

ORIGINAL ARTICLE

Graphical methods for understanding changes in states: Understanding medication use pathways

Elizabeth A. Wise  | Roy J. Adams | Constantine G. Lyketsos | Jeannie-Marie Leoutsakos

Department of Psychiatry and Behavioral Sciences, Johns Hopkins Bayview and Johns Hopkins University, Baltimore, Maryland, USA

Correspondence

Jeannie-Marie Leoutsakos, Department of Psychiatry and Behavioral Sciences, Johns Hopkins Bayview and Johns Hopkins University, 4300 Alpha Commons Drive, Baltimore, MD 21224, USA.
Email: jeannie-marie@jhu.edu

Funding information

NIA/NIH, Grant/Award Number: U01 AG016976

Abstract

Objectives: As epidemiological studies become longer and larger, the field needs novel graphical methods to visualize complex longitudinal data. The aim of this study was to present the Slinkyplot, a longitudinal crosstabulation, to illustrate patterns of antidepressant use in a large prospective cohort of older adults with mild cognitive impairment.

Methods: Data from the National Alzheimer's Coordinating Center are used to track switches between different states and types of antidepressant use. A Slinkyplot is populated with rows representing the state of medication use at each timepoint and columns representing the state at each subsequent visit.

Results: The constructed Slinkyplots display the common practice of switching on and off different antidepressants over time, with citalopram, sertraline, and bupropion most commonly used followed by switching to another SSRI or SNRI as second-line treatment.

Conclusions: Slinkyplots are an innovative graphical means of visualizing complex patterns of transitions between different states over time for large longitudinal studies.

KEYWORDS

antidepressants, dementia, methodology

1 | INTRODUCTION

Epidemiological studies are becoming more complex and longer in duration. Given that chronic diseases - such as diabetes and ischemic heart disease - are significant contributors to disability and global disease burden, we need improved ways of visualizing longitudinal data, particularly on complex disorders. In psychiatry, we describe and explain mental disorders and emotional states according to a combination of different perspectives (McHugh & Slavney, 1983). In thinking about changes over time, one can apply the logic of the

narrative, or the life story perspective. The narrative of the life story, which consists of a chronological recounting of setting, sequence, and outcome, helps patients and providers explain emotional states.

The increasing use of electronic medical records (EMR) means we have more data, on more individuals, and with more frequent visits than we would have from typical prospective cohort studies. This new resource makes precision medicine possible, in that it allows us to progress from asking questions like, 'Do antidepressants improve affect, on average?' to, 'Which kinds of patients would benefit from antidepressants, which one(s) should they take, and for

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. International Journal of Methods in Psychiatric Research published by John Wiley & Sons Ltd.

how long?’ These new resources and new questions require new methods for visualizing such complex data.

To begin to answer these questions about antidepressants, one first has to understand how they are used. Medication adherence among people with depression varies; individuals may stop taking their antidepressants because a mood episode has resolved or they may decide to stop due to side effects. Individuals may also fear long-term side effects. Researchers have speculated on the relationship between antidepressant use and future cognitive decline (Moraros et al., 2017), though evidence for antidepressant use contributing to cognitive decline is inconclusive, and the relationship may be a result of confounding by indication. Some studies have demonstrated an association between antidepressant use and the development of cognitive impairment or dementia (Burke et al., 2018; Goveas et al., 2012; Kodesh et al., 2019; Leng et al., 2018; Then et al., 2017; Wang et al., 2016), while other research has found no association with the development of cognitive impairment (Han et al., 2020; Saczynski et al., 2015).

In order to examine more granularly the relationship between antidepressant use and long-term effects on cognition, we first need to understand antidepressant medication usage in older adults. For instance, we need to know which medications they take, for how long, and how often they switch to a different antidepressant. We also want to explore medication use in people taking multiple antidepressants: at what time point and how often do they add another antidepressant and which one? We need a method to visualize patterns of medication usage in older adults in order to answer these questions.

Longitudinal data, such as medication usage over time, are typically depicted via tree plots and spaghetti plots. A tree plot or structure consists of a root with linked nodes depicting presence of discrete states. This structure is not ideal for visualizing switching over time such as with medication usage particularly when multiple state changes occur, because it can be difficult to summarize across multiple small nodes representing the same state. In a spaghetti plot, each person's outcome measure is plotted on the vertical axis against time on the horizontal axis, with a line connecting outcome measures over time. Such plots are excellent for showing patterns of change over time on a single continuous variable, but are not helpful in demonstrating changes in states (discrete variables). With large

samples, spaghetti plots exhibit ‘over-plotting’ with multiple intersecting lines and no clear patterns (Swihart et al., 2010). Another option is the lasagna plot, which uses color to depict outcome and allows for more data to be clearly depicted than in spaghetti plots (Swihart et al., 2010). The lasagna plot, however, is not effective at depicting switching patterns, which is a common occurrence with antidepressant usage. For both spaghetti and lasagna plots, it can be difficult to represent missingness. Stacked bar plots that use color to denote state at each timepoint are also suboptimal, because they do not convey who has switched to each state at each timepoint or from what state they switched.

More recently, several types of plots have been described which approach the current aim of demonstrating patterns of transition between states over time. A state distribution plot, also known as a chronogram, describes changes in the composition of a group over time (see Figure 1 which relates state distribution plots to Slinkyplots). These plots do not capture quantities of transitions among states nor the states between which people fluctuate. While transition plots show these shifts explicitly, they do not capture quantities (Cicchinelli et al., 2018). Finally, sequence index plots show aggregate individual transition sequences by general groups (Counil, 2020; Vanhoutte et al., 2019). These sequence index plots use line segments to graph individual sequences, with changes in color denoting transitions. They rely on preprocessing to identify groups of sequences and are therefore less useful in early exploratory stages of data analysis where one wants to see the actual data. Finally, a Sankey plot (Zovaleta-Ramirez et al., 2020) uses arrows or arcs to show flow between states, with the width of the arcs proportional to flow rate. While visually appealing, large numbers of states or timepoints results may unintelligible figures. Table 1 includes descriptions of these various plot types.

In an effort to address the shortcomings of available plots, we developed the Slinkyplot. A Slinkyplot can best be described as a longitudinal crosstabulation, such that it is possible to determine switches between states at each subsequent visit, and this is achieved by alternating the orientation of the crosstabulations. This produces a stair-shaped figure, and one can follow the progression of state changes down this stairway in the same way a slinky toy travels down a stairway, flipping over as it goes. Python

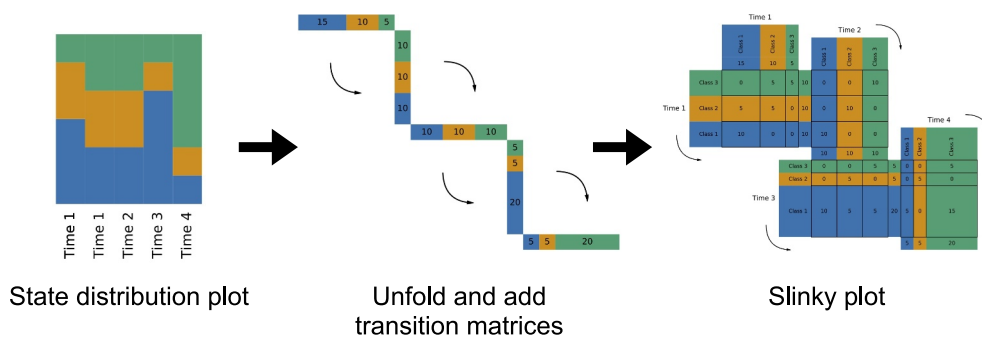
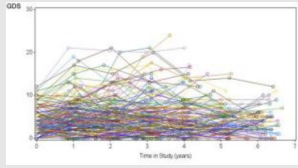
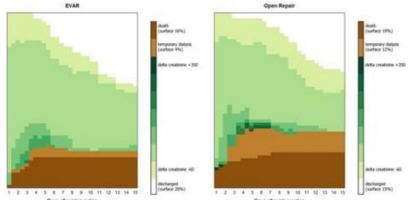
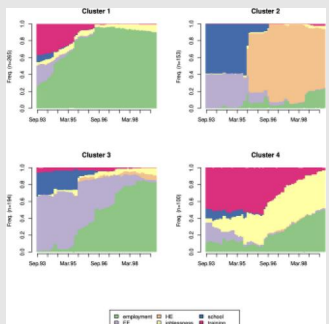
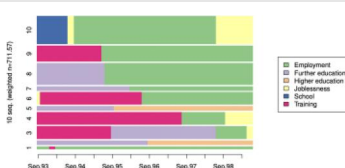
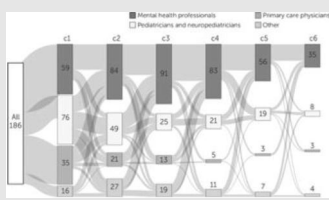


FIGURE 1 Demonstration of relationship between a state distribution plot and a Slinkyplot

TABLE 1 Comparison of available graphical methods to depict changes in states

Method	Description	Pros	Cons	Example
Tree plot	Root with linked nodes depicting discrete states	Visually appealing, clear, intuitive	Difficult to visualize multiple state changes over time	
Spaghetti plot	Repeated outcome measure plotted on vertical axis versus time on the horizontal axis, with dots connected chronologically	Clearly show patterns of change over time on a single continuous variable	Exhibit 'over-plotting' without clear patterns when used for large samples Challenges in displaying repeated-measures data	 <p>Gatchel et al., 2019</p>
Lasagna plot	Each subject's trajectory over time is a single horizontal layer, with color/shading depicting magnitude of outcome measurement	Useful for large samples	Not effective at depicting switching patterns Challenges in displaying missingness	 <p>Jalalzadeh et al., 2017</p>
State distribution plot	Displays sequence of cross-sectional state frequencies by position	Describes changes in the composition of a group over time	Do not capture quantities of transitions among states or states between which people fluctuate	 <p>Gabardino et al., 2011</p>
Sequence index plot	Use line segments to graph individual sequences, with changes in color indicating transitions	Alignment allows easy comparisons at each position	Relies on preprocessing of data, less useful in early exploratory stages of data analysis	 <p>Gabardino et al., 2011</p>
Sankey plot	Nodes (or events) are rectangles or text with arrows or arcs that show flows between them; width of arrow proportional to flow rate	Visually appealing, intuitive	Length of time not provided	 <p>Zavaleta-Ramirez-et al., 2020</p>

code and documentation to produce these plots is available at https://github.com/royadams/slinky_plot. Click or tap if you trust this link. https://github.com/royadams/slinky_plot. While we will show one version of these plots, there are a number of built-in options including arguments to include/exclude and position the legend, alter the minimum counts below which cell counts will be suppressed, alter the minimum cell dimensions to ensure that even very small margins will be rendered, and alter the transparency of cell fills such that the transparency is set to the outgoing proportion of that cell. For example, if the cell corresponding to the

number moving from class 1 at time 1 to class 2 at time 2 is 50 and the class 2 total at time 2 is 100, then the transparency for that cell is set to 50%.

While there is a wide variety of applications for Slinkyplots, in this manuscript we demonstrate how to construct a Slinkyplot for the specific application of understanding patterns of antidepressant use among older adults with mild cognitive impairment using data from the National Alzheimer's Coordinating Center (NACC), and how to utilize Slinkyplots to draw conclusions about those use patterns that would have been difficult to elucidate otherwise.

2 | METHOD

2.1 | Data decisions

Preparing the data is an important step that requires the user to make a number of decisions. The first is what 'states' to track: this might be specific medications, classes of medications, or medication combinations. In our experience, limiting the number of states to 6 or 7, and no more than 10, yields the most usable results.

The second decision is the interval between potential transitions. In the case of the NACC, for example, which collects data approximately yearly from participants, yearly intervals are the most logical choice. In the case of EMR data, however, where data are collected at intervals whose lengths vary both within and between participants, the decision is more complex and will depend both on what is being tracked and the range and variability of contact intervals. In the case of antidepressant use among elderly people with MCI, it might make sense to have semi-annual or annual intervals because individuals tend to stay on these medications for relatively long periods and are likely to have contact with healthcare providers at least semi-annually.

The third decision is how to handle gaps. By 'gaps,' we mean a scenario where an individual is recorded as taking a medication, then at the next contact the medication is not reported, but at a subsequent contact it is again reported. In the case of a prospective cohort study such as the NACC, with approximately annual visits, we elected to view such apparent interruptions as true interruptions, rather than reporting omissions. In the case of an EMR, where data collection by a clinician might be more perfunctory, and if visits were closely spaced, it might be reasonable to specify an allowable gap (in terms of both time and number of contacts) beyond which the medication use would be assumed to have been interrupted. For example, if a patient were seen and noted to be on sertraline at one point, and 1 week later did not mention it to a different clinician, but a week after that reported it to a third clinician, it is reasonable to assume that the failure to report it to the second clinician represented a memory lapse or data entry error rather than interruption in use. Some researchers have opted to use the number of pills prescribed in EMRs to estimate the end date or discontinuation date (Farmer, 1999; Vik et al., 2004). The drawback to this approach is that it assumes that individuals actually take every dose that is prescribed, and also it does not consider the possibility that participants might receive refills from providers who do not access the same EMR. In general, such decisions should be made based on the nature of the data, and what is already known about how individuals inhabit and transition between states, or in this case, how individuals use medications.

The fourth decision is how to handle missingness in both start and stop dates for medications. In the case of a prospective study such as the NACC, both the start and stop date of the medication is missing, and we know only that these events occurred within a particular window of time. In previous analyses of medication use in NACC (Mielke et al., 2012; Oh et al., 2021), we have opted to consider the date of the visit on which a medication is first reported to be the start date, and have calculated the end date as having

occurred 6 months (the halfway point) following the date of the last visit at which the medication was reported. In the case of an EMR, if the prescribing provider has access to the EMR, it may be possible to know the exact start date, but if not, the same practice as that used in the NACC could be used. It may also be necessary to impose some limit on how far forward to extend the end date. For example, if an EMR record showed a participant taking sertraline on a particular date, and the next recorded contact did not occur until 5 years later, at which time sertraline use was not reported, it might be unreasonable to assume that the individual continued to take the medication for 2.5 years following the last report. In such cases, it might be best to adopt, a priori, rules for handling these situations, such as only including individuals seen at least once a year.

2.2 | Data processing

Having determined the structure of the Slinkyplot, the next step is to configure the data. First, we determine the period of data that each participant will contribute. For our purposes, the first visit is the first visit at which a medication of interest is reported, though in other scenarios it might be of interest to show the period of time prior to use. A new visit index is then created based on that index visit. The NACC lists each medication by generic name in separate variables (up to 20) at each annual visit, and each participant has a row of data for each visit that occurred. Significant pre-processing may be required if medications are listed in a single text field and/or if there are spelling errors or variations in how medications are reported (e.g., sertraline appearing as sertraline, Sertraline, setraline [sic], Zoloft, etc). For each state (medication) that we are tracking, we create a dichotomous indicator variable with a 1 if the participant reported that medication at that visit, and a 0 otherwise.

In the case of EMR data, we would create a dataset with state indicator variables similar to that for a prospective cohort study, but with rows for each contact in the EMR. We would then create a second dataset with rows for each intended Slinkyplot interval ('pseudovisits'), and populate it using any rules as discussed in the previous paragraph. For example, suppose a participant is first prescribed sertraline on January 1, 2017, and continues to report sertraline use at various healthcare contacts throughout 2017 and 2018, and on visits up to and including one on August 1, 2019, but not at the next visit recorded in the EMR on August 1, 2020, or any visits that follow. We would represent that use pattern as follows: the participant would have a 1 for the sertraline indicator at visit 1, and for 'pseudovisits' 2 and 3 occurring on the anniversaries of initiation on January 1 of 2018 and 2019. They would also have a 1 for the indicator at pseudovisit 4 occurring on January 1, 2020, because we would estimate their stop date to have occurred halfway between the last two visits on August 1, 2019 and February 1, 2020. Assuming the medication were not restarted, they would have 0s for all subsequent pseudovisits.

The next step is to 'reshape' the data such that there is one row of data per participant and separate state indicator variables for each

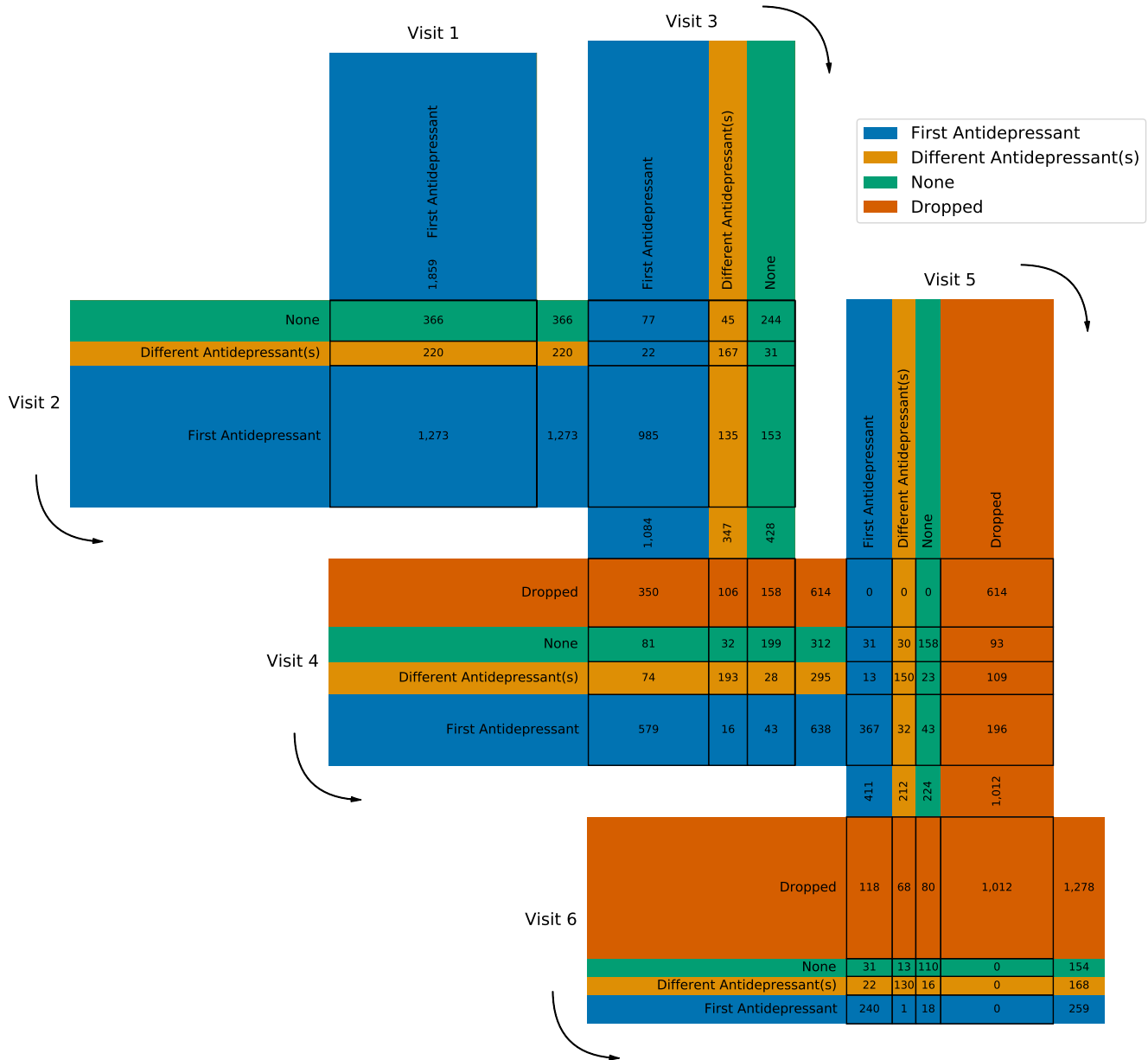


FIGURE 2 Slinkyplot showing transitions among medication states over 6 National Alzheimer's Coordinating Center (NACC) visits. Lengths and Widths of cells in crosstabulations are determined by the relative frequency of the sending and receiving states. The color of the cells is determined by the receiving state. For example, at visit 1 there are 1859 participants on an antidepressant, but at the second visit, 366 of those people are on no antidepressant, and that cell is shaded green to denote their state at visit 2

visit rather than separate rows of data for each visit. To populate the Slinkyplot, two sets of data must be generated. The first are the margins, which contain the number of participants at each state for each visit. These data can be collected in a matrix with a row for each visit and a column for each state. The second set of data is for the crosstabulations, which represent transitions between states. For each transition (there will be one less transition than there are visits), we create a matrix where the rows represent the state at visit k , and the columns represent the state at visit $k + 1$. Entries on the diagonals represent counts of participants who did not transition. Finally, the plot is rendered, with counts of participants at each type of transition (or non-transition) drawn in each box, and with the

length and width of those boxes determined by the relative count of both the sending and receiving state.

3 | RESULTS

Figure 2 is a portion of a Slinkyplot of 1859 participants who were on a single antidepressant and had at least two additional visits. A year later, two thirds (1273) were still taking the same antidepressant, though substantial proportions had switched to a different antidepressant regimen (220, 12%) or had stopped taking an antidepressant (366, 20%). Over time, we can see that individuals who switch from

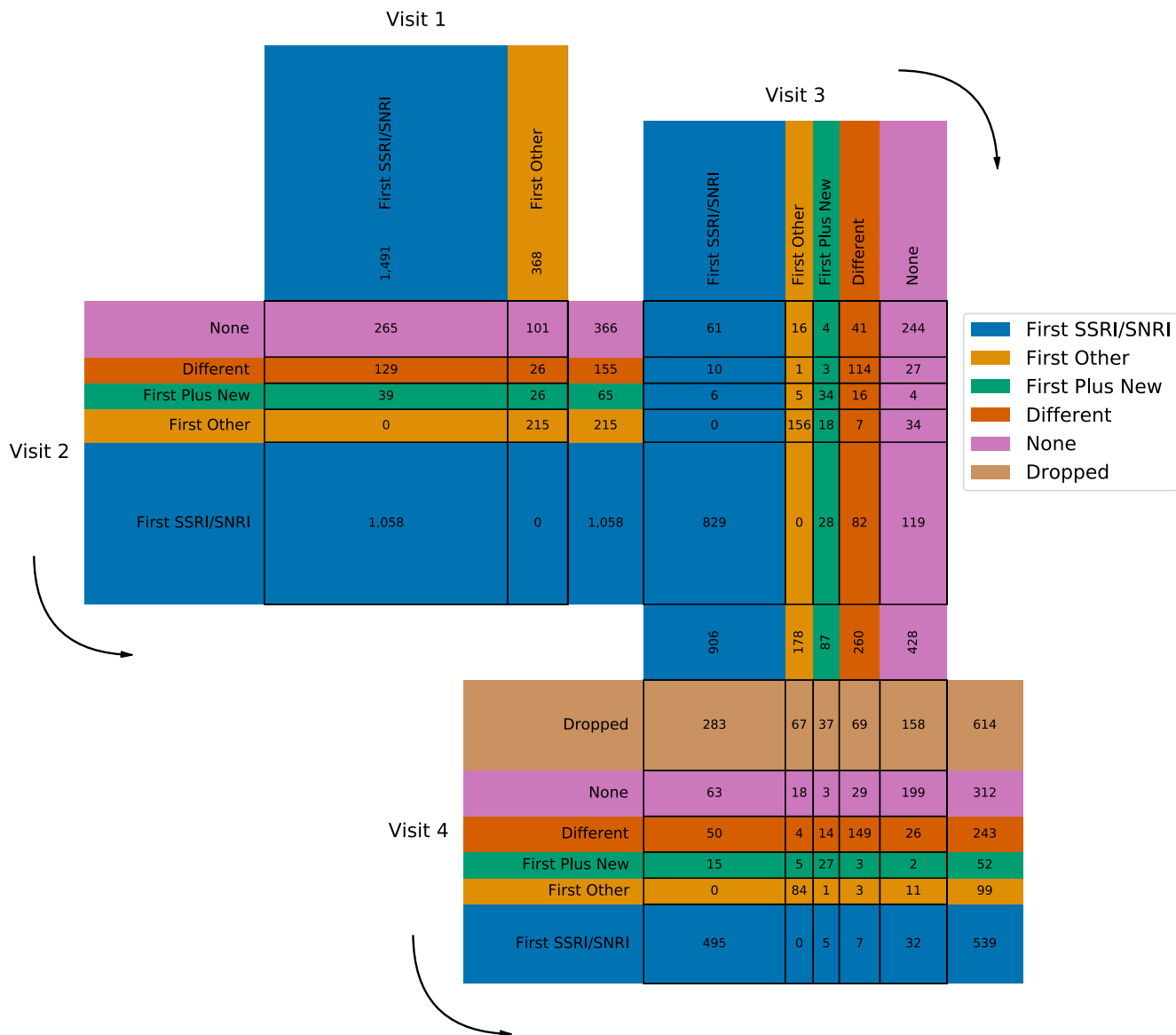


FIGURE 3 Slinkyplot showing transitions among antidepressant regimens over 4 National Alzheimer's Coordinating Center (NACC) visits. Lengths and Widths of cells in crosstabulations are determined by the relative frequency of the sending and receiving states. The color of the cells is determined by the receiving state. 'First SSRI/SNRI' denotes individuals starting out on either a selective serotonin reuptake inhibitor or a selective serotonin and norepinephrine reuptake inhibitor, while 'First Other' denotes individuals starting on another class of antidepressants. 'First Plus New' denotes individuals who have remained on the original antidepressant but also added one or more additional antidepressants, while 'Different' denotes individuals who are taking one or more antidepressants but not the antidepressant they started out on

their original antidepressant regimen only occasionally switch back to it. Participants who transitioned off antidepressants were more likely to have done so if they had remained on their original regimen rather than having switched to a second regimen, suggesting that switchers had more intransigent affective disorders. Transitions back onto antidepressants after having transitioned off them were fairly common (for example, of the 366 participants who were off antidepressants at visit 2, 122 (32%) transitioned back to their original antidepressant or to a new antidepressant regimen). Notably, at the sixth visit, of the 581 participants still being followed, 427 (73%) were still on at least one antidepressant. Finally, loss to follow-up is substantial, with 1278 (69%) lost by the sixth visit.

The Slinkyplot in Figure 2, while informative, is limited in that it details transitions among only 4 broad categories. Knowledge of particular classes of medication from which a participant was more likely to switch, or more likely to come off, could guide treatment algorithms. Figure 3 sheds light on this question, by using the same data but different states.

Now we see that of the 1859 who were on a single antidepressant at the onset, 1491 (80%) were on either an SSRI or an SNRI (Figure 3). After the first visit, of the 1491 who started on an SSRI or SNRI, 1058 (71%) were taking the same antidepressant at the next visit, 39 (3%) had added one or more additional antidepressant(s), 129 (9%) had switched to one or more different antidepressants, and 265 (18%)

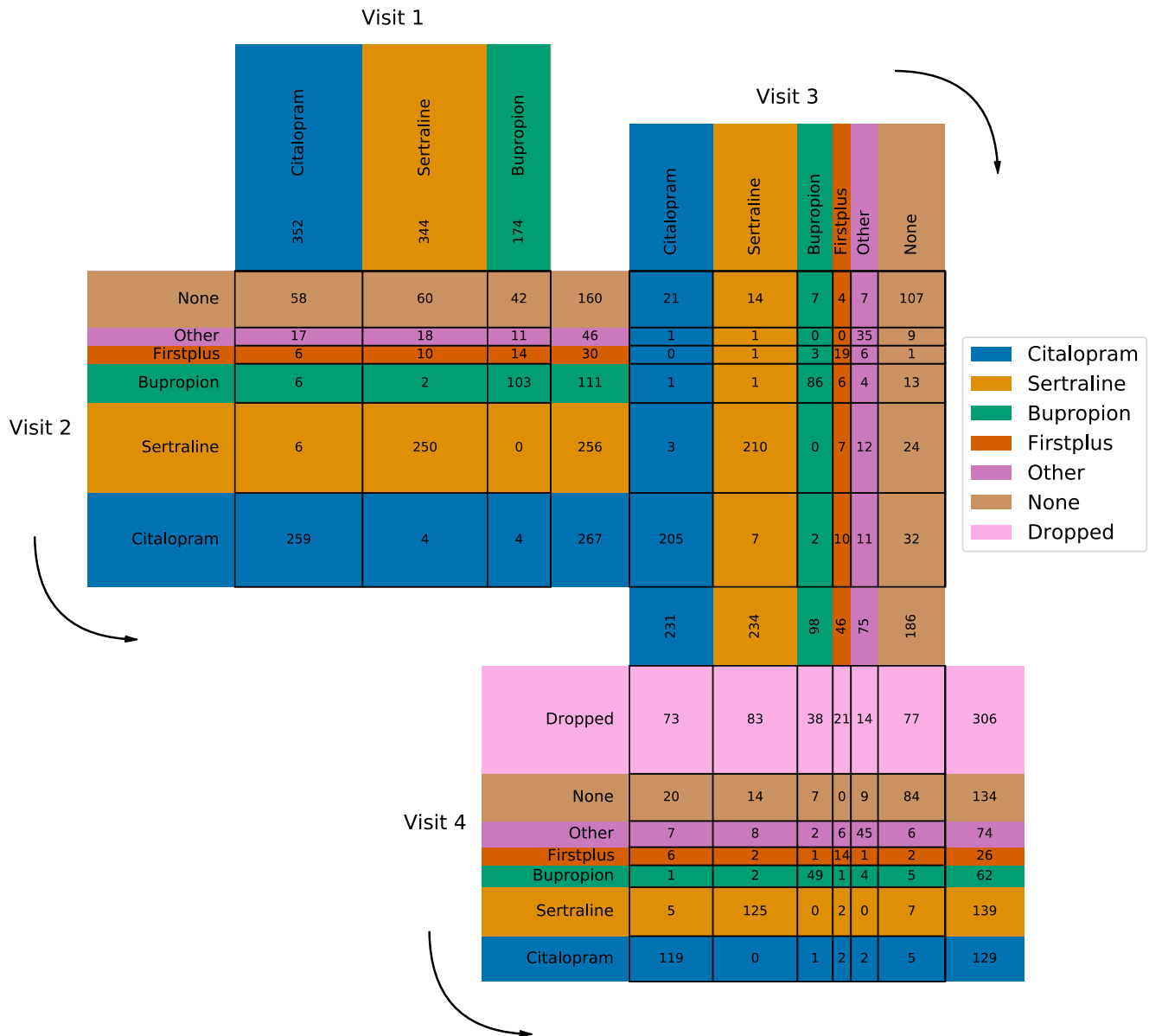


FIGURE 4 Slinkyplot showing transitions among individuals starting out on the 3 most common antidepressants (citalopram, sertraline, and bupropion) over 4 National Alzheimer's Coordinating Center (NACC) visits. 'FirstPlus' denotes individuals who have remained on the original antidepressant but also added one or more additional antidepressants, while 'Other' denotes individuals who are taking one or more antidepressants but not the antidepressant they started

were no longer taking antidepressants. Of the 368 who were on a single antidepressant that was not an SSRI or SNRI at the first visit, 215 (58%) were still taking the same antidepressant, 26 (7%) had added one additional antidepressant, 26 (7%) had switched to one or more different antidepressants, and 101 (27%) were not taking antidepressants at the next visit. Interestingly, at visits 2 through 4, among individuals switching regimen after having been on a single SSRI or SNRI, individuals switching to a completely different antidepressant regimen outnumbered those who added one or more antidepressants, whereas the opposite pattern appeared among people switching from a single antidepressant that was not an SSRI or SNRI.

Figure 4 explores the data in yet more detail, focusing on individuals who began on the 3 most commonly used antidepressants:

citalopram, sertraline, and bupropion, representing 47% of the total. At the second visit, 259 (74%) participants starting on citalopram remained on citalopram while 58 (16%) were on no antidepressant. Among those starting on sertraline at the first visit, 250 (73%) remained on sertraline, and 60 (17%) were on no antidepressant at the next visit. Among those starting on bupropion, 103 (59%) remained on bupropion and 42 (24%) were on no antidepressant. Despite being the most commonly used antidepressants at the onset, switches among them were relatively rare at subsequent visits, with additions or substitutions of other antidepressants being generally more common.

This begs the question, if these three antidepressants represent the most typical 'first line' treatment, what was the preferred

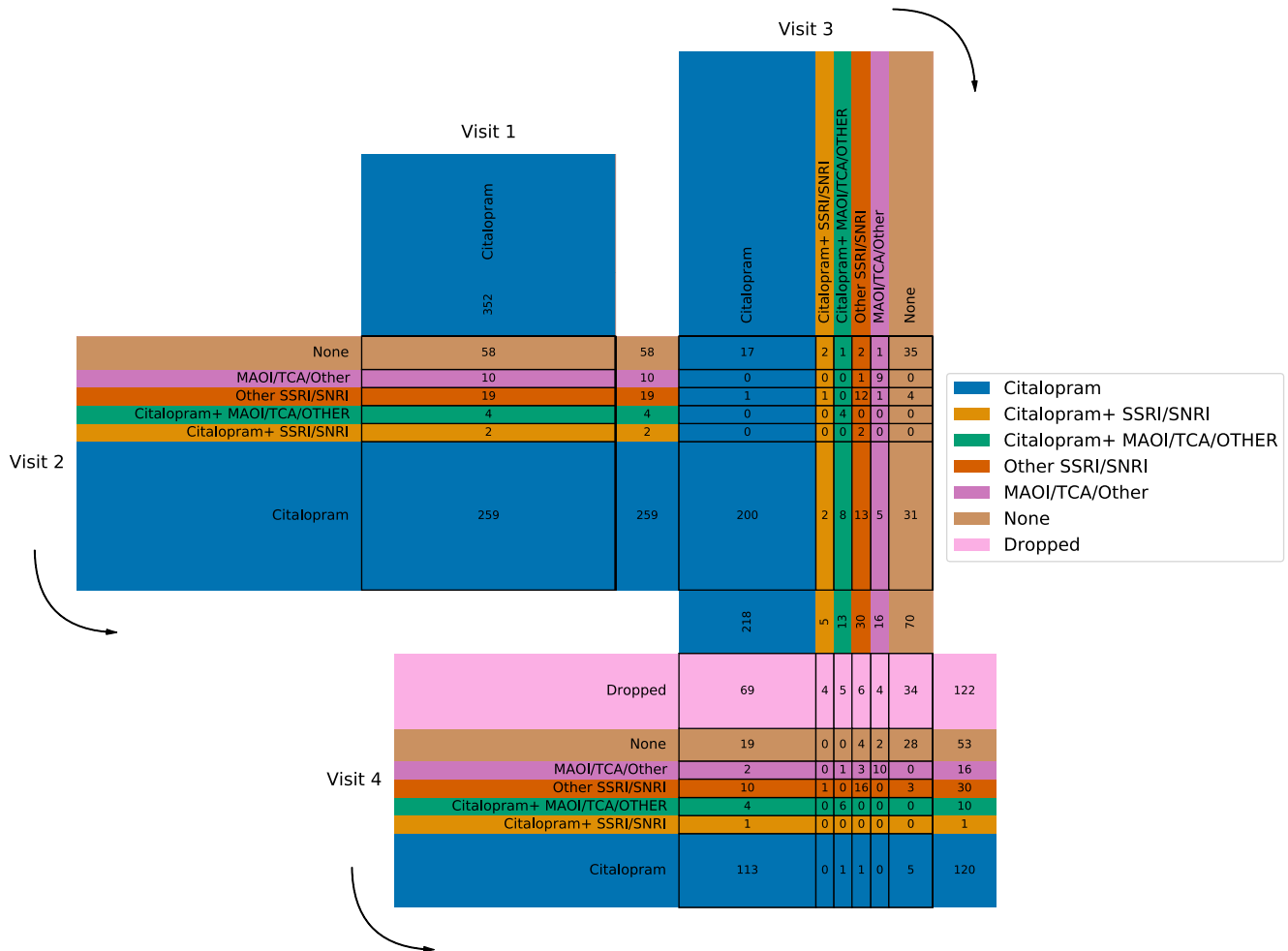


FIGURE 5 Slinkyplot showing transitions among individuals starting out on citalopram. Individuals added additional antidepressants (e.g., other SSRI/SNRI, MAOI – monoamine oxidase inhibitors or TCA – tricyclic antidepressants), switched to other antidepressants in the same or different classes, or transitioned completely off antidepressants

‘second line’ treatment? To explore that question, we limit the plot to the 352 individuals taking citalopram alone at the onset. The most common outcome at any visit is continuation of citalopram alone or discontinuation of all antidepressants. Figure 5 shows that among individuals who changed their antidepressant regimen, switching to a different SSRI or an SNRI was more common than adding another medication or switching to a different class of antidepressant.

4 | DISCUSSION

We describe a novel method of demonstrating changes among states over time using Slinkyplots. We illustrate their utility by constructing a series of plots that elucidate patterns of antidepressant use over time in a large prospective cohort study of older adults with mild cognitive impairment. We have also described the data decision-making and processing necessary to prepare data for these plots. In this specific example of Slinkyplot utility, we demonstrate that the

majority of individuals who are on an antidepressant remain on an antidepressant 5 years later, but switches to different antidepressants occur, as well as cessation of antidepressant use. Individuals who stop taking an antidepressant often restart them again. While citalopram, sertraline, and bupropion appear to be the first-line antidepressants in older adults with MCI, switching to another antidepressant, particularly a different SSRI or an SNRI, is fairly common at subsequent visits. Understanding these patterns of use is the first step in determining the effects of antidepressant use on depression symptoms and risk of dementia.

Slinkyplots allow for the visualization of switching among medications, depicting patterns in longitudinal data that would have been difficult or impossible to elucidate through more typical analyses or plots, such as tree plots and spaghetti plots. In contrast to state distribution plots, transition plots, and sequence index plots, Slinkyplots explicitly depict quantities and changes in individual sequences. Slinkyplots enable the researcher to pack a large amount of quantitative information into a small space with visual clarity. Further, as epidemiological studies become more

complex and use of EMR data becomes more common, Slinkyplots are a way of following people over time that allow us to find patterns in large samples. There is an enormous range of potential applications for such plots. Apart from a plethora of medication usage questions that could be addressed, other uses include changes in health states, living situations, functional status, or disease severity.

Despite their demonstrated utility, there are limitations to Slinkyplots. Transitions among a large (10+) number of states result in Slinkyplots that are visually overwhelming. This can be addressed in some cases by 'drilling down' and concentrating on the series of transitions that occur after a specific node, as demonstrated in Figure 4 when we limited the plot to individuals who began on citalopram. Another limitation is that the plots have no 'memory' after one transition, meaning that while a plot can depict how many individuals transition from one state to the next, it cannot demonstrate how many follow paths involving more than two nodes, for example, people who switch from citalopram to another SSRI, and then back to citalopram at a later time. If there are both a small number of timepoints and a small number of states, it may be preferable to use a tree plot to visualize data under those circumstances.

Future directions could include dynamic/animated Slinkyplots that magnify certain areas on demand (for example, in response to mouse hover), or which can highlight particular full trajectories. We look forward to seeing how other researchers make use of this tool.

ACKNOWLEDGEMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The National Alzheimer's Coordinating Center (NACC) database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA-funded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen

Strittmatter, MD, PhD). We appreciate the assistance of Richard Leoutsakos in previewing the plots and Paige Seegan for naming them. This work is supported by the Richman Family Precision Medicine Center of Excellence in Alzheimer's Disease including significant contributions from the *Richman Family Foundation*, the *Rick Sharp Alzheimer's Foundation*, the *Sharp Family Foundation* and others.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

NACC data are freely available to all researchers, via a data request process on the NACC website.

ORCID

Elizabeth A. Wise  <https://orcid.org/0000-0002-0346-7744>

REFERENCES

- Burke, S. L., Maramaldi, P., Cadet, T., & Kukull, W. (2018). Decreasing hazards of Alzheimer's disease with the use of antidepressants: Mitigating the risk of depression and apolipoprotein E. *International Journal of Geriatric Psychiatry*, 33(1), 200–211. <https://doi.org/10.1002/gps.4709>
- Cicchinelli, A., Veas, E., Pardo, A., Pammer-Schindler, V., Fessler, A., Barreiros, C., & Lindstädt, S. (2018). Finding traces of self-regulated learning in activity streams. In *Proceedings of the 8th international conference on learning analytics and knowledge*. <https://doi.org/10.1145/3170358.3170381>
- Counil, É. (2020). In R. Gilbert & S. Matthias (Eds.), *Sequence analysis and related approaches: Innovative methods and application* (Vol. 75). Springer International Publishing, II-298 p. In *Population*, 1134. <https://doi.org/10.3917/popu.2001.0134>
- Farmer, K. C. (1999). Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. In *Clinical therapeutics* (Vol. 21, pp. 1074–1090). [https://doi.org/10.1016/s0149-2918\(99\)80026-5](https://doi.org/10.1016/s0149-2918(99)80026-5)
- Gabadoh, A., Ritschard, G., Muller, N. S., & Studer, M. (2011). Analyzing and visualizing state sequences in R with TraMineR. *Journal of Statistical Software*, 40(4), 1–37. <https://doi.org/10.18637/jss.v040.i04>
- Gatchel, J. R., Rabin, J. S., Buckley, R. F., Locascio, J. J., Quiroz, Y. T., Yang, H. S., Vannini, P., Amariglio, R. E., Rentz, D. M., Properzi, M., Donovan, N. J., Blacker, D., Johnson, K. A., Sperling, R. A., & Marshall, G. A. (2019). Harvard aging brain study. Longitudinal association of depression symptoms with cognition and cortical amyloid among community-dwelling older adults. *JAMA Network Open*, 2(8), e198964. <https://doi.org/10.1001/jamanetworkopen.2019.8964>
- Goveas, J. S., Hogan, P. E., Kotchen, J. M., Smoller, J. W., Denburg, N. L., Manson, J. E., Tummala, A., Mysiw, W. J., Ockene, J. K., Woods, N. F., Espeland, M. A., & Wassertheil-Smoller, S. (2012). Depressive symptoms, antidepressant use, and future cognitive health in postmenopausal women: The women's health initiative memory study. *International Psychogeriatrics*, 24(8), 1252–1264. <https://doi.org/10.1017/s1041610211002778>
- Han, F., Bonnett, T., Brenowitz, W. D., Teylan, M. A., Besser, L. M., Chen, Y. C., Chan, G., Cao, K. G., Gao, Y., & Zhou, X. H. (2020). Estimating associations between antidepressant use and incident mild cognitive impairment in older adults with depression. *PLoS One*, 15(1), e0227924. <https://doi.org/10.1371/journal.pone.0227924>

- Jalalzadeh, H., van Beek, S. C., Indrakusuma, R., Bemelman, W. A., Busch, O. R., & Balm, R. (2017). Lasagna plots to visualize results in surgical studies. *International Journal of Surgery*, 43, 119–125. <https://doi.org/10.1016/j.ijssu.2017.05.063>
- Kodesh, A., Sandin, S., Reichenberg, A., Rotstein, A., Pedersen, N. L., Ericsson, M., Karlsson, I. K., Davidson, M., & Levine, S. Z. (2019). Exposure to antidepressant medication and the risk of incident dementia. *American Journal of Geriatric Psychiatry*, 27(11), 1177–1188. <https://doi.org/10.1016/j.jagp.2019.05.019>
- Leng, Y., Diem, S. J., Stone, K. L., & Yaffe, K. (2018). Antidepressant use and cognitive outcomes in very old women. *The Journals of Gerontology, Series A Biological Sciences and Medical Sciences*, 73(10), 1390–1395. <https://doi.org/10.1093/geron/glx226>
- McHugh, P. R., & Slavney, P. R. (1983). *The perspectives of psychiatry*. Johns Hopkins University Press.
- Mielke, M. M., Leoutsakos, J.-M., Corcoran, C. D., Green, R. C., Norton, M. C., Welsh-Bohmer, K. A., Tschanz, J. T., & Lyketsos, C. G. (2012). Effects of Food and Drug Administration-approved medications for Alzheimer's disease on clinical progression. *Alzheimer's and Dementia: The Journal of the Alzheimer's Association*, 8(3), 180–187. <https://doi.org/10.1016/j.jalz.2011.02.011>
- Moraros, J., Nwankwo, C., Patten, S. B., & Mousseau, D. D. (2017). The association of antidepressant drug usage with cognitive impairment or dementia, including alzheimer disease: A systematic review and meta-analysis. *Depression and Anxiety*, 34(3), 217–226. <https://doi.org/10.1002/da.22584>
- Oh, E. S., Rosenberg, P. B., Rattinger, G. B., Stuart, E. A., Lyketsos, C. G., & Leoutsakos, J.-M. S. (2021). Psychotropic medication and cognitive, functional, and neuropsychiatric outcomes in Alzheimer's disease (AD). *Journal of the American Geriatrics Society*, 69(4), 955–963. <https://doi.org/10.1111/jgs.16970>
- Saczynski, J. S., Rosen, A. B., McCammon, R. J., Zivin, K., Andrade, S. E., Langa, K. M., Vijan, S., Pirraglia, P. A., & Briesacher, B. A. (2015). Antidepressant use and cognitive decline: The health and retirement study. *The American Journal of Medicine*, 128(7), 739–746. <https://doi.org/10.1016/j.amjmed.2015.01.007>
- Swihart, B. J., Caffo, B., James, B. D., Strand, M., Schwartz, B. S., & Punjabi, N. M. (2010). Lasagna plots: A saucy alternative to spaghetti plots. *Epidemiology*, 21, 621–625. <https://doi.org/10.1097/ede.0b013e3181e5b06a>
- Then, C. K., Chi, N. F., Chung, K. H., Kuo, L., Liu, K. H., Hu, C. J., Shen, S. C., & Lin, Y. K. (2017). Risk analysis of use of different classes of antidepressants on subsequent dementia: A nationwide cohort study in taiwan. *PLoS One*, 12(4), e0175187. <https://doi.org/10.1371/journal.pone.0175187>
- Vanhoutte, B., Wahrendorf, M., & Prattley, J. (2019). Sequence analysis of life history data. In *Handbook of research methods in health social sciences* (pp. 935–953). https://doi.org/10.1007/978-981-10-5251-4_146
- Vik, S. A., Maxwell, C. J., & Hogan, D. B. (2004). Measurement, correlates, and health outcomes of medication adherence among seniors. *The Annals of Pharmacotherapy*, 38(2), 303–312. <https://doi.org/10.1345/aph.1d252>
- Wang, C., Gao, S., Hendrie, H. C., Kesterson, J., Campbell, N. L., Shekhar, A., & Callahan, C. M. (2016). Antidepressant use in the elderly is associated with an increased risk of dementia. *Alzheimer Disease and Associated Disorders*, 30(2), 99–104. <https://doi.org/10.1097/wad.000000000000103>
- Zavaleta-Ramírez, P., Rosetti, M. F., Albores-Gallo, L., Vargas-Soberanis, M. A., Lopez, O. N., & Medina-Mora, M. E. (2020). Pathways to a diagnosis of autism spectrum disorder. *Psychiatric Services*, 71(11), 1120–1126. <https://doi.org/10.1176/appi.ps.201900518>

How to cite this article: Wise, E. A., Adams, R. J., Lyketsos, C. G., & Leoutsakos, J.-M. (2022). Graphical methods for understanding changes in states: Understanding medication use pathways. *International Journal of Methods in Psychiatric Research*, 31(4), e1932. <https://doi.org/10.1002/mpr.1932>