BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034305
Article Type:	Original research
Date Submitted by the Author:	13-Sep-2019
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Keywords:	Drug utilization, Drug evaluation, Drug repositioning, Episode of care, Parkinson-s disease < NEUROLOGY

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HOW TO CONSTRUCT TREATMENT EPISODES FROM CONCOMITANT MEDICATION LOGS: A PROSPECTIVE OBSERVATIONAL STUDY

Running title: Constructing episodes from concomitant medication logs

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MeSH key words: Drug utilization; Drug evaluation; Drug repositioning; Episode of care; Parkinson Disease

Key points:

- Unlike prescription and dispensing records, concomitant medication logs collect utilization data.
- We construct treatment episodes on the premise that gaps in logs represent gaps in medication use; and temporal overlaps represent various regimens of the same medication or a change in dose.
- The proposed approach offers a method of estimating duration and dose of treatment from log records.
- We recommend improving the quality of log records for research in drug safety and drug repurposing.

Word count, excluding abstract, tables, figures and references: 2,737

Number of Figures: 1

Number of Tables and Boxes: 2

ABSTRACT

Objectives: To offer guidelines on constructing treatment episodes from concomitant medication logs. Concomitant medication log records are routinely collected in clinical studies. Unlike prescription and dispensing records, concomitant medication logs collect utilization data. Logs can provide information about drug safety and drug repurposing.

Design: A prospective multi-centre, multi-cohort observational study.

Setting: Twenty-one clinical sites in the United States, Europe, Israel, and Australia.

Participants: 415 subjects from the de novo cohort of the Parkinson Progression Marker Initiative.

Methods: We construct treatment episodes of concomitant medication use. Our guidelines treat temporal gaps as a stoppage of medication and temporal overlaps as simultaneous use or changes in dose. Log records with no temporal gaps were combined into a single treatment episode.

Results: 5,723 concomitant medication log records were used to construct 3,655 treatment episodes for 65 medications. There were 405 temporal gaps representing a stoppage of medication; 985 temporal overlaps representing simultaneous regimens of the same medication; and 2,696 temporal overlaps representing a change in dose regimen. The median episode duration was 37 months (interquartile interval: 11 to 73 months).

Conclusions: The proposed approach for constructing treatment episodes offers a method of estimating duration and dose of treatment from concomitant medication log records. The accompanying recommendations guides log data collection to improve their quality for drug safety and drug repurposing.

Strengths and limitations of this study

- A large, observational study prospectively capturing information on medication use in an internationally representative cohort of individuals with Parkinson's disease.
- To our knowledge, we offer the first guidelines for constructing treatment episodes from concomitant medication log records.
- Assumes concomitant medication logs accurately capture subjects' medication use.

1. INTRODUCTION

Concomitant medication log records are routinely collected in clinical studies. Their collection is important for establishing safety of new investigational drugs, e.g., medications may interact with study interventions or interact with contrast media used in imaging procedures. Regulatory agencies, such as Health Canada and the US Food and Drug Administration, require that concomitant medications be recorded during clinical trials and prospective cohort studies [1].

Concomitant medication records can add to the drug safety profiles of commonly used, approved drugs. For example, concomitant medication records from a completed clinical trial were used to test whether a common anti-spasticity medication interfered with motor neurologic recovery [2]. Concomitant medication records can also identify targets for drug repurposing. For example, a concomitant medication for treating neuropathic pain was found to be unintentionally beneficial for muscle strength recovery after spinal cord injury [3,4]. This led to drug repurposing to maximize neurological outcomes [5].

Concomitant medication use varies by the time spent on the medication and changes in dose. The period between the start and end of the administration of a medication regardless of changes in dose regimen is referred to as a *treatment episode* [6]. Construction of treatment episodes helps to estimate the exposure to and intensity of medication use [7]. *Episode duration* is the time exposed to the medication. *Episode dose* is the total daily dosage over the course of the episode. Describing medication intake through a series of episodes identifies when the subject is exposed to and unexposed to the medication.

Guidelines about constructing treatment episodes using data from concomitant medication logs are needed to estimate duration and dose of medication treatment. Different methods and assumptions used in episode construction influence measures of exposure and effect [6]. Underestimating treatment effects may result in missed opportunities for therapeutic development, while overestimating treatment effects may result in wasted resources. While the pharmaco-epidemiology literature describes treatment episode construction [8–10], the data used in these cases is information about medications prescribed or dispensed as opposed to medication utilization [11–13]. Our objective was to provide the first guidelines for the construction of treatment episodes in the context of concomitant medication logs. We also provide recommendations for collecting concomitant medication data to improve their quality and use in drug safety and drug repurposing strategies.

2. METHODS

2.1 Data Source

Data were obtained from the Parkinson's Progression Markers Initiative (PPMI) database. The PPMI is a comprehensive prospective observational study designed to improve understanding of disease etiology and progression [14]. The PPMI database is comprised of multiple cohorts including recently diagnosed Parkinson's Disease (PD) subjects and healthy participants followed longitudinally for clinical, imaging, behavioural, and biospecimen assessments, using standardized data acquisition protocols at twenty-one clinical sites in the United States, Europe, Israel, and Australia. Study data are publicly available through the PPMI website (www.ppmi-info.org). We downloaded the PPMI data files on April 6, 2018. This study was exempt from ethics review according to the publicly available data clause in the Tri-Council Policy Statement for Ethical Conduct for Research involving humans at the University of British Columbia. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research.

2.2 PPMI Concomitant Medication Log

The collection of concomitant medications in PPMI is done through a standardized Case Report Form (CRF) [14]. In PPMI, medications taken at Screening Visit (the visit used to screen for study eligibility) are entered into the log. At subsequent visits, new medications, and changes/discontinuation of previously listed medications are recorded. The following instructions are provided on the CRF:

> *Enter all medications taken at Screening Visit. At subsequent visits record new meds, and changes/discontinuation of previously listed meds. Changes in total daily dose or route require a new line. Row: enter 1, 2, 3, etc. Medication: Record generic name; if unknown, enter brand name. For multiple ingredient medications, indicate strength if possible, e.g., carbidopa/levodopa 25/100. Dose: Record dose for each administration. Date: Please specify if the Start and Stop dates are ACTUAL or ESTIMATED. If the exact date is unknown, please enter your best reasonable estimate of the date and specify which part(s) are estimated. Ongoing: Answer yes if medication is still being taken at end of study. Indication: Reason for use, not drug category.*

Data from this CRF are entered into the PPMI publicly accessible concomitant medication log data file. This data file includes medication name, dose, dose units, frequency, route, start/stop date [or ongoing], indication, and whether the medication is indicated for PD (Table 1). Only month and year of the start and stop dates are publicly accessible. The data file also contains derived medication variables, including the World Health Organization (WHO) drug code [15]. The WHO drug code has 3 parts: Drug Record Number (RECNO), Sequence number 1(SEQNO1) and Sequence number 2 (SEQNO2). RECNO uniquely identifies active moieties.

We included log records for RECNOs that a minimum of 20 de novo PD subjects were taking at the screening visit or during follow-up. This number was an arbitrary cut-off to identify common medications. We also excluded the "all other non-therapeutic products" (i.e., RECNO=900475) due to a lack of known biological activity. Examples of this included products such as blueberry extract, probiotics, and Neuroplex.

2.3 Episode construction

Our proposed guidelines assume temporal gaps represent a stoppage of medication; temporal overlaps of more than one time unit (e.g., month) represent simultaneous regimens of the same medication; and temporal overlaps of one time unit represent a change in dose regimen. Temporal gaps are the elapsed time between the end of one log record and the start of the subsequent log record. Temporal overlaps are the time during which a log record starts before a previous log record ends. Since only the year and month of the medication start and stop dates were accessible, we distinguished between simultaneous regimens and changes in dose regimens to not overestimate total daily dose. Log records with the same RECNO and no temporal gaps were combined into a single treatment episode.

Log records with a medication frequency of "as needed" (e.g., "PRN", "OCCASIONAL", "ON DEMAND", "QS", or "SOS") did not contribute to exposure because we could not confirm medication utilization. When the log record had a vague unit (e.g., tablet or capsule) the daily dose could not be computed, however the record still contributed to episode duration.

2.4 Episode duration

We identified the start and end dates of medication use for each log record. If there was no start date or if the dates were non-chronological, we marked the log record as incomplete. If there was no stop date, we imputed with the date of the last concomitant medication review.

Among log records belonging to the same treatment episode, the episode start date was the start date of the earliest log record and the episode end date was the stop date of the latest log record. The episode duration was computed as the number of months between the episode start and end dates.

2.5 Episode dose

We calculated the daily dose from each log record. First, we determined the multiplicative factor, representing how often the reported dose is taken per day. For example, "BID" means twice a day, so the multiplicative factor is 2. Next, we converted doses to a common unit (e.g., mg). The daily dose is the product of the reported dose in common units and the multiplicative factor based on the frequency.

We calculated the total daily dose among log records belonging to the same treatment episode. The total daily dose at a time with simultaneous regimens was the sum of the daily doses of log records containing the time point (Figure 1). The total daily dose at a time with changes in dose regimen was the average of the doses (Figure 1). If there was only one log record constructing an episode, then the total daily dose was equal to the daily dose. The total daily dose and its changes were computed over the course of the treatment episode.

3. RESULTS

3.1 Episode durations

Of the 423 enrolled de novo PD subjects, 415 had a baseline visit and at least one follow-up visit. Of the 8,771 concomitant medication log records, we excluded 2,619 (29.9%) log records of medications taken by fewer than 20 PD subjects, 352 (4.0%) records with drug frequencies of "as needed", and 77 (0.9%) log records for "all other non-therapeutic products" (i.e., RECNO=900475). The remaining 5,723 log records were used to construct treatment episodes for 65 medications among the 415 PD subjects. Two-fifths of the log records were incomplete: 3 (0.05%) had no start date, 2,328 (40.7%) had no stop date (so were imputed), and 2 (0.03%) had non-chronological start and stop dates. For example, REC_ID 282665101, recorded that PATNO 3606 had no start date or stop date for a vitamin B complex. REC_ID 226846701 recorded that PATNO 3400 started Lexapro in February 2010, but had no stop date. REC_ID 538226701 had a start date on February 2013 and a stop date on March 2012; and REC_ID 413205901 had a start date on September 2013 and stop date on August 2013. These log records, as with records with data entry errors (e.g., REC_ID 667793101 with a stop date of "03/0218"), were considered incomplete.

About half of the log records were combined to form treatment episodes: 543 (9.5%) log records had identical start and stop dates; 132 (2.3%) records started and stopped a medication regimen before stopping the previous regimen; 2,260 (39.5%) records started another regimen of the same medication before stopping the previous regimen. The remaining log records each corresponded to a single treatment episode. There were 405 temporal gaps among subjects with multiple log records for a given medication. The gaps had a median duration of 8 months (interquartile interval [IQI]: 1 to 14 months).

The 415 de novo PD subjects had 60 months median follow-up time (IQI: 54 to 86). We constructed 3,655 treatment episodes for 65 medications among these subjects. The median episode duration was 37 months (IQI: 11 to 73 months).

3.2 Episode doses

There was significant variation in units and frequencies: 66 different units and 136 different frequencies among the 5,723 log records. For example, for RECNO 3686, some of the units were reported as TAB, TABS, CAP, or CAPS, and some of the frequencies were reported as 4 X DAILY, 4 X QD, 4X, 4X/D, 4XD, 4XDAY, 4XQD, or 4XS/DAY. We revised the reported units to be consistent across records. For example, G, GM, GR, GRAM, ",G", GRAMS were recoded as GRAM. We determined the multiplicative factor for computing daily doses. For example, 6 PER DAY, 6X A DAY, 6/DAY, 6X DAY, 6X/DAY, 6XD, 6XS/DAY; SIX DAILY had a multiplicative factor of 6. In 8 (0.1%) and 95 (1.7%) of the log records, the values for units or frequencies, respectively, were vague.

We calculated the total daily dose during a treatment episode, by accounting for temporal gaps and overlaps. There were 405 temporal gaps representing a stoppage of the medication; 985 temporal overlaps of more than one time unit (e.g., month) representing simultaneous regimens of the same medication; and 2,696 temporal overlaps of one time unit representing a change in dose regimen.

3.3 Example: Gabapentin

To illustrate these steps with respect to a single medication, we provide here an example with gabapentin (primarily indicated for neuropathic pain). Among the 415 de novo PD subjects, there were 49 log records of gabapentin use among 30 subjects. For each record of gabapentin, we computed the daily dose. First, we identified log records of interest; those with RECNO = 10030. Second, we determined the multiplicative factors for calculating daily dose. Third, we converted all units to mg. Finally, we computed the daily dose for gabapentin. For example, PATNO 3625 has a dose of 300 with units MG and frequency BID. Therefore, the daily dose is 300 MG * 2 = 600 MG. One log record indicated that the subject was on the medication "as needed" and another log record reported units as tablet (i.e., "TAB"), so the records did not contribute to episode duration or dose. Among the remaining gabapentin log records, the median daily dose was 600 mg, and ranged from 100 mg to 3,600 mg per day.

We constructed 37 episodes of gabapentin use among subjects. Each user of gabapentin had one or two episodes during the study period. About three-quarters (23 of 30) of these subjects had episodes of gabapentin use starting after the baseline visit. The median cumulative months of exposure was 16 months (IQI: 7 to 29 months). The median cumulative total daily dose was 156,000 mg (IQI: 42,600 to 667,800 mg).

4. DISCUSSION

We offer the first guidelines for the construction of treatment episodes from concomitant medication logs to estimate duration and dose. Our guidelines treat temporal gaps as a stoppage of medication and temporal overlaps as simultaneous use or changes in dose. Log records with no temporal gaps were combined into a single treatment episode.

Construction of treatment episodes using concomitant medication log data differs from construction using drug prescribing and dispensing data [8–10]. Data from prescription and dispensing databases are typically less comprehensive (e.g., may not include a route of administration, generally do not capture non-prescription drugs, sometimes limited to a specific setting such as a single hospital or pharmacy, often restricted in terms of number of years captured). Second, in concomitant medication logs, temporal gaps in medication use identify when the subject was not actually taking the drug. This is in contrast to prescription and dispensing data, where gaps of pre-defined length are filled when constructing episodes to account for assumed medication use during those gaps. In some cases, patient-reported medication use is the reference standard for prescribing/dispensing records [16], supporting treating gaps as a stoppage of the medication. Lastly, in concomitant medication logs, temporal overlaps identify when the subject is administering simultaneous regimens of the same medication. This is in contrast to prescription and dispensing data, where the overlapping time is used to extend the duration of the episode.

Recommendations

Applying our guidelines to the data from the PPMI concomitant medication log yielded recommendations for data collection for future prospective studies (Box 1). When collecting data for a concomitant medication log, we recommend: 1) Quality checks for valid start dates (e.g., no data entry errors); 2) Quality checks for valid stop dates (e.g., start and stop dates are chronologically ordered); 3) Record medication start and stop dates with day, month, and year (i.e., complete dates for precise account of medication use); 4) Quality checks for valid dose (e.g., dose is within the recommended range); 5) Quality checks for valid unit (e.g., no vague units like “tablet”); 6) Quality checks for valid frequency (e.g., confirm the use of “as needed” medication with the subject); 7) Quality checks for overlapping log records with the same medication, dose, and frequency; 8) Continuous recording of concomitant medication status (so start and stop dates are more accurate), by e-diaries, for example; 9) Electronic log records to prevent users from creating another log record for the same medication, if a log record for the medication with no stop date exists (i.e., is there a need to have two “active” records

for the same medication"); 10) Use standardized drug/indication systems, such as the World Health Organization system.

Study Limitations

Our study has a few limitations. First, we assumed that the concomitant medication log data accurately captures the subjects' medication use. While patient-report has been used as a standard in prior studies, the validity may differ with respect to different medications. Second, we assumed no medication use when the medication frequency was "as needed" which could underestimate the medication duration and dose. The advantage of our study is that we had longitudinal medication information in an internationally representative cohort of individuals with PD.

Conclusion

The proposed approach to constructing treatment episodes offers a method of estimating duration and dose of medication treatment using data from concomitant medication logs. The accompanying recommendations guide log data collection in clinical studies to improve their quality and use in drug safety and drug repurposing strategies.

ACKNOWLEDGEMENTS

PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbvie, Allergan, Avid Radiopharmaceuticals, Biogen, BioLegend, Bristol-Myers Squibb, Celgene, Denali, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Prevail Therapeutics, Roche, Sanofi Genzyme, Servier, Takeda, Teva, UCB, Verily, and Voyager Therapeutics.

Contributors: All authors contributed to and approved the final manuscript. JC conceived the work and obtained study funding; LK and MT analysed the data; LK, BS, PB, MT and JC interpreted the data for the work; LK and JC drafted the manuscript; and LK, BS, PB, MT and JC revised the manuscript for important intellectual content.

Funding: This work was supported by the Michael J. Fox Foundation for Parkinson's research [grant number 14834].

Competing interests: None declared.

REFERENCES

[1] U.S. Department of Health and Human Services, Food and Drug Administration C for DE and R (CDER). Guidance for Industry. Drug Interaction Studies- Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Guid Doc 2012.

[2] Geisler F, Kramer JLK, Cashman N, Warner FM, Cragg JJ, Jutzeler CR, et al. A Longitudinal Study of the Neurologic Safety of Acute Baclofen Use After Spinal Cord Injury. Neurotherapeutics 2019. doi:10.1007/s13311-019-00713-8.

[3] Cragg JJ, Haefeli J, Jutzeler CR, Röhrich F, Weidner N, Saur M, et al. Effects of Pain and Pain Management on Motor Recovery of Spinal Cord-Injured Patients: A Longitudinal Study. Neurorehabil Neural Repair 2016. doi:10.1177/1545968315624777.

[4] Warner FM, Cragg JJ, Jutzeler CR, Röhrich F, Weidner N, Saur M, et al. Early Administration of Gabapentinoids Improves Motor Recovery after Human Spinal Cord Injury. Cell Rep 2017;18:1614–8. doi:10.1016/j.celrep.2017.01.048.

[5] Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov 2004;3:673–83. doi:10.1038/nrd1468.

[6] Gardarsdottir H, Souverein PC, Egberts TCG, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. J Clin Epidemiol 2010;63:422–7. doi:10.1016/j.jclinepi.2009.07.001.

[7] Pazzagli L, Linder M, Zhang M, Vago E, Stang P, Myers D, et al. Methods for time-varying exposure related problems in pharmacoepidemiology: An overview. Pharmacoepidemiol Drug Saf 2018. doi:10.1002/pds.4372.

[8] Pazzagli L, Linder M, Zhang M, Vago E, Stang P, Myers D, et al. Methods for time-varying exposure related problems in pharmacoepidemiology: An overview. Pharmacoepidemiol Drug Saf 2018;27:148–60. doi:10.1002/pds.4372.

[9] Phadnis MA, Shireman TI, Wetmore JB, Rigler SK, Zhou X, Spertus JA, et al. Estimation of Drug Effectiveness by Modeling Three Time-Dependent Covariates: An Application to Data on Cardioprotective Medications in the Chronic Dialysis Population. Stat Biopharm Res 2014;6:229–40. doi:10.1080/19466315.2014.920275.

[10] Stricker BHC, Stijnen T. Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies. Eur J Epidemiol 2010;25:245–51. doi:10.1007/s10654-010-9451-7.

[11] McKenzie DA, Semradek J, McFarland BH, Mullooly JP, McCamant LE. The validity of Medicaid pharmacy claims for estimating drug use among elderly nursing home residents: The Oregon experience. J Clin Epidemiol 2000. doi:10.1016/S0895-4356(00)00259-6.

[12] Løkkegaard EL, Johnsen SP, Heitmann BL, Stahlberg C, Pedersen AT, Obel EB, et al. The validity of self-reported use of hormone replacement therapy among Danish nurses. Acta Obstet Gynecol Scand 2004. doi:10.1111/j.0001-6349.2004.00376.x.

[13] Kramer JLK, Taylor P, Haefeli J, Blum J, Zariffa J, Curt A, et al. Test–Retest Reliability of

Contact Heat-Evoked Potentials From Cervical Dermatomes. J Clin Neurophysiol 2012;29:70–5. doi:10.1097/WNP.0b013e318246ada2.

[14] Marek K, Jennings D, Lasch S, Siderowf A, Tanner C, Simuni T, et al. The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol 2011;95:629–35. doi:10.1016/j.pneurobio.2011.09.005.

[15] Nahler G. WHO collaborating centre for international drug monitoring. Dict. Pharm. Med., 2010. doi:10.1007/978-3-211-89836-9_1469.

[16] Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the Risk of Cardiovascular Death. N Engl J Med 2012;366:1881–90. doi:10.1056/NEJMoa1003833.

TABLES

Table 1 Data dictionary for concomitant medication log data file from PPMI study

Variable	Description	Type
REC_ID	Record ID	NUMBER
F_STATUS	Data status: Verified, Secured or Locked	CHAR
CNO	Center Number	CHAR
PATNO	Patient Number	CHAR
EVENT_ID	Event Name	CHAR
PAG_NAME	Page Name	CHAR
INVSTAFF	Investigator staff code	CHAR
CMSEQ	Row #	NUMBER
CMTRT	Medication	CHAR
CMDOSE	Dose	NUMBER
CMDOSU	Units	CHAR
CMDOSFRQ	Frequency	CHAR
ROUTE	Route	CHAR
STARTDT	Start Date	DATE
STARTEST	Start Date estimation	CHAR
STOPDT	Stop Date	DATE
STOPEST	Stop Date estimation	CHAR
ONGOING	Ongoing	CHAR
CMINDC	Indication	CHAR
DISMED	PD Med ?	CHAR
TOTDDOSE	Total Daily Dose	NUMBER
RECNO	WHO RECNO	CHAR
SEQNO1	WHO SEQNO1	CHAR
SEQNO2	WHO SEQNO2	CHAR
WHODRUG	WHO DRUG NAME	CHAR
EXCLMED	Exclusionary Med flag	CHAR
LEDD	LEDD calculation for PD medication	NUMBER
ORIG_ENTRY	Date of original data entry	DATE
LAST_UPDATE	Date of most recent update to record	DATE
QUERY	Any open/pending queries on this record	NUMBER
SITE_APRV	Date site approved the data	DATE

FIGURE LEGENDS

Figure 1. Treatment episodes constructed from overlapping log records for the same medication. The log records have varying durations and different daily doses with common units, d_1, d_2, d_3, and d_4. Log records 1 and 2 belong to a treatment episode with simultaneous regimens of the same medication. Log records 3 and 4 belong to another treatment episode with a change in dose regimen. Constructed episodes show total daily dose for each month.

BOXES

Box 1. Recommendations for collecting concomitant medication log data

- Check validity of start and stop dates.
- Record start and stop dates with year, month and day.
- Check validity of dose, unit and frequency.
- Check validity of overlapping log records.
- Record medication status continuously.
- Electronic logs to prevent invalid entries.
- Use standardized drug and indication systems.

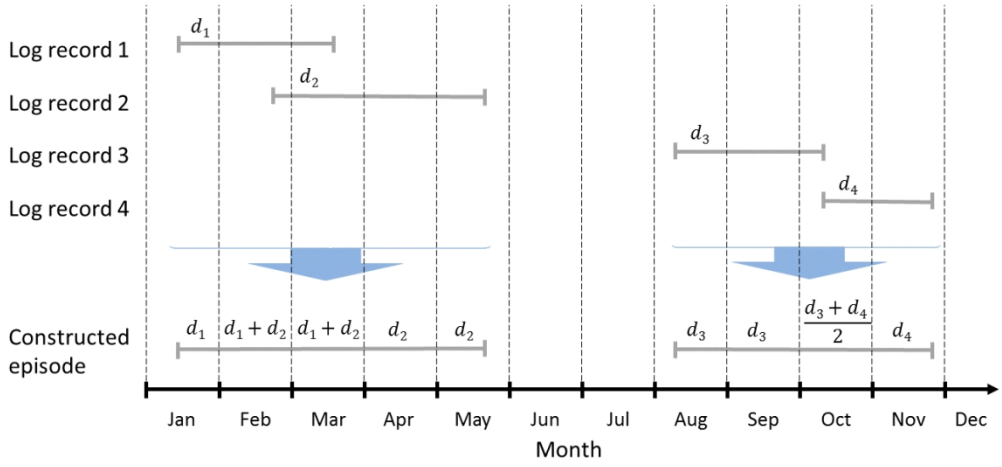

Figure 1. Treatment episodes constructed from overlapping log records for the same medication. The log records have varying durations and different daily doses with common units, d1, d2, d3, and d4. Log records 1 and 2 belong to a treatment episode with simultaneous regimens of the same medication. Log records 3 and 4 belong to another treatment episode with a change in dose regimen. Constructed episodes show total daily dose for each month.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8, 9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8, 9
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9, 10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Constructing treatment episodes from concomitant medication logs: a prospective observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034305.R1
Article Type:	Original research
Date Submitted by the Author:	23-Jan-2020
Complete List of Authors:	Kuramoto, Lisa; The University of British Columbia, Centre for Clinical Epidemiology & Evaluation, Vancouver Coastal Health Research Institute Sobolev, Boris; The University of British Columbia, School of Population and Public Health Brasher, Penelope; The University of British Columbia, Centre for Clinical Epidemiology & Evaluation, Vancouver Coastal Health Research Institute Tang, Michael; The University of British Columbia, Centre for Clinical Epidemiology & Evaluation, Vancouver Coastal Health Research Institute Cragg, Jacquelyn; The University of British Columbia, Faculty of Pharmaceutical Sciences
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Epidemiology
Keywords:	Drug utilization, Drug evaluation, Drug repositioning, Episode of care, Parkinson-s disease < NEUROLOGY

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CONSTRUCTING TREATMENT EPISODES FROM CONCOMITANT MEDICATION LOGS: A PROSPECTIVE OBSERVATIONAL STUDY

Running title: Constructing episodes from concomitant medication logs

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MeSH key words: Drug utilization; Drug evaluation; Drug repositioning; Episode of care; Parkinson Disease

Word count, excluding abstract, tables, figures and references: 3,020

Number of Figures: 1

Number of Tables and Boxes: 3

ABSTRACT

Objectives: To describe an approach using concomitant medication logs records for the construction of treatment episodes. Concomitant medication log records are routinely collected in clinical studies. Unlike prescription and dispensing records, concomitant medication logs collect utilization data. Logs can provide information about drug safety and drug repurposing.

Design: A prospective multi-centre, multi-cohort observational study.

Setting: Twenty-one clinical sites in the United States, Europe, Israel, and Australia.

Participants: 415 subjects from the de novo cohort of the Parkinson Progression Marker Initiative.

Methods: We construct treatment episodes of concomitant medication use. The proposed approach treats temporal gaps as a stoppage of medication and temporal overlaps as simultaneous use or changes in dose. Log records with no temporal gaps were combined into a single treatment episode.

Results: 5,723 concomitant medication log records were used to construct 3,655 treatment episodes for 65 medications. There were 405 temporal gaps representing a stoppage of medication; 985 temporal overlaps representing simultaneous regimens of the same medication; and 2,696 temporal overlaps representing a change in dose regimen. The median episode duration was 37 months (interquartile interval: 11 to 73 months).

Conclusions: The proposed approach for constructing treatment episodes offers a method of estimating duration and dose of treatment from concomitant medication log records. The accompanying recommendations guides log data collection to improve their quality for drug safety and drug repurposing.

Strengths and limitations of this study

- A large, observational study prospectively capturing information on medication use in an internationally representative cohort of individuals with Parkinson's disease.
- We describe an approach using concomitant medication log records for constructing treatment episodes.
- Assumes concomitant medication logs accurately capture subjects' medication use.

1. INTRODUCTION

Concomitant medication log records are routinely collected in clinical studies. Their collection is important for establishing safety of new investigational drugs. For example, medications may interact with study interventions or interact with contrast media used in imaging procedures. Regulatory agencies, such as Health Canada and the US Food and Drug Administration, require that concomitant medications be recorded during clinical trials and prospective cohort studies [1]. Concomitant medication records can add to the drug safety profiles of commonly used, approved drugs. For example, concomitant medication records from a completed clinical trial were used to test whether a common anti-spasticity medication interfered with motor neurologic recovery [2]. Concomitant medication records can also identify targets for drug repurposing. For example, a concomitant medication for treating neuropathic pain was found to be unintentionally beneficial for muscle strength recovery after spinal cord injury [3,4]. This could lead to drug repurposing to maximize neurological outcomes [5].

Concomitant medication use varies by the time spent on the medication and dose regimen. These variations are captured by *treatment episodes*, the events from the start to the end of the administration of a medication [6]. Specifically, construction of treatment episodes identifies events of medication use belonging to the same treatment, and identifies dose changes during the episode. Construction of treatment episodes plays a key role in calculating measures of exposure which are used in statistical analyses for estimating medication effects [7–10]. Some measures of exposure, which can be derived from episodes, include an indicator of current use, episode duration, or episode dose [11]. *Episode duration* is the time exposed to the medication. *Episode dose* is the total daily dosage over the course of the episode.

Different methods and assumptions used in episode construction influence measures of exposure and effect [6]. Underestimating treatment effects may result in missed opportunities for therapeutic development, while overestimating treatment effects may result in wasted resources. While the pharmaco-epidemiology literature describes treatment episode construction [6,7,12,13], the data used in these cases is information about medications prescribed or dispensed as opposed to medication utilization [14,15]. Our objective was to describe an approach using concomitant medication log records for the construction of treatment episodes. We also provide recommendations for collecting concomitant medication data to improve their quality and use in drug safety and drug repurposing strategies.

2. METHODS

2.1 Data Source

Data were obtained from the Parkinson's Progression Markers Initiative (PPMI) database. The PPMI is a comprehensive prospective observational study designed to improve understanding of disease etiology and progression [16,17]. The PPMI database is comprised of multiple cohorts including recently diagnosed Parkinson's Disease (PD) subjects and healthy participants followed longitudinally for clinical, imaging, behavioural, and biospecimen assessments, using standardized data acquisition protocols at twenty-one clinical sites in the United States, Europe, Israel, and Australia. Anonymized study data are publicly available through the PPMI website (www.ppmi-info.org). We downloaded the PPMI data files on April 6, 2018. This study, which involved publicly available data, was exempt from ethics review according to National policy [18].

2.2 Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research.

2.3 PPMI Concomitant Medication Log

The collection of concomitant medications in PPMI is done through a standardized Case Report Form (CRF) [16]. In PPMI, medications taken at Screening Visit (the visit used to screen for study eligibility) are entered into the log. At subsequent visits, new medications, and changes/discontinuation of previously listed medications are recorded. The following instructions are provided on the CRF:

> *Enter all medications taken at Screening Visit. At subsequent visits record new meds, and changes/discontinuation of previously listed meds. Changes in total daily dose or route require a new line. Row: enter 1, 2, 3, etc. Medication: Record generic name; if unknown, enter brand name. For multiple ingredient medications, indicate strength if possible, e.g., carbidopa/levodopa 25/100. Dose: Record dose for each administration. Date: Please specify if the Start and Stop dates are ACTUAL or ESTIMATED. If the exact date is unknown, please enter your best reasonable estimate of the date and specify which part(s) are estimated. Ongoing: Answer yes if medication is still being taken at end of study. Indication: Reason for use, not drug category.*

Data from this CRF are entered into the PPMI publicly accessible concomitant medication log data file. This data file includes medication name, dose, dose units, frequency, route, start/stop date [or ongoing], indication, and whether the medication is indicated for PD (Table 1). Only month and year of the start and stop dates are publicly accessible. The data file also contains derived medication variables, including the World Health Organization (WHO) drug code [19]. The WHO drug code has 3 parts: Drug Record Number (RECNO), Sequence number 1 (SEQNO1) and Sequence number 2 (SEQNO2). RECNO uniquely identifies active moieties.

We included log records for RECNOs that a minimum of 20 de novo PD subjects were taking at the screening visit or during follow-up. This number was an arbitrary cut-off to identify common medications. We also excluded the "all other non-therapeutic products" (i.e., RECNO=900475) due to a lack of known biological activity. Examples of this included products such as blueberry extract, probiotics, and Neuroplex.

2.4 Episode construction

The proposed approach is founded on the assumption that concomitant medication logs capture the patients' actual medication use. We assume temporal gaps represent a stoppage of medication; temporal overlaps of more than one time unit (e.g., month) represent simultaneous regimens of the same medication; and temporal overlaps of one time unit represent a change in dose regimen. Temporal gaps are the elapsed time between the end of one log record and the start of the subsequent log record. Temporal overlaps are the time during which a log record starts before a previous log record ends. Since only the year and month of the medication start and stop dates were accessible, we distinguished between simultaneous regimens and changes in dose regimens to not overestimate total daily dose. Log records with the same RECNO and no temporal gaps were combined into a single treatment episode.

Log records with a medication frequency of "as needed" (e.g., "PRN", "OCCASIONAL", "ON DEMAND", "QS", or "SOS") did not contribute to exposure because we could not confirm medication utilization. When the log record had a vague unit (e.g., tablet or capsule) the daily dose could not be computed; however, the record still contributed to episode duration.

2.5 Episode duration

We identified the start and end dates of medication use for each log record. If there was no start date or if the dates were non-chronological, we marked the log record as incomplete. If there was no stop date, we imputed with the date of the last concomitant medication review as the PPMI protocol instructed to leave this field blank until either the subject ended participation or the study was over.

Among log records belonging to the same treatment episode, the episode start date was the start date of the earliest log record and the episode end date was the stop date of the latest log record. The episode duration was computed as the number of months between the episode start and end dates.

2.6 Episode dose

We calculated the daily dose from each log record. First, we determined the multiplicative factor, representing how often the reported dose is taken per day. For example, "BID" means twice a day, so

the multiplicative factor is 2. Next, we converted doses to a common unit (e.g., mg). The daily dose is the product of the reported dose in common units and the multiplicative factor based on the frequency.

We calculated the total daily dose among log records belonging to the same treatment episode. The total daily dose at a time with simultaneous regimens was the sum of the daily doses of log records containing the time point (Figure 1). The total daily dose at a time with changes in dose regimen was the average of the doses (Figure 1). If there was only one log record constructing an episode, then the total daily dose was equal to the daily dose. The total daily dose and any changes were computed over the course of the treatment episode.

3. RESULTS

3.1 Episode durations

Of the 423 enrolled de novo PD subjects, 415 had a baseline visit and at least one follow-up visit. Of the 8,771 concomitant medication log records, we excluded 2,619 (29.9%) log records of medications taken by fewer than 20 PD subjects, 352 (4.0%) records with drug frequencies of "as needed", and 77 (0.9%) log records for "all other non-therapeutic products" (i.e., RECNO=900475). The remaining 5,723 log records were used to construct treatment episodes for 65 medications among the 415 PD subjects. Two-fifths of the log records were incomplete: 3 (0.05%) had no start date, 2,328 (40.7%) had no stop date (so were imputed), and 2 (0.03%) had non-chronological start and stop dates. For example, REC_ID 282665101, recorded that PATNO 3606 had no start date or stop date for a vitamin B complex. REC_ID 226846701 recorded that PATNO 3400 started Lexapro in February 2010, but had no stop date. REC_ID 538226701 had a start date on February 2013 and a stop date on March 2012; and REC_ID 413205901 had a start date on September 2013 and stop date on August 2013. These log records, as with records with data entry errors (e.g., REC_ID 667793101 with a stop date of "03/0218"), were considered incomplete.

About half of the log records were combined to form treatment episodes: 543 (9.5%) log records had identical start and stop dates; 132 (2.3%) records started and stopped a medication regimen before stopping the previous regimen; 2,260 (39.5%) records started another regimen of the same medication before stopping the previous regimen. The remaining log records each corresponded to a single treatment episode. There were 405 temporal gaps among subjects with multiple log records for a given medication. The gaps had a median duration of 8 months (interquartile interval [IQI]: 1 to 14 months).

The 415 de novo PD subjects had 60 months median follow-up time (IQI: 54 to 86 months). We constructed 3,655 treatment episodes for 65 medications among these subjects. The median episode duration was 37 months (IQI: 11 to 73 months).

3.2 Episode doses

There was significant variation in units and frequencies: 66 different units and 136 different frequencies among the 5,723 log records. For example, for RECNO 3686, some of the units were reported as TAB, TABS, CAP, or CAPS, and some of the frequencies were reported as 4 X DAILY, 4 X QD, 4X, 4X/D, 4XD, 4XDAY, 4XQD, or 4XS/DAY. We revised the reported units to be consistent across records. For example, G, GM, GR, GRAM, ",G", GRAMS were recoded as GRAM. We determined the multiplicative factor for computing daily doses. For example, 6 PER DAY, 6X A DAY, 6/DAY, 6X DAY, 6X/DAY, 6XD, 6XS/DAY; SIX DAILY had a multiplicative factor of 6. In 8 (0.1%) and 95 (1.7%) of the log records, the values for units or frequencies, respectively, were vague.

We calculated the total daily dose during a treatment episode, by accounting for temporal gaps and overlaps. There were 405 temporal gaps representing a stoppage of the medication; 985 temporal overlaps of more than one time unit (e.g., month) representing simultaneous regimens of the same medication; and 2,696 temporal overlaps of one time unit representing a change in dose regimen.

3.3 Example: Gabapentin

To illustrate these steps with respect to a single medication, we provide here an example with gabapentin (primarily indicated for neuropathic pain). Among the 415 de novo PD subjects, there were 49 log records of gabapentin use among 30 subjects. For each record of gabapentin, we computed the daily dose. First, we identified log records of interest; those with RECNO = 10030. Second, we determined the multiplicative factors for calculating daily dose. Third, we converted all units to mg. Finally, we computed the daily dose for gabapentin. For example, PATNO 3625 has a dose of 300 with units MG and frequency BID. Therefore, the daily dose is 300 MG * 2 = 600 MG. One log record indicated that the subject was on the medication "as needed" and another log record reported units as tablet (i.e., "TAB"), so the records did not contribute to episode duration or dose. Among the remaining gabapentin log records, the median daily dose was 600 mg, and ranged from 100 mg to 3,600 mg per day.

We constructed 37 episodes of gabapentin use among subjects. Each user of gabapentin had one or two episodes during the study period. About three-quarters (23 of 30) of these subjects had episodes of gabapentin use starting after the baseline visit. The median cumulative months of exposure was 16

months (IQI: 7 to 29 months). The median cumulative total daily dose was 156,000 mg (IQI: 42,600 to 667,800 mg).

4. DISCUSSION

We described an approach for the construction of treatment episodes from concomitant medication logs to estimate duration and dose. The approach treats temporal gaps as a stoppage of medication and temporal overlaps as simultaneous use or changes in dose. Log records with no temporal gaps were combined into a single treatment episode.

Construction of treatment episodes using concomitant medication log data differs from construction using drug prescribing and dispensing data (Table 2) [6,7,12,13]. Approaches for constructing episodes from prescription or dispensing records are used to infer medication use, whereas the proposed approach is based on actual medication use. Data from prescription and dispensing databases are typically less comprehensive (e.g., may not include a route of administration, generally do not capture non-prescription drugs, sometimes limited to a specific setting such as a single hospital or pharmacy, often restricted in terms of number of years captured, generally do not include drug indication). Second, in concomitant medication logs, temporal gaps in medication use identify when the subject was not actually taking the drug. This is in contrast to prescription and dispensing data, where gaps of pre-defined length are filled when constructing episodes to account for assumed medication use during those gaps. In some cases, patient-reported medication use is the reference standard for prescribing/dispensing records [20], supporting treating gaps as a stoppage of the medication. Lastly, in concomitant medication logs, temporal overlaps identify when the subject is administering simultaneous regimens of the same medication. This is in contrast to prescription and dispensing data, where the overlapping time is used to extend the duration of the episode.

Recommendations

We submit that concomitant medication logs can be used as a surveillance tool for drug safety and drug repurposing studies. For example, the cumulative exposure to gabapentin for pain management, computed using the proposed approach, could, in future studies, be correlated with motor disease progression to see if the drug is detrimental (i.e., drug safety) or beneficial (i.e., candidate for repurposing) in Parkinson's disease. In addition, both sponsors and regulatory agencies may inspect these types of logs over a study lifespan to ensure compliance with trial design and patient adherence [21].

Applying the proposed approach to the data from the PPMI concomitant medication log yielded recommendations for data collection and data quality checks for future prospective studies (Box 1). When collecting data for a concomitant medication log, we recommend: 1) Quality checks for valid start dates (e.g., no data entry errors); 2) Quality checks for valid stop dates (e.g., start and stop dates are chronologically ordered); 3) Record medication start and stop dates with day, month, and year (i.e., complete dates for precise account of medication use); 4) Quality checks for valid dose (e.g., dose is within the recommended range); 5) Quality checks for valid unit (e.g., no vague units like "tablet"); 6) Quality checks for valid frequency (e.g., confirm the use of "as needed" medication with the subject); 7) Quality checks for overlapping log records with the same medication, dose, and frequency; 8) Continuous recording of concomitant medication status (so start and stop dates are more accurate), by e-diaries, for example; 9) Electronic log records to prevent users from creating another log record for the same medication, if a log record for the medication with no stop date exists (i.e., is there a need to have two "active" records for the same medication"); 10) Use standardized drug/indication systems, such as the World Health Organization system.

Study Limitations

Our study has a few limitations. First, the proposed approach assumes that the concomitant medication log data accurately capture the subjects' medication use. The PPMI data indicate whether start and stop dates were actual or estimated. The month of the start and stop dates was estimated in 39% and 21% of records, respectively. While patient-report has been used as a standard in prior studies, the validity may differ with respect to different medications.

Second, the approach does not specify how to handle errors in medication start dates, stop dates, or doses. These errors could result in underestimating or overestimating episode durations or doses. For example, the approach assumes that temporal overlaps represent simultaneous use; however, it could be an error of double reporting. In this case, the approach would overestimate the episode dose, but episode duration could be unaltered. In a sensitivity analysis, we re-constructed episodes assuming that temporal overlaps represented an error in double reporting. We retained the overlap from the most recent record. For gabapentin, the cumulative months of exposure and the cumulative total daily dose had medians that remained the same, but the interquartile interval became narrower for the latter (42,600 to 580,500 mg).

Third, we assumed no medication use when the medication frequency was "as needed" which could underestimate the medication duration and dose.

The advantage of our study is that we had longitudinal medication information in an internationally representative cohort of individuals with PD.

Conclusion

The proposed approach to constructing treatment episodes offers a method of estimating duration and dose of medication treatment using data from concomitant medication logs. The accompanying recommendations guide log data collection in clinical studies to improve their quality and use in drug safety and drug repurposing strategies.

ACKNOWLEDGEMENTS

PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbvie, Allergan, Avid Radiopharmaceuticals, Biogen, BioLegend, Bristol-Myers Squibb, Celgene, Denali, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Prevail Therapeutics, Roche, Sanofi Genzyme, Servier, Takeda, Teva, UCB, Verily, and Voyager Therapeutics.

Contributors: All authors contributed to and approved the final manuscript. JC conceived the work and obtained study funding; LK and MT analysed the data; LK, BS, PB, MT and JC interpreted the data for the work; LK and JC drafted the manuscript; and LK, BS, PB, MT and JC revised the manuscript for important intellectual content.

Funding: This work was supported by the Michael J. Fox Foundation for Parkinson's research [grant number 14834].

Competing interests: None declared.

Data availability: Anonymized study data are publicly available through the PPMI website (www.ppmi-info.org). Investigators seeking access to PPMI data must submit an online application, which requires signing the Data Use Agreement and compliance with the study Publications Policy.

REFERENCES

[1] U.S. Department of Health and Human Services, Food and Drug Administration C for DE and R (CDER). Guidance for Industry. Drug Interaction Studies- Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Guid Doc 2012.

[2] Geisler F, Kramer JLK, Cashman N, Warner FM, Cragg JJ, Jutzeler CR, et al. A Longitudinal Study of the Neurologic Safety of Acute Baclofen Use After Spinal Cord Injury. Neurotherapeutics 2019. doi:10.1007/s13311-019-00713-8.

[3] Cragg JJ, Haefeli J, Jutzeler CR, Röhrich F, Weidner N, Saur M, et al. Effects of Pain and Pain Management on Motor Recovery of Spinal Cord-Injured Patients: A Longitudinal Study. Neurorehabil Neural Repair 2016. doi:10.1177/1545968315624777.

[4] Warner FM, Cragg JJ, Jutzeler CR, Röhrich F, Weidner N, Saur M, et al. Early Administration of Gabapentinoids Improves Motor Recovery after Human Spinal Cord Injury. Cell Rep 2017;18:1614–8. doi:10.1016/j.celrep.2017.01.048.

[5] Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov 2004;3:673–83. doi:10.1038/nrd1468.

[6] Gardarsdottir H, Souverein PC, Egberts TCG, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. J Clin Epidemiol 2010;63:422–7. doi:10.1016/j.jclinepi.2009.07.001.

[7] Pazzagli L, Linder M, Zhang M, Vago E, Stang P, Myers D, et al. Methods for time-varying exposure related problems in pharmacoepidemiology: An overview. Pharmacoepidemiol Drug Saf 2018;27:148–60. doi:10.1002/pds.4372.

[8] Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. Stat Med 2009. doi:10.1002/sim.3701.

[9] Abrahamowicz M, Beauchamp ME, Sylvestre MP. Comparison of alternative models for linking drug exposure with adverse effects. Stat Med 2012. doi:10.1002/sim.4343.

[10] Thomas DC. Models for exposure-time-response relationships with applications to cancer epidemiology. Annu Rev Public Health 1988. doi:10.1146/annurev.publhealth.9.1.451.

[11] Abrahamowicz M, Bartlett G, Tamblyn R, Du Berger R. Modeling cumulative dose and exposure duration provided insights regarding the associations between benzodiazepines and injuries. J Clin Epidemiol 2006;59:393–403. doi:10.1016/j.jclinepi.2005.01.021.

[12] Mantel-Teeuwisse AK, Klungel OH, Verschuren WMM, Porsius A, De Boer A. Comparison of different methods to estimate prevalence of drug use by using pharmacy records. J Clin Epidemiol 2001. doi:10.1016/S0895-4356(01)00396-1.

[13] Khotimah PH, Sugiyama Y, Yoshikawa M, Hamasaki A, Sugiyama O, Okamoto K, et al. Medication Episode Construction Framework for Retrospective Database Analyses of Patients with Chronic Diseases. IEEE J Biomed Heal Informatics 2018. doi:10.1109/JBHI.2017.2786741.

[14] McKenzie DA, Semradek J, McFarland BH, Mullooly JP, McCamant LE. The validity of

Medicaid pharmacy claims for estimating drug use among elderly nursing home residents: The Oregon experience. J Clin Epidemiol 2000. doi:10.1016/S0895-4356(00)00259-6.

[15] Løkkegaard EL, Johnsen SP, Heitmann BL, Stahlberg C, Pedersen AT, Obel EB, et al. The validity of self-reported use of hormone replacement therapy among Danish nurses. Acta Obstet Gynecol Scand 2004. doi:10.1111/j.0001-6349.2004.00376.x.

[16] Marek K, Jennings D, Lasch S, Siderowf A, Tanner C, Simuni T, et al. The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol 2011;95:629–35. doi:10.1016/j.pneurobio.2011.09.005.

[17] Latourelle JC, Beste MT, Hadzi TC, Miller RE, Oppenheim JN, Valko MP, et al. Large-scale identification of clinical and genetic predictors of motor progression in patients with newly diagnosed Parkinson's disease: a longitudinal cohort study and validation. Lancet Neurol 2017. doi:10.1016/S1474-4422(17)30328-9.

[18] Interagency Advisory Panel on Research Ethics. TCPS 2 (2014)— the latest edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Panel Res Ethics 2014.

[19] Nahler G. WHO collaborating centre for international drug monitoring. Dict. Pharm. Med., 2010. doi:10.1007/978-3-211-89836-9_1469.

[20] Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the Risk of Cardiovascular Death. N Engl J Med 2012;366:1881–90. doi:10.1056/NEJMoa1003833.

[21] ICH E3. Structure and content of clinical study reports. Good Clin Pract J 2001.

Table 1 Data dictionary for concomitant medication log data file from the Parkinson's Progression Markers Initiative study

Variable	Description	Type
REC_ID	Record ID	NUMBER
F_STATUS	Data status: Verified, Secured or Locked	CHAR
CNO	Center Number	CHAR
PATNO	Patient Number	CHAR
EVENT_ID	Event Name	CHAR
PAG_NAME	Page Name	CHAR
INVSTAFF	Investigator staff code	CHAR
CMSEQ	Row #	NUMBER
CMTRT	Medication	CHAR
CMDOSE	Dose	NUMBER
CMDOSU	Units	CHAR
CMDOSFRQ	Frequency	CHAR
ROUTE	Route	CHAR
STARTDT	Start Date	DATE
STARTEST	Start Date estimation	CHAR
STOPDT	Stop Date	DATE
STOPEST	Stop Date estimation	CHAR
ONGOING	Ongoing	CHAR
CMINDC	Indication	CHAR
DISMED	PD Med ?	CHAR
TOTDDOSE	Total Daily Dose	NUMBER
RECNO	WHO RECNO	CHAR
SEQNO1	WHO SEQNO1	CHAR
SEQNO2	WHO SEQNO2	CHAR
WHODRUG	WHO DRUG NAME	CHAR
EXCLMED	Exclusionary Med flag	CHAR
LEDD	LEDD calculation for PD medication	NUMBER
ORIG_ENTRY	Date of original data entry	DATE
LAST_UPDATE	Date of most recent update to record	DATE
QUERY	Any open/pending queries on this record	NUMBER
SITE_APRV	Date site approved the data	DATE

Table 2 Approaches for Constructing Treatment Episodes for Medication Utilization

Issue	Proposed Approach	Alternative Approaches	Pros of Proposed Approach	Cons of Proposed Approach
Data source	• Concomitant medication log	• Prescription data • Drug dispensing data	• Aims to capture drug utilization, as opposed to prescribing or dispensing of medications • More comprehensive (e.g., captures route of administration, non-prescription drugs)	• Relies on accurate reporting of medication use • Not subjected to same level of data quality checks as primary data
Temporal gaps	• Assumes gaps represent a stoppage in medication use • Do not fill gaps • Records with gaps between them come from different episodes.	• Assumes gaps could represent medication use • Fills gaps of predefined length • Records with gaps within the predefined length come from the same episode.	• Objectively identifies when medication is not in use • Predefined gap length is not medication dependent	• Short gaps may be misclassified as no medication use
Temporal overlap	• Assumes overlaps represent simultaneous or change in medication regimen • Total daily dose is computed as a sum or average over records • Overlapping records come from the same episode	• Assumes overlaps represent re-filling prescriptions early • Overlapping time added to episode duration or ignored • Overlapping records come from the same episode	• Objectively identifies episode end date	• Potential overestimation of total daily dose, if overlap erroneously represents double reporting
Total daily dose	• Assumes record captures actual dose • Vague units (e.g., TAB) or frequency (e.g., PRN) do not contribute to episode dose	• Assumes a defined daily dose (DDD), such that the dose is the average among adults with the main indication for the medication	• Recorded dose represents actual dose	• Records with vague entries do not contribute to episode dose; potential underestimation of the dose
Medication start and stop dates	• Assumes record captures actual medication start and stop dates • Impute missing stop dates with date of last medication review • Mark records with no start date as incomplete	• Assumes medication start date is the prescription or dispensing date • Infers medication stop date from prescription order • Mark records with no start/stop dates as incomplete	• Uses actual medication start and stop dates	• Potential overestimation of episode duration, if imputing stop date

FIGURE LEGENDS

Figure 1. Treatment episodes constructed from overlapping log records for the same medication. The log records have varying durations and different daily doses with common units, d_1, d_2, d_3, and d_4. Log records 1 and 2 belong to a treatment episode with simultaneous regimens of the same medication. Log records 3 and 4 belong to another treatment episode with a change in dose regimen. Constructed episodes show total daily dose for each month.

BOXES

Box 1. Recommendations for collecting concomitant medication log data

- Check validity of start and stop dates.
- Record start and stop dates with year, month and day.
- Check validity of dose, unit and frequency.
- Check validity of overlapping log records.
- Record medication status continuously.
- Electronic logs to prevent invalid entries.
- Use standardized drug and indication systems.

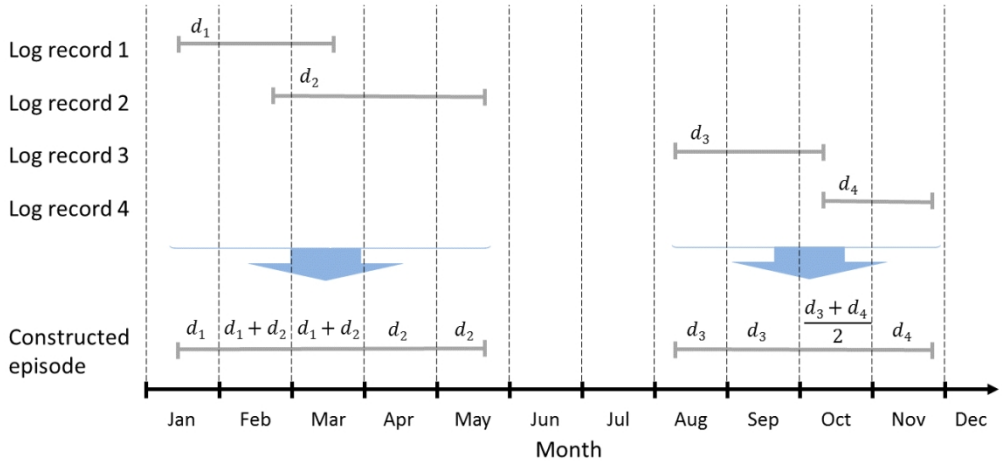

Figure 1. Treatment episodes constructed from overlapping log records for the same medication. The log records have varying durations and different daily doses with common units, d1, d2, d3, and d4. Log records 1 and 2 belong to a treatment episode with simultaneous regimens of the same medication. Log records 3 and 4 belong to another treatment episode with a change in dose regimen. Constructed episodes show total daily dose for each month.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8, 9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8, 9
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9, 10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.