study period (31 Dec 2019) 5. Non-adherence to assigned therapy (for per-protocol)	Same as for target trial.
Outcome	*Primary*: 3, 6 and 12-month risk of opioid cessation indicated by a 30 day gap in days' supply of opioids. *Secondary*: 3, 6 and 12-month risk of chronic opioid cessation indicated by a 30 day gap in days' supply of opioids.	Same as for target trial.
Causal contrasts of interest	Per-protocol effect Intention-to-treat	Observational analog of the intention-to-treat and per-protocol effect.
Analysis Plan	Estimate the 3, 6 and 12-month risk ratio of opioid cessation among those assigned to bDMT versus leflunomide.	Estimate the risk ratio of opioid cessation among those assigned to bDMT versus leflunomide using pooled logistic regression, weighted by IPTW (inverse probability of treatment weighting).

Supplementary Table 15 – Clinical Classifications Software Refined (CCSR) code list for comorbidities of interest.

	CCSR code	Description
Pain	'MUS038'	Low back pain
	'MUS010'	Musculoskeletal pain, not low back pain
	'NVS019'	Nervous system pain and pain syndromes
Opioid Contraindications	'SYM008'	Symptoms of mental and substance use conditions
	'MBD017'	Alcohol-related disorders
	'MBD018'	Opioid-related disorders
	'MBD019'	Cannabis-related disorders
	'MBD020'	Sedative-related disorders
	'MBD021'	Stimulant-related disorders
	'MBD022'	Hallucinogen-related disorders
	'MBD023'	Inhalant-related disorders
	'MBD028'	Opioid-related disorders subsequent encounter
	'MBD029'	Stimulant-related disorders subsequent encounter
	'MBD030'	Cannabis-related disorders subsequent encounter
	'MBD031'	Hallucinogen-related disorders subsequent encounter
	'MBD032'	Sedative-related disorders subsequent encounter
	'MBD033'	Inhalant-related disorders subsequent encounter
	'MBD034'	Mental and substance use disorders sequela
	'MBD025'	Other specified substance-related disorders
	'MBD026'	Mental and substance use disorders in remission
	'MBD024'	Tobacco-related disorders (?)
Gastrointestinal contraindications	'DIG005'	Gastroduodenal ulcer
	'DIG011'	Regional enteritis and ulcerative colitis
	'DIG021'	Gastrointestinal hemorrhage
	'DIG022'	Noninfectious gastroenteritis

Clinical Classifications Software Refined (CCSR)

Supplementary Table 16 – Balance of IPTWs for per-protocol analysis of all prevalent users across follow-up with percentile cut-offs (primary analysis with 30-day criteria for opioid use discontinuation).

Person-month of follow-up	N	P[A=1]	Untruncated stabilized IPT weights				Truncated stabilized IPT weights				Percentile cut-offs				
			Mean	Median	Min	Max	Mean	Median	Min	Max	99.5th	99th	98.5th	98th	97th
1	3,967	0.746	1.01	0.955	0.3450	4.9	1.01	0.955	0.4230	2.5	2.5	2.2	2	1.9	1.7
2	1,275	0.744	1.00	0.955	0.3830	4.9	1.00	0.955	0.4000	2.7	2.7	2.3	2	1.9	1.6
3	936	0.739	1.01	0.957	0.3800	4.9	1.00	0.957	0.3970	3.1	3.1	2.1	2	1.9	1.7
4	750	0.736	1.13	0.907	0.1560	32.0	1.08	0.907	0.1860	6.3	6.3	4.4	4.1	3.5	2.7
5	583	0.741	1.61	0.847	0.0520	234.0	1.16	0.847	0.0936	8.6	12	8.6	7	5.2	3.4
6	462	0.745	5.20	0.793	0.0189	1595.0	1.41	0.793	0.0426	15.2	64	20	15	12	5.8
7	379	0.755	2.27	0.743	0.0062	257.0	1.36	0.743	0.0174	14.3	40	34	14	8.3	6.2
8	310	0.761	4.97	0.694	0.0020	786.0	1.64	0.694	0.0135	18.2	92	69	47	18	11
9	262	0.756	3.34	0.659	0.0008	184.0	1.66	0.659	0.0096	17.3	140	79	25	17	11
10	212	0.769	6.60	0.648	0.0009	450.0	2.14	0.648	0.0151	23.0	274	214	64	27	23
11	179	0.782	7.81	0.615	0.0003	533.0	2.37	0.615	0.0042	26.4	401	164	63	41	26
12	147	0.769	13.80	0.581	0.0001	876.0	3.01	0.581	0.0020	32.9	696	409	134	68	33

Supplementary Table 17 – Balance of IPTWs for per-protocol analysis of all chronic users across follow-up with percentile cut-offs (primary analysis with 30-day criteria for opioid use discontinuation).

Person-month of follow-up	N	P[A=1]	Untruncated stabilized IPT weights				Truncated stabilized IPT weights				Percentile cut-offs				
			Mean	Median	Min	Max	Mean	Median	Min	Max	99.5th	99th	98.5th	98th	97th
1	1,046	0.73	1.01	0.943	0.35	3.5	1.05	0.943	0.3930	3.5	2.8	2.5	2.4	2.2	2.1
2	419	0.726	1.01	0.914	0.379	2.9	0.99	0.914	0.3920	2.9	2.5	2.2	2	1.9	1.9
3	382	0.717	1.01	0.912	0.379	2.9	0.99	0.912	0.3940	2.9	2.6	2.3	2	1.9	1.8
4	336	0.723	1.67	0.827	0.13	11.3	1.17	0.827	0.1740	11.3	7	6.2	5.2	4.4	4.2
5	277	0.726	14	0.731	0.0285	28.3	1.29	0.731	0.0724	13.6	14	10	9.3	5.4	4.5
6	233	0.73	257	0.636	0.0062	109	1.61	0.636	0.0313	19.6	26	20	16	8.7	7.8
7	199	0.734	4.22	0.561	0.0013	81.9	1.85	0.561	0.0129	23.1	39	23	22	12	10
8	172	0.738	12.3	0.497	0.0003	365	2.74	0.497	0.0065	38.8	102	56	39	23	19
9	153	0.725	40.6	0.422	0.0001	1624	2.99	0.422	0.0019	39.3	249	62	39	30	26
10	123	0.74	236	0.358	0.0005	11356	4.38	0.358	0.0027	57.9	869	292	102	58	54
11	104	0.76	27.9	0.32	0.0002	1197	5.51	0.320	0.0013	79.6	234	169	110	80	76
12	87	0.759	58.6	0.289	0.0001	2536	9.76	0.289	0.0004	166.0	900	321	253	166	136

Supplementary Table 18 – Intention to treat effect for risk of opioid use discontinuation (analysis with 60-day criteria for opioid use discontinuation).

	Risk in Treatment 0: leflunomide (95%CLs)	Risk in Treatment 1: bDMT (95%CLs)	Risk Difference, per 1,000 person-trials (95%CLs)	Risk Ratio (95%CLs)
Prevalent Opioid Use				
3-month Discontinuation	38.02% (34.54, 41.51)	39.83% (37.74, 41.93)	18.07 (-23.29, 59.81)	1.05 (0.94, 1.17)
6-month Discontinuation	61.66% (57.90, 65.28)	63.41% (61.33, 65.63)	17.55 (-25.17, 62.42)	1.03 (0.96, 1.11)
12-month Discontinuation	85.40% (82.20, 88.00)	86.04% (84.14, 87.82)	6.45 (-25.02, 42.73)	1.01 (0.97, 1.05)
Chronic Opioid Use				
3-month Discontinuation	12.09% (7.01, 17.62)	17.28% (13.40, 21.24)	51.94 (-16.80, 122.85)	1.42 (0.91, 2.65)
6-month Discontinuation	27.23% (18.35, 35.51)	34.87% (28.92, 40.76)	76.33 (-31.56, 184.32)	1.28 (0.91, 1.98)
12-month Discontinuation	63.03% (52.78, 70.87)	66.91% (58.79, 73.53)	38.74 (-82.96, 169.58)	1.06 (0.87, 1.32)

Supplementary Table 19 – Intention to treat effect for risk of opioid use discontinuation (analysis with 90-day criteria for opioid use discontinuation).

	Risk in Treatment 0: leflunomide (95%CLs)	Risk in Treatment 1: bDMT (95%CLs)	Risk Difference, per 1,000 person-trials (95%CLs)	Risk Ratio (95%CLs)
Prevalent Opioid Use				
6-month Discontinuation	51.58% (47.56, 55.16)	50.18% (47.87, 52.48)	-14.02 (-56.88, 32.88)	0.97 (0.90, 1.07)
12-month Discontinuation	82.64% (78.71, 86.07)	81.86% (79.69, 83.74)	-7.82 (-47.94, 40.16)	0.99 (0.94, 1.05)
Chronic Opioid Use				
6-month Discontinuation	25.81% (17.78, 34.10)	23.70% (18.70, 29.12)	-21.14 (-116.36, 70.00)	0.92 (0.65, 1.36)
12-month Discontinuation	50.58% (38.86, 60.87)	53.53% (45.73, 61.70)	29.48 (-98.44, 173.45)	1.06 (0.83, 1.42)

Supplementary Table 20 – Per-protocol effect for risk of opioid use discontinuation (analysis with 60-day criteria for opioid use discontinuation).

	Risk in Treatment 0: leflunomide (95%CLs)	Risk in Treatment 1: bDMT (95%CLs)	Risk Difference, per 1,000 person-trials (95%CLs)	Risk Ratio (95%CLs)
Prevalent Opioid Use				
3-month Discontinuation	67.99% (61.03, 74.15)	69.86% (67.32, 72.64)	18.68 (-46.66, 88.17)	1.03 (0.94, 1.14)
6-month Discontinuation	84.99% (81.05, 89.31)	86.16% (84.19, 87.98)	11.72 (-37.24, 53.43)	1.01 (0.96, 1.07)
12-month Discontinuation	93.31% (88.45, 97.30)	93.78% (90.80, 96.26)	4.67 (-49.07, 56.45)	1.01 (0.95, 1.06)

Supplementary Table 21 – Balance of IPTW for per-protocol analysis of all prevalent opioid users across follow-up with percentile cut-offs (analysis with 60-day criteria for opioid use discontinuation).

Person-month of follow-up	N	P[A=1]	The (untruncated) stabilized IPT weights				Truncated stabilized IPT weights				Percentile cut-offs				
			Mean	Median	Min	Max	Mean	Median	Min	Max	99.5th	99th	98.5th	98th	97th
1	3,967	0.746	1.02	0.953	0.341	4.98	1.02	0.953	0.4070	2.9	2.9	2.4	2.2	2	1.8
2	1,561	0.746	1	0.94	0.353	4.66	1.00	0.940	0.4030	2.9	2.9	2.3	1.9	1.8	1.7
3	1,115	0.745	1	0.938	0.349	4.66	1.00	0.938	0.4030	3.1	3.1	2.4	1.9	1.9	1.7
4	863	0.732	1.1	0.874	0.142	24.7	1.08	0.874	0.1860	7.8	7.8	4.8	4.2	3.3	2.8
5	672	0.726	1.41	0.813	0.0516	107	1.18	0.813	0.0974	8.3	20	8.3	6.3	5.4	4.5
6	557	0.722	2.56	0.761	0.0185	577	1.36	0.761	0.0489	10.4	31	11	10	8.8	7.4
7	446	0.733	9	0.73	0.0065	3147	1.70	0.730	0.0238	17.3	57	21	17	14	11
8	365	0.753	2.56	0.705	0.0032	128	2.11	0.705	0.0189	20.7	39	28	22	21	17
9	313	0.744	3.38	0.665	0.0011	240	2.48	0.665	0.0095	30.7	61	36	32	31	24
10	257	0.751	4.17	0.68	0.0006	142	3.28	0.680	0.0098	40.1	80	60	55	52	40
11	221	0.751	4.67	0.62	0.0002	141	3.30	0.620	0.0030	39.8	104	88	81	63	40
12	192	0.745	7.64	0.623	0.0001	233	5.02	0.623	0.0013	61.1	173	153	131	126	61

Supplementary Table 22 – Per-protocol effect for risk of opioid use discontinuation (analysis with 90-day criteria for opioid use discontinuation).

	Risk in Treatment 0: leflunomide (95%CLs)	Risk in Treatment 1: bDMT (95%CLs)	Risk Difference, per 1,000 person-trials (95%CLs)	Risk Ratio (95%CLs)
Prevalent Opioid Use				
6-month Discontinuation	86.54% (82.93, 93.97)	84.31% (81.62, 86.46)	-22.36 (-106.13, 12,73)	0.97 (0.89, 1.02)
12-month Discontinuation	93.12% (89.40, 98.65)	92.97% (88.38, 96.72)	-1.60 (-77.99, 50.13)	1.00 (0.92, 1.06)

Supplementary Table 23 – Balance of IPTW for per-protocol analysis of all prevalent opioid users across follow-up with percentile cut-offs (analysis with 90-day criteria for opioid use discontinuation).

Person-month of follow-up	N	P[A=1]	The (untruncated) stabilized IPT weights				Truncated stabilized IPT weights				Percentile cut-offs				
			Mean	Median	Min	Max	Mean	Median	Min	Max	99.5th	99th	98.5th	98th	97th
1	3,967	0.746	1.02	0.963	0.333	4.84	1.02	0.963	0.3960	2.9	2.9	2.3	2.1	2	1.8
2	1,695	0.759	1	0.95	0.345	3.91	1.00	0.950	0.4010	2.5	2.5	2.2	1.9	1.8	1.7
3	1,355	0.759	0.99	0.951	0.345	3.91	1.00	0.951	0.3950	2.5	2.5	2.1	1.9	1.8	1.6
4	987	0.761	1.11	0.886	0.109	28.5	1.08	0.886	0.1530	8.0	8	5.2	3.9	3.5	2.8
5	738	0.76	1.57	0.829	0.0447	176	1.26	0.829	0.0726	13.5	19	14	8.2	6	4.8
6	603	0.758	4.21	0.777	0.0153	1308	1.38	0.777	0.0353	12.5	80	39	13	11	8.1
7	489	0.761	23	0.742	0.00479	9842	1.68	0.742	0.0159	21.7	176	32	22	17	10
8	404	0.785	190	0.72	0.00164	74815	2.12	0.720	0.0128	29.2	343	68	36	29	17
9	340	0.782	6.49	0.716	0.00059	858	2.75	0.716	0.0058	44.9	223	62	54	45	25
10	286	0.78	17.3	0.693	0.00019	2685	3.64	0.693	0.0073	49.2	560	223	95	75	49
11	246	0.789	45	0.664	0.00006	8693	4.36	0.664	0.0026	59.4	897	158	118	98	59
12	206	0.757	152	0.631	0.00002	27729	6.14	0.631	0.0006	89.6	2045	196	181	176	90

Supplementary Table 24 – Chapter 3: Target Trial Emulation Framework.

Protocol component	Target trial	Emulation study of hypothetic target trial
Eligibility criteria	• Enrolled in Medicare fee-for-service, with continuous enrollment in Medicare Parts A, B and D for at least one year prior to trial start. • Not a member of an HMO currently or in year prior to trial start. • Age >= 65 as of January 1, 2007. • New users of a bDMT with FDA approval for the treatment of RA, initiated between January 1, 2007 and December 31, 2019. • An existing diagnosis of rheumatoid arthritis. • Initiated a prescription NSAID or opioid within three months of initiating a bMDT. • No history of contraindications to treatment with opioids: opioid use disorder, substance use disorder, or alcohol use disorder. • No history of contraindications to therapy with NSAIDs: chronic kidney disease, gastrointestinal bleeding, peptic ulcer, or diagnosis of Crohn's or ulcerative colitis. • Self-reported moderate to severe pain requiring analgesic therapy, assessed as >= 5 on the Numeric Pain Rating Scale (NPRS).	Same as for target trial, except there is no information on self-reported pain severity available in Medicare claims, so we are unable to ensure included individuals are reporting moderate to severe pain. Initiators of opioids or NSAIDs are those with no days' supply of medication on hand in the 30 days prior to bDMT initiation.
Treatment strategies	1. Treat self-reported moderate to severe pain with opioid analgesics within 3 months of bDMT initiation and sustain treatment. Individuals prescribed opioids should follow their dosing schedule according to prescribing clinician's recommendations. 2. Treat self-reported moderate to severe pain with prescription NSAIDs within 3 months of bDMT initiation and sustain treatment. Individuals prescribed opioids should follow their dosing schedule according to prescribing clinician's recommendations. Individual analgesic requirements are assessed by a clinician after randomization to either treatment strategy. Individuals are treated with the lowest possible clinically effective dose. When warranted, an individual may switch to an analgesic outside of their treatment assignment after the end of bDMT days' supply.	Same as for target trial, except we will assess treatment at set (weekly/monthly) intervals according to the days' supply of medications dispensed in Medicare Part D. Each month the exposures are assessed as follows: 1. Continue use of opioid, determined by day's supply of opioid dispensed. A gap of 30 days in opioid exposure is cause for censoring due to treatment non-adherence. 2. Continue use of prescription NSAID, determined by day's supply of opioid dispensed. A gap of 30 days in opioid exposure is cause for censoring due to treatment non-adherence. If an individual is treated with both opioids and prescription NSAIDs, they are compliant with neither treatment strategy and both clones are censored.

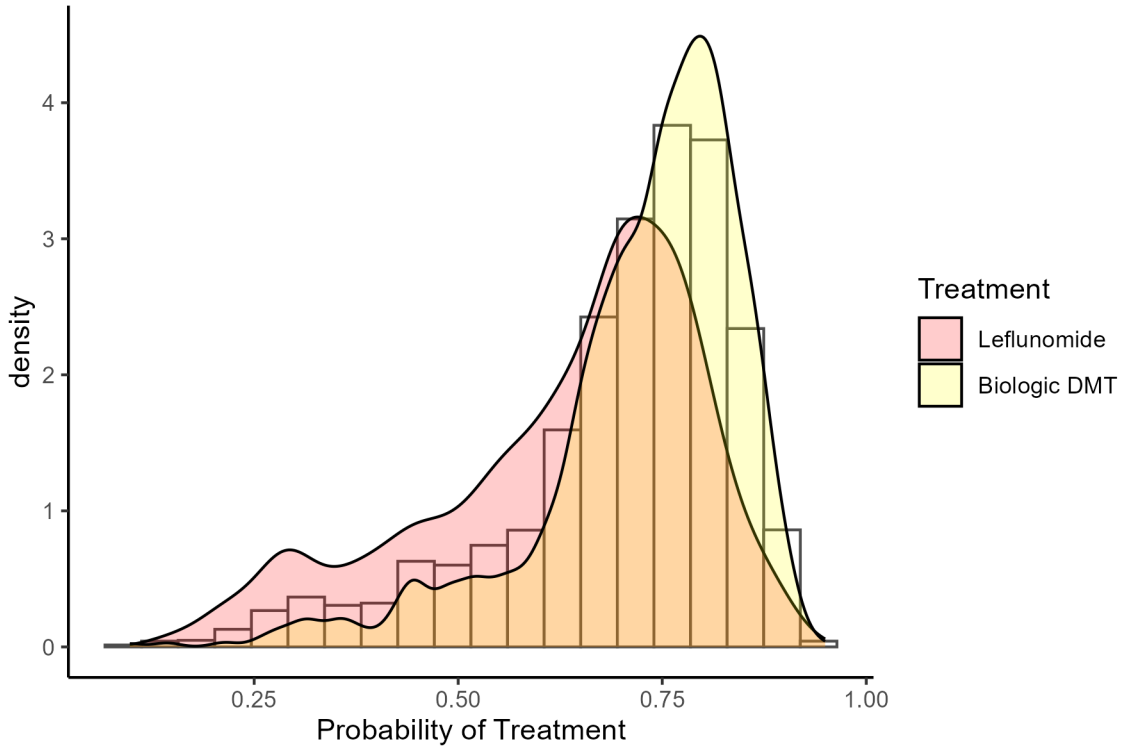
Assignment procedures	Participants with a requirement for analgesic use are randomly assigned to a treatment group and are aware of their assigned strategy due to the known risks of opioid use.	Participants are assigned to a treatment strategy based on medication use observed in Part D Medicare Claims. Assume that individuals are exchangeable conditional on measured baseline covariates.
Follow-up period	Starts at bDMT initiation and ends after 12 months of follow up or until one of the following: 1. Discontinuation of bDMT 2. Death 3. Disenrollment from Medicare Part A, B or D or enrollment in an HMO 4. End of study period (31 Dec 2019)	Same as for target trial.
Outcome	Primary: 12-month risk of bDMT discontinuation. Discontinuation of bDMT therapy, indicated by a 90 day gap in days' supply of bDMT. Secondary: 12-month risk of bDMT switching. Switching of bDMT therapy, indicated by the dispensing of a different bDMT before the end of current bDMT days' supply or within 90 days of the end of the previous bDMT days' supply.	Same as for target trial.
Causal contrasts of interest	Per-protocol effect	Observational analog of the per-protocol effect.
Analysis Plan	Estimate the 12-month risk ratio of discontinuation and switching of bDMT therapy among those assigned to treat pain with opioids versus with prescription NSAIDs. IPCW will account for censoring due to death or loss to follow-up.	Estimate the 12-month risk ratio of discontinuation and switching of bDMT therapy among those treating pain with opioids versus with prescription NSAIDs using pooled logistic regression, weighted by IPCW (inverse probability of remaining uncensored).

Supplementary Table 25 – Balance of IPTW for clone-censoring weights across follow-up with percentile cut-offs.

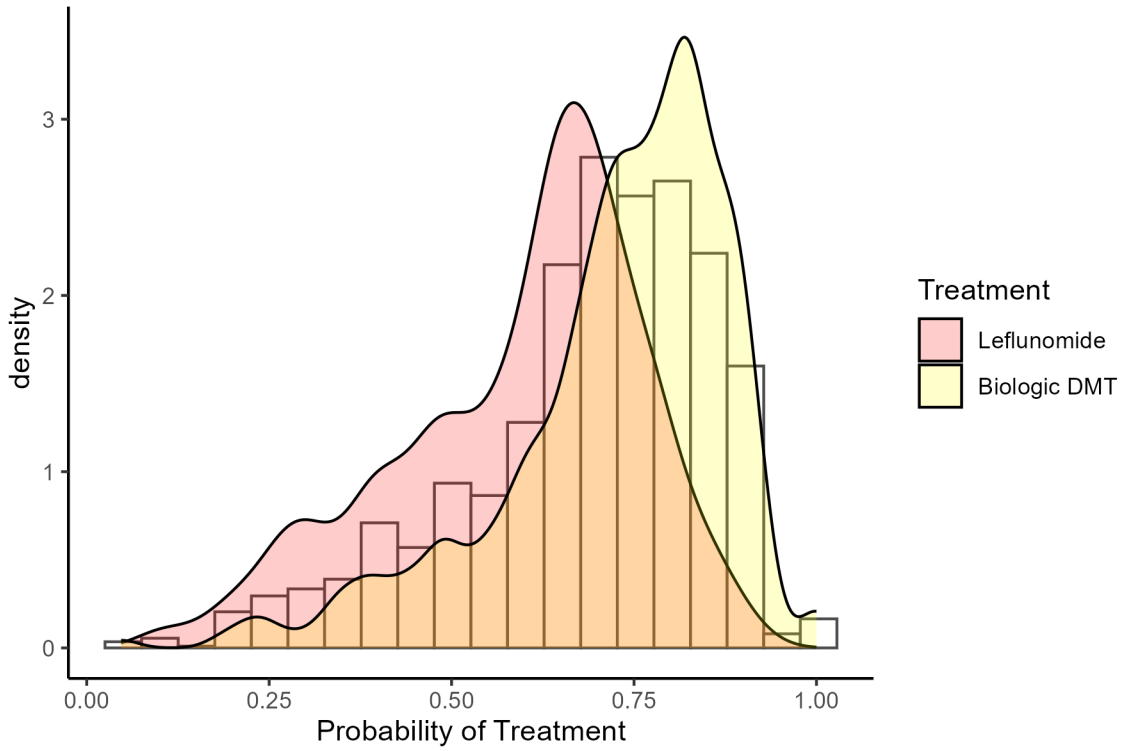
Person-month of follow-up	N	P[A=1]	The (untruncated) stabilized IPT weights*				Truncated stabilized IPT weights*			
			Mean	Median	Min	Max	Mean	Median	Min	Max
1	19,530	0.5	1.01	0.997	0.905	1.84	1.01	0.997	0.9050	1.8
2	18,286	0.501	1.01	0.999	0.85	1.76	1.01	0.999	0.8500	1.8
3	17,261	0.498	1.18	1.03	0.135	27.4	1.16	1.030	0.1350	4.2
4	1842	0.604	1.13	1	0.18	12.1	1.11	1.000	0.1800	4.2
5	1469	0.57	1.17	0.987	0.166	17.3	1.14	0.987	0.1660	4.2
6	1100	0.537	1.24	0.965	0.125	26.2	1.17	0.965	0.1250	4.2
7	848	0.507	1.31	0.932	0.0836	43.3	1.20	0.932	0.0836	4.2
8	740	0.499	1.51	0.919	0.0526	67.4	1.25	0.919	0.0526	4.2
9	647	0.495	1.84	0.865	0.0324	118	1.26	0.865	0.0324	4.2
10	573	0.496	2.34	0.875	0.02	210	1.33	0.875	0.0200	4.2
11	504	0.49	3.37	0.815	0.0119	455	1.36	0.815	0.0119	4.2
12	450	0.493	5.33	0.772	0.00784	926	1.37	0.772	0.0078	4.2

*Summary statistics excluding weights of 0 at each time point, indicating an individual was censored.

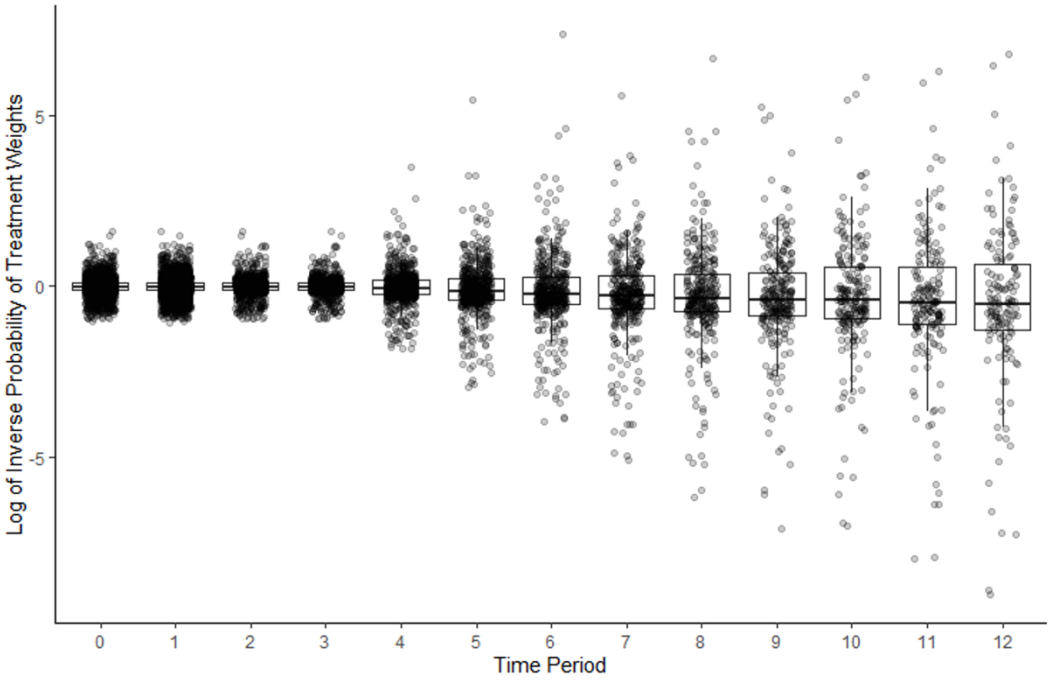
SUPPLEMENTARY FIGURES



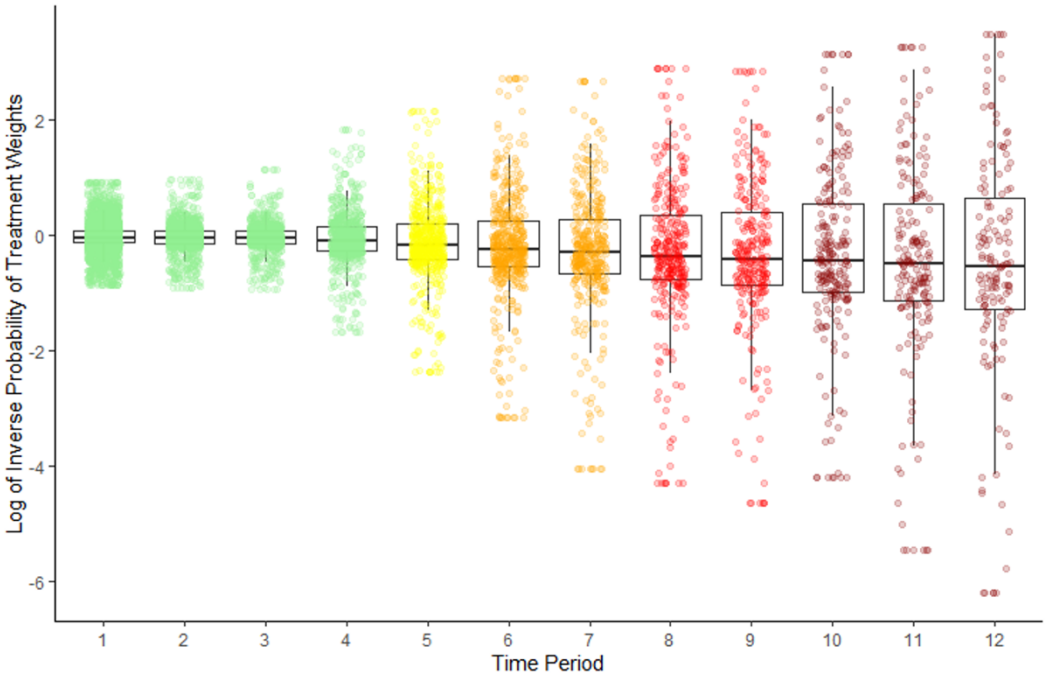
Supplementary Figure 1 – Propensity Score distribution for baseline covariates in prevalent opioid use.



Supplementary Figure 2 – Propensity Score distribution for baseline covariates in chronic opioid use.



Supplementary Figure 3 – Balance of treatment adherence weights by person-month of follow-up for primary analysis in all prevalent opioid users, pre-truncation (30-day definition for opioid use discontinuation).



Supplementary Figure 4 – Balance of truncated treatment adherence weights by person-month of follow-up for primary analysis in all prevalent opioid users (30-day definition for opioid use discontinuation).

(green = truncated at the 99.5th percentile; yellow = truncated at the 99th percentile; orange = truncated at the 98.5th percentile; red = truncated at the 98th percentile; purple = truncated at the 97th percentile)