

Title: TreatmentPatterns: An R package to analyze treatment patterns of a study population of interest

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Background

Several treatment pattern studies have been performed on databases mapped to the OMOP-CDM (1-3). However, there is no R package available for this type of studies and the standard analytics tool available in ATLAS has the disadvantage that it is not customizable to specific research needs. A wide range of R packages is already available to support research on the OMOP-CDM (e.g. FeatureExtraction, CohortDiagnostics, and PatientLevelPrediction) and we aim to add the open-source R package TreatmentPatterns to this collection to analyze treatment patterns of a study population of interest.

Methods

We defined the process of constructing pathways following earlier work (1), highlighting decisions in the process that need to be made (and correspond to study settings in the R package that can be changed). Figure 1 shows an example of the medical file for an individual receiving treatments A, B and C. The figure visualizes the decisions that need to be made to construct the treatment pathway for this individual.

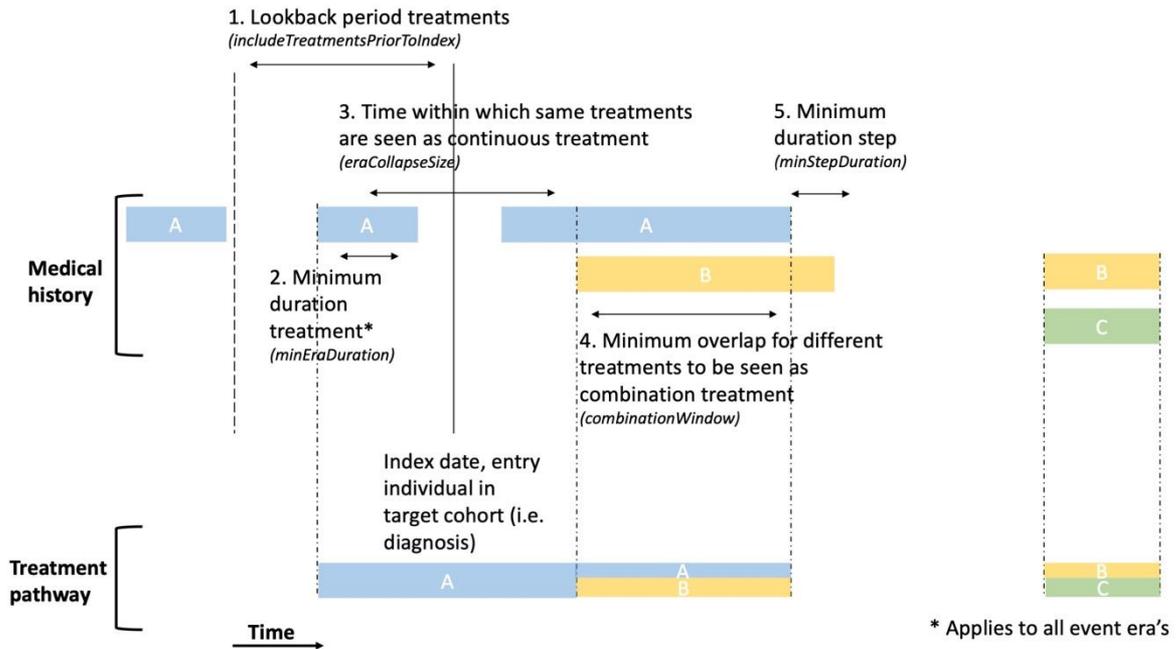


Figure 1: Summary of decisions to construct individual treatment pathways. The letters A, B, and C refer to the treatments of interest.

The five identified decisions are:

1. Lookback period treatments, *includeTreatmentsPriorToIndex* specifies the period (number of days) prior to the index date of the target cohort from which treatments should be included.
2. Minimum duration treatment, *minEraDuration* specifies the minimum time an event era should last to be included in the analysis.
3. Time within which two subsequent same treatments are seen as one continuous treatment, *eraCollapseSize* allows to indicate the number of days within which two eras of the same event cohort are collapsed into one era (i.e. seen as continuous treatment) instead of a stop and re-initiation of the same treatment.
4. Minimum overlap for different treatments to be seen as combination treatment, *combinationWindow* specifies the time that two event cohorts need to overlap to be considered a combination treatment.

5. Minimum duration step, *minStepDuration* specifies the minimum time an event era before or after a generated combination treatment should last to be included in the analysis as a separate treatment.

The R package TreatmentPatterns (<https://github.com/mi-erasmusmc/treatmentpatterns>) implements the problem formalization described above. The main inputs of the package are the target and event cohorts of interest, which can be cohort definitions to allow automatic cohort extraction from databases mapped to the OMOP-CDM or a file with already generated cohorts for databases in other formats. The main body of the package executes the characterization (only for databases mapped to OMOP-CDM), then constructs the individual treatment pathways and then aggregates these for the target cohort. The package creates sunburst plots, Sankey diagrams, and various other outputs (e.g. percentage of people treated, average duration of event cohorts) to give insight in first-, second- and higher line treatments. All results can be explored in an interactive Shiny application.

We demonstrate the functionalities of the package and outputs by analyzing treatment patterns of three common chronic diseases (type 2 diabetes, hypertension, and depression) in the Dutch Integrated Primary Care Information (IPCI) database. We create target cohorts of patients with index date at first treatment, at least 365 days prior observation database time, and 1095 days follow-up time after index date. We only include patients initiating their first treatment after 2010. An overview of the study is given in Table 1.

	Type 2 diabetes	Hypertension	Depression
Target cohorts	Drug era of diabetes drugs, and condition occurrence of: - Diabetes mellitus (201820) And NO - Type 1 diabetes (35506621)	Drug era of hypertension drugs, and condition occurrence of: - Hypertensive disorder (316866)	Drug era of depression drugs, and condition occurrence of: - Depressive disorder (440383) And NO - schizophrenia (435783) - bipolar disorder (432876)

Event cohorts	Exenatide (1583722) Gliclazide (19059796) Glimepiride (1597756) Glipizide (1560171) Glyburide (1559684) Insulin, Aspart, Human (1567198) Insulin, Glargine, Human (1502905) Liraglutide (40170911) Metformin (1503297) Pioglitazone (1525215) Rosiglitazone (1547504) Saxagliptin (40166035) Sitagliptin (1580747)	Amlodipine (1332418) Atenolol (1314002) Benazepril (1335471) Diltiazem (1328165) Furosemide (956874) Hydrochlorothiazide (974166) Lisinopril (1308216) Losartan (1367500) Metoprolol (1307046) Olmesartan (40226742) Ramipril (1334456) Spironolactone (970250) Triamterene (904542) Valsartan (1308842)	Amitriptyline (710062) Bupropion (750982) Citalopram (797617) Desvenlafaxine (717607) Doxepin (738156) Duloxetine (715259) Escitalopram (715939) Fluoxetine (755695) Mirtazapine (725131) Nortriptyline (721724) Paroxetine (722031) Sertraline (739138) Trazodone (703547) Venlafaxine (743670) Clonidine (1398937)
Study settings	includeTreatmentsPriorToIndex = 0 minEraDuration = 5 splitEventCohorts = none eraCollapseSize = 30 combinationWindow = 30 minStepDuration = 30 filterTreatments = Changes maxPathLength = 5 minCellCount = 5 minCellMethod = Adjust groupCombinations = 10 addNoPaths = TRUE		
Data source	Integrated Primary Care Information (IPCI), Dutch GP database		

Table 1: Overview of type 2 diabetes, hypertension, and depression study. Concept IDs

used to identify the cohorts are listed in brackets.

Results

We find 39,488 type 2 diabetes patients, 99,303 hypertension patients, and 31,885 patients with depression. Treatment pathways are visualized in the form of sunburst plots and Sankey diagrams, see Figure 2. For type 2 diabetes, metformin was the most frequently prescribed first-line treatment (62.0 % of patients) followed by gliclazide (8.0% of patients). Here, we thus observe agreement on the first prescribed medication. For hypertension, hydrochlorothiazide (26.2% of patients), metoprolol (17.5% of patients), and amlodipine (12.8% of patients) are most often used as starting medication. For depression, there are four types of medication that at least 10% of the patients receive as first treatment: amitriptyline, paroxetine, citalopram, and mirtazapine. Combination treatments occur in

19.7% of patients as first treatment for hypertension, but only in 10.6% of type 2 diabetes patients, and are rare for depression patients (1.8%).

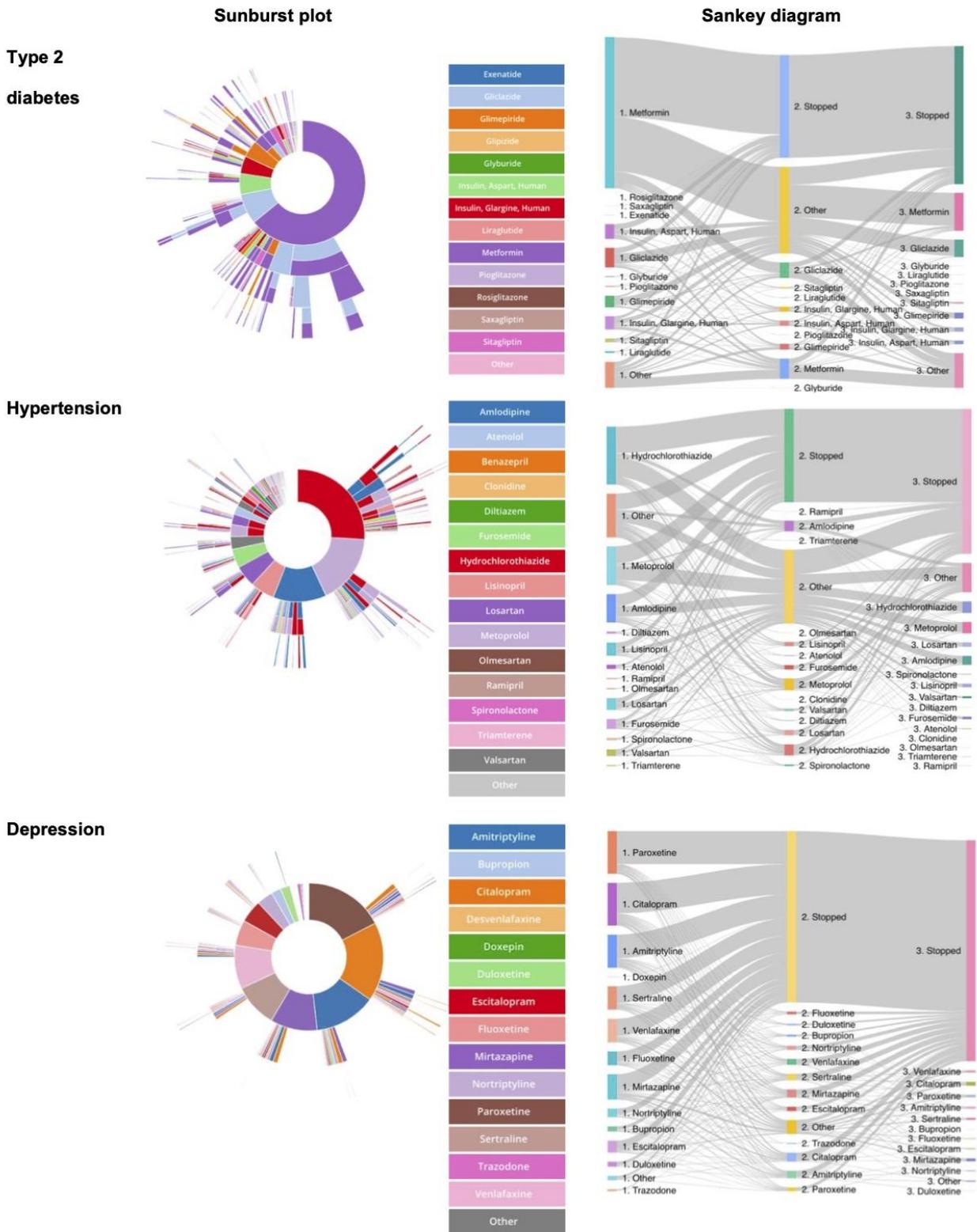


Figure 2: Sunburst plots and Sankey diagrams visualizing the treatment pathways of patients with type 2 diabetes, hypertension, and depression.

Conclusion

TreatmentPatterns is freely available for other researchers to analyze treatment patterns of a study population of interest. The package partially relies on the OMOP-CDM, but the main parts of the package are also usable with different data formats. This tool is intended to make the analysis of treatment patterns more accessible, more standardized, and more interpretation friendly. We hope it thereby contributes to the accumulation of knowledge on real-world treatment patterns across disease domains. We encourage researchers to further adjust and add custom analysis to the package based on their research needs.

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