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Evaluating the use of prescription sequence symmetry analysis as a pharmacovigilance tool: A scoping review

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ABSTRACT

Background: The (prescription) sequence symmetry analysis (PSSA) design has been used to identify potential prescribing cascade signals by assessing the prescribing sequence of an index drug relative to a marker drug presumed to treat an adverse drug event provoked by the index drug.
Objectives: This review aimed to explore the use of the PSSA design as a pharmacovigilance tool with a particular focus on the breadth of identified signals and advances in PSSA methodology.
Methods: We searched Embase, PubMed/Medline, Google Scholar, Web of Science and grey literature to identify studies that used the PSSA methodology. Two reviewers independently extracted relevant data for each included article. Study characteristics including signals identified, exposure time window, stratified analyses, and use of controls were extracted.
Results: We identified 53 studies which reported original results obtained using PSSA methodology or quantified the validity of components of the PSSA design. Of those, nine studies provided validation metrics showing reasonable sensitivity and high specificity of PSSA to identify prescribing cascade signals. We identified 340 unique index drug – marker drug signals published in the PSSA literature, representing 281 unique index – marker pharmacological class dyads (i.e., unique fourth-level Anatomical Therapeutic Chemical [ATC] classification dyads). Commonly observed signals were identified for index drugs acting upon the nervous system (34%), cardiovascular system (21%), and blood and blood-forming organs (15%), and many marker drugs were related to the nervous system (25%), alimentary tract and metabolism (23%), cardiovascular system (17%), and genitourinary system and sex hormones (14%). Negative controls and positive controls were utilized in 21% and 13% of studies, respectively.
Conclusions: The PSSA methodology has been used in 53 studies worldwide to detect and evaluate over 300 unique prescribing cascades signals. Researchers should consider sensitivity analyses incorporating negative and/or positive controls and additional time windows to evaluate time-varying biases when designing PSSA studies.

1. Introduction

The (prescription) symmetry sequence analysis (PSSA) method is a pharmacovigilance tool employed to rapidly identify adverse drug event adverse drug event signals and potential prescribing cascades within large administrative health databases.[1] Prescribing cascades occur when an adverse drug event is misinterpreted as a new medical condition, prompting practitioners to prescribe a new medication to treat effects caused by the first medication.[2] This often suboptimal prescribing practice increases a patient's risk of adverse drug events, either from the potentiation of adverse drug events caused by the first medication or from additional adverse drug events from the new medication.[2]

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Polypharmacy, which may be a result of prescribing cascades,[3] has also been associated with an increased risk for drug-drug interactions and can negatively impact patients' adherence to their current medications.[4–8] Furthermore, prescribing cascades, especially when considered problematic, have the potential to increase healthcare utilization and costs due to the increased medication burden among patients.[3]

The PSSA method exists within the family of self-controlled methods and employs a case-only design including only patients who are users of both drugs of interest (i.e., index drug and marker [e.g., outcome] drug).[9,10] Conceptually, PSSA is applied to investigate a scenario where drug B (marker drug) is prescribed to treat an adverse drug event possibly caused by drug A (index drug).[9] For example, the PSSA method was first used to investigate whether beta-blockers (index drug) have depression-provoking effects and lead to an excess risk of being prescribed antidepressants (marker drug).[1] In assessing the association between the index drug and marker drug, the PSSA uses a population of new users of both index drug and marker drug within a given timeframe and compares the number of subjects who used the index drug before the marker drug to the number of users who used the marker drug before the index drug.[1] Notably, individuals who initiate both the index drug and marker drug on the same day are not included in the analysis as it is impossible to distinguish a prescribing order for such individuals.[9,10] Therefore, risk is estimated by calculating the ratio (crude sequence ratio [cSR]; Fig. 1) of subjects who initiate index drug before marker drug to subjects who initiate marker drug before index drug, while accounting for secular trends of prescribing of these medications over time (adjusted sequence ratio [aSR]; Appendix A).

If there is no association between index drug and the initiation of the marker drug, symmetry is expected as there should be equal chances of initiating the marker drug before or after the index drug. However, if the index drug does indeed increase the risk of an adverse drug event leading to the initiation of a marker drug, asymmetry will occur with an accompanying aSR and lower limit of confidence interval (CI) greater than 1. Because PSSA includes only those individuals who are users of both the index drug and marker drug, time-invariant patient characteristics like age, sex, and other demographic and environmental factors are inherently controlled.[1] In other words, factors that are stable over time within the study time window cannot predict the prescribing order of index drug and marker drug for a given individual, since every individual included in the study is required to be started on both index drug and marker drug.[1]

The objective of this scoping review is to explore published PSSA studies and associated index drug – marker drug dyad signals to expand the current list of potential prescribing cascades.[11,12] Additionally, we hope to describe the utility and methodological advances of PSSA to be used to investigate future potential prescribing cascades in pharmacovigilance studies.

2. Methods

This scoping review adhered to the PRISMA Extension for Scoping Reviews (PRISMA-ScR) checklist.[13]

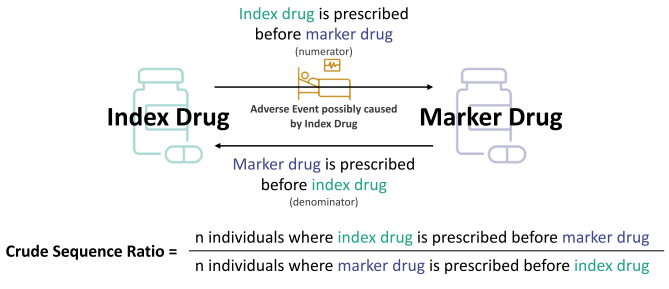

Fig. 1. Diagram of prescription sequence symmetry analysis key concepts.

2.1. Search strategy

Led by our health sciences librarian (L.A.), we searched the medical literature on PSSA and prescribing cascades. Databases searched included Embase, PubMed/Medline, Google Scholar, and Web of Science as well as appropriate and relevant grey literature sources. Each database was searched using a combination of controlled vocabulary specific to that database and keywords from synonyms for the concepts of prescription sequence symmetry analysis and prescribing cascades. We searched articles from January 1st, 1990, to the present, with searches completed on July 31st, 2020. Additional cross-referencing from reference lists of relevant articles was performed. We included full search strategies in Appendix B.

2.2. Inclusion and exclusion criteria

We included original research studies that deployed and/or validated PSSA methodology. Of note, we only included studies that used the *prescription* sequence symmetry analysis design, where the index exposure and the marker outcome were both defined as the prescription of a medication, medication class, or medication classification (e.g., ATC classification) based on pharmacy claims. In other words, articles were required to report and/or validate results for index drug/class – marker drug/class pair(s).

2.3. Study selection

The results of the searches were combined, and duplicates were removed (L.A.). Non-relevant titles and abstracts were removed by independent agreement of two authors (E.J.M., J.H. [second author]). Full-text abstracts and articles were subsequently reviewed independently by at least two authors (E.J.M., J.H. [second author], A.H., H.B., R.O.). Each author independently screened each full-text article and excluded articles. Disagreements between reviewers were resolved by consensus during group discussions led by a third reviewer (S.M.V.). Articles were excluded if they met any of the following criteria: 1) no sequence symmetry analysis; 2) only included original results which analyzed non-drug index exposure and/or marker outcome); 3) were conference proceedings or abstract-only; 4) were editorials, letters to the editor, or opinion pieces; or 5) were only available in non-English language.

2.4. Study extraction

We conducted a team training exercise by screening several full-text test articles using a data collection tool that was created for this review (E.J.M., J.H. [second author]).[14] At least two reviewers (E.J.M., J.H. [second author], A.H., H.B., R.O.) utilized the data collection tool to independently extract relevant data for each included article. All entries were further evaluated by an additional reviewer to ensure accuracy and completeness (E.J.M., J.H. [second author], A.H., H.B., R.O.). Any disagreements were resolved by S.M.V. The following study characteristics were extracted: title, author, year published, journal, country, database utilized, index drugs evaluated, marker drugs evaluated, all significant signals (e.g., aSRs and lower limit of CIs > 1), exposure time window, washout window, stratified analysis/es, use of negative control, use of positive control, use of logistic regression for identifying prescribing cascade predictors, graphical representation of PSSA, number of incident index drugs reported, incidence reported, number needed to harm (NNTH) reported, use of the term "prescribing cascade," and main findings. Authors were not contacted by email as we wanted to evaluate what was presented in the published literature for these analyses. In other words, only results reported in the main study text and/or appendix were extracted in cases where a study did not publish the full list of index drugs, marker drugs, and/or signals evaluated. The full study protocol is available upon request from the corresponding author.

2.5. Data synthesis

Cumulative number of articles published per year were analyzed and plotted by article type (hypothesis-free, hypothesis-testing, or validation). Articles were considered hypothesis-free if the study aimed to detect previously unknown prescribing cascade signals, and articles were considered hypothesis-testing if the aim was to evaluate prespecified hypotheses. Articles that aimed to validate PSSA estimates or PSSA methods were classified as validation studies. Published PSSA articles were further plotted by country via heat mapping. An article was counted if it utilized data from a given country. Therefore, a single article could be counted for multiple countries if data was utilized from multiple countries. Study design characteristics and results of PSSA articles were presented descriptively as counts and frequencies.

Prescribing cascade signals were counted and analyzed among PSSA articles which presented original signal evaluation/detection results. A signal was considered significant if the lower limit of aSR CI was >1. All significant signals were further classified into unique index-marker pharmacological class (e.g., fourth-level ATC classification) pairs. Cumulative unique prescribing cascade signals for individual drug pairs and pharmacological class pairs were then plotted by year. Additionally, an alluvial graph representing index drug-marker drug combinations stratified by anatomical drug group (e.g., first-level ATC classification) was created where width of the linkages between index drug and marker drug group is proportional to the number of unique index drug-marker drug pharmacological class (e.g., fourth-level ATC classification) signals.

All data visualization was produced using R statistical software (version 4.0.2; R Development Core Team).

3. Results

3.1. Included Prescription Sequence Symmetry Analysis Studies

The flowchart of study inclusion is illustrated in Fig. 2. A total of 678 studies were identified during the study period across all databases and through reference screening. After removing duplicates and screening for eligibility, 53 studies remained that met the inclusion criteria.[1,15–55,56-66] Among those, 47 studies reported original PSSA results (e.g., aSRs for signals evaluated/detected),[1,15–55,56-60] and nine reported results of validation metrics (e.g., sensitivity, specificity, negative predictive value, positive predictive value, etc.) or formal comparison to other study designs.[19,35,37,61–66] Of note, three studies reported original prescribing cascade signals and conducted some level of method validation, and therefore pertinent results from these studies are included in the review among both signal detection and validation categories.[19,35,37]

The 53 included studies were published between 1996 and 2020, with most studies published in 2013 or later (Fig. 3). The PSSA design has been employed across 4 continents and 14 countries. A large number of studies were conducted using data from Japan (n = 14), Australia (n = 14), and Denmark (n = 9). Other countries commonly utilizing the PSSA design to identify prescribing cascades include South Korea, the Netherlands, Taiwan, the United States, and Canada (Fig. 4).

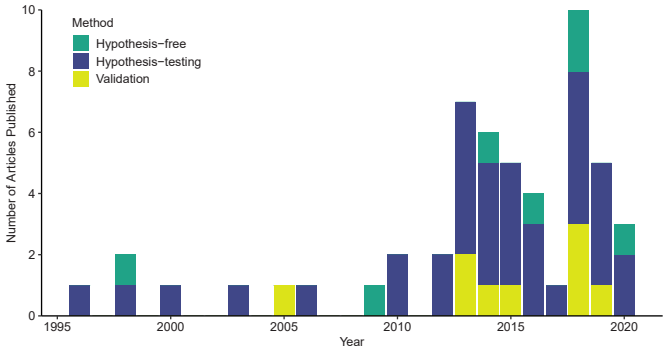

Fig. 3. Published Prescription Sequence Symmetry Analysis Articles by Year*. r*Data extracted through July 31st, 2020. For this figure, studies that investigated the validity of PSSA or correlation of PSSA estimates compared to other study designs were classified as validation studies, regardless of the reporting of original signal detection results.

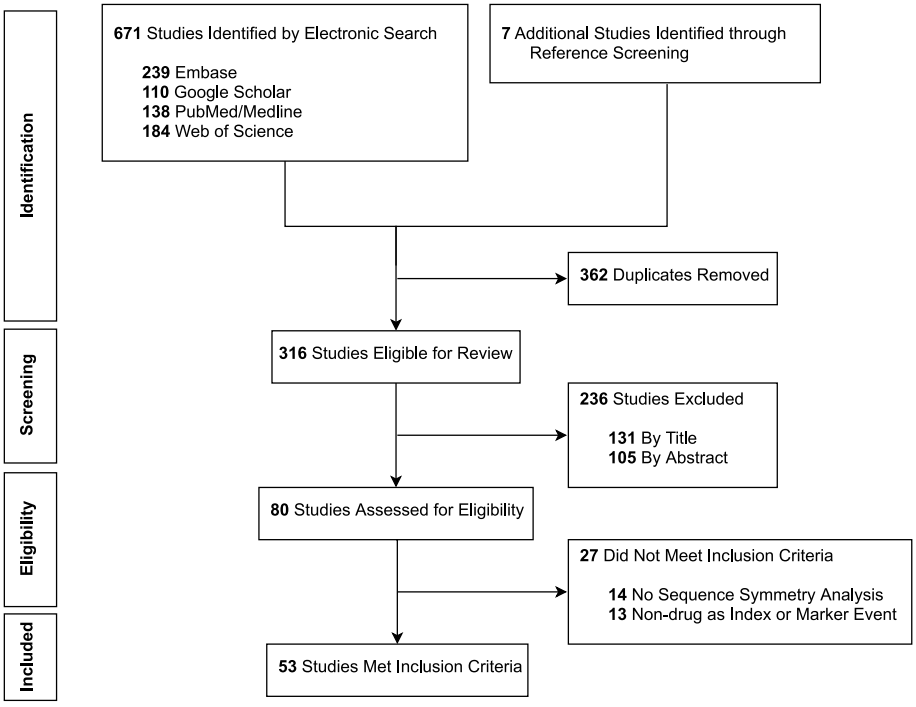

Fig. 2. Flow Diagram of Prescription Sequence Symmetry Analysis Studies included in Scoping Review.

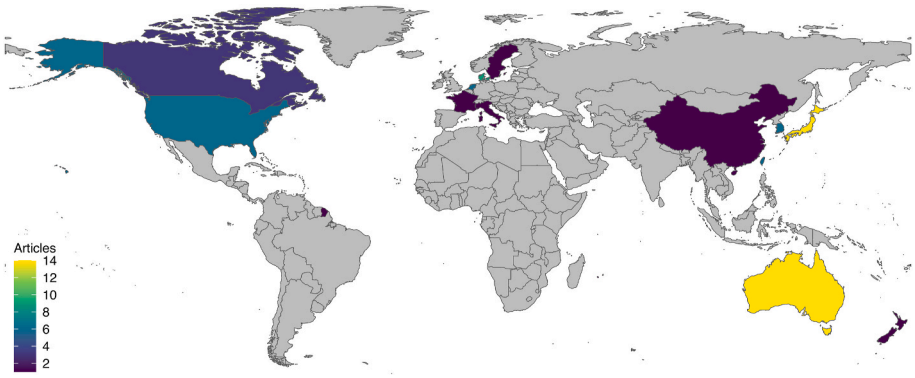

Fig. 4. Number of Published Prescription Sequence Symmetry Analysis Articles by Country* Australia – 14; Japan – 14; Denmark – 9; South Korea – 6; The Netherlands – 6; Taiwan – 6; United States of America – 6; Canada – 3; China – 1; France – 1; Hong Kong – 1; Italy – 1; New Zealand – 1; Sweden – 1. *Countries with no published PSSA articles are colored grey.

3.2. Study design characteristics

Of the 47 included PSSA studies that reported original results for signal evaluation/detection,[1,15–55, 56-60] most evaluated a prespecified hypothesis (85%), while 15% of articles employed a hypothesis-free or screening approach. In terms of identifying index drug use, signals for drug class(es) were reported in 30% of studies, individual drug(s) within a class were reported in 30% of studies, and a combination of class(es) and individual drug(s) within a class were reported in 40% of studies. Marker drug use was more commonly identified by drug class only in 66% or individual drug(s) in 32% of studies, with one study reporting signals for both marker drug class(es) and individual marker drug(s).

The most frequently utilized exposure window in primary analyses to assess use of both index drug and marker drug was 1 year (53%), with studies also using windows > 1 year (26%), 6 months (13%), and <6 months (9%). Washout windows were also frequently used to identify incident index/marker drug users, with a 6-month period (36%) and 1-year period (26%) as the most commonly used washout window. Of note, 21% of studies did not report a washout window for index/marker drug exposure (Table 1).

Controls were employed to confirm results in some PSSA studies. A negative control was used in 21% of studies (n = 10), where an index drug – marker drug dyad was evaluated under the assumption the finding would be null. Conversely, a positive control, where an index drug – marker drug dyad represented a known prescribing cascade and aSR was expected to be significant, was utilized in 13% of studies (Table 1).

A number of PSSA articles used stratified analyses or a logistic regression model to further characterize signals, particularly among studies that were testing a prespecified hypothesis. Of the 47 PSSA studies that aimed to evaluate/detect signals,[1,15–55, 56-60] 55% used stratified analysis to further characterize their results. The most frequently employed stratum was varying exposure window (34%), with windows of 1 year, 6 months, and 3 months between index drug and marker drug initiation commonly used in stratified analyses. Other strata explored included sex (11%), age (11%), concomitant drugs or drug-switching (11%), comorbid diagnosis/es (9%), and country (9%). Five studies (11%) used a logistic regression model to identify predictors of prescribing sequence order, rather than reporting separate aSRs among strata. Predictors that were included in logistic regression models included age, sex, dose, and concomitant drug use (Table 1).

Table 1
Study design characteristics of original prescription sequence symmetry analysis articles (Signal evaluation/detection).

Total	n	%
	47	
Signal Detection Method		
Hypothesis-Testing	40	85%
Hypothesis-Free	7	15%
Index Drug/Class		
Class	14	30%
Individual Drug(s)	14	30%
Combination	19	40%
Marker Drug/Class		
Class	31	66%
Individual Drug(s)	15	32%
Combination	1	2%
Primary Exposure Window		
>1 year	12	26%
1 year	25	53%
6 months	6	13%
<6 months	4	9%
Washout Window for Index/Marker Drug Exposure		
>1 year	6	13%
1 year	12	26%
6 months	17	36%
<6 months	2	4%
Not mentioned	10	21%
Negative Control Utilized		
Yes	10	21%
Positive Control Utilized		
Yes	6	13%
Logistic Regression Utilized		
Yes	5	11%
Stratified Analysis Utilized		
Yes	26	55%
Time		
Exposure Window	16	34%
Time Period	3	6%
Demographics		
Sex	5	11%
Age	5	11%
Ethnicity	1	2%
Medication		
Concomitant Drugs/Drug-Switching	5	11%
Dose	1	2%
Days' Supply	1	2%
Comorbidities		
Diagnosis/es	4	9%
Comorbidity Index	1	2%
Geographical		
Country	4	9%

3.3. Reporting of results

Studies consistently reported crude and adjusted sequence ratios for index drug-marker drug dyads. Fifty-seven percent of studies reported the number of incident index drug users, with 10% of studies reporting

some measure of prescribing cascade incidence or a number needed to harm (NNTH) for entering the given prescribing cascade. Forty percent of studies presented the traditional histogram visualization of marker drug initiation relative to index drug initiation (Table 2).

3.4. Prescribing cascades signals identified

We identified 340 unique prescribing cascade signals published in the PSSA literature, representing 281 unique index drug class–marker drug class dyads (Fig. 5). Signals were most commonly seen for index drugs within the anatomical groups of the nervous system (34%), cardiovascular system (21%), and blood and blood forming organs (15%). For marker drugs, signals were commonly seen for drugs that act on the nervous system (25%), alimentary tract and metabolism (23%), cardiovascular system (17%), and genitourinary system and sex hormones (14%) (Fig. 6). The most commonly reported index drug–marker drug dyads were classified within the anatomical group pairs of nervous system – nervous system (8%), nervous system–alimentary tract and metabolism (7%), cardiovascular system–genitourinary system and sex hormones (6%), and blood and blood forming organs–alimentary tract and metabolism (6%).

3.5. Timeline of PSSA methodological expansions

The proof-of-concept study was published in 1996 and employed a hypothesis-testing approach investigating a cardiovascular medication – antidepressant prescribing cascade.[1] Since the publication of this study there have been several iterations which expanded on this methodology (Fig. 7). The first hypothesis-free PSSA approach screening multiple drug classes for drug-related dyspepsia was employed in 1998 and was also the first article to visualize timing of marker drug initiation relative to index drug initiation.[15] The first widespread hypothesis-free screening of a large dataset for active surveillance of adverse drug events was published in 2018 and attempted to classify signals as known adverse drug reactions, reverse causation, mutual indications, time-dependent confounding, or unknown (e.g. potential unknown adverse drug reaction).[52]

The first study to use a control was published in 2003 and aimed to investigate isotretinoin-induced depression and used minocycline as a negative control index drug.[18] The first study to use a positive control was later published in 2006 and investigated acetylcholinesterase inhibitor-induced complications of chronic airway disorders. This study used beta-blockers (known to cause bronchoconstriction in those with chronic airway disorders) as a positive control to confirm their main PSSA results.[20] In 2013, Lai et al. published a study which aimed to investigate antiepileptic drug-induced hypothyroidism using thyroxine as a proxy. Of note, this study conducted five additional analyses replacing index drug and/or marker drug to confirm results using three negative control dyads (antiepileptic drug – methimazole; rosuvastatin – thyroxine; and rosuvastatin – methimazole) and two positive control dyads (amiodarone – thyroxine; amiodarone – methimazole).[29]

Table 2
Reporting of results by original prescription sequence symmetry analysis articles (Signal evaluation/detection).

Total	n	%
	47	
Number of Incident Index Drug Users Reported		
Yes	27	57%
Measures of Incidence Reported		
Yes	3	6%
Number Needed to Harm (NNTH) Reported		
Yes	2	4%
PSSA Histogram Included		
Yes	19	40%
Mentioned as a Prescribing Cascade		
Yes	5	11%

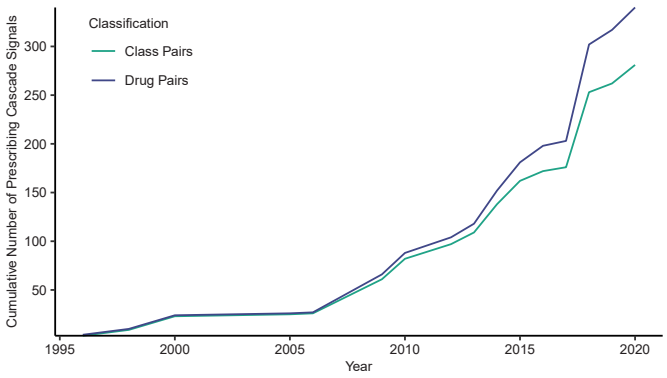

Fig. 5. Cumulative Prescribing Cascade Signals by Year. Cumulative unique prescribing cascade signals for individual drug pairs and pharmacological class pairs are plotted by year. All significant prescribing cascade signals are plotted by year as 1) cumulative count of unique index drug – marker drug (e.g., fifth-level ATC classification) pairs and 2) unique index-marker pharmacological class (e.g., fourth-level ATC classification) pairs.. Abbreviation: ATC, Anatomical Therapeutic Chemical.

PSSA methods to characterize signals in subpopulations and/or to identify predictors of prescribing order mostly include the use logistic regression models or stratified analyses. The proof-of-concept study was the first to use a logistic regression model with the index drug relative to marker drug prescribing order fitted as a dichotomous dependent variable.[1] Stratified analyses were later introduced in 2009 by Tsiropoulos et al. in a hypothesis-free investigation of antiepileptic adverse drug event adverse drug events. This study stratified on exposure window using intervals of 6, 12, and 18 months.[21] Studies later introduced stratified analyses on comorbidities and demographic characteristics to further characterize prescribing cascade signals.[28,39] Notably, a study by Pratt et al., in 2015, which aimed to investigate the consistency of PSSA results across countries, was the first to use the generic inverse variance method to pool aSR estimates from different populations to obtain a single pooled estimate.[14,37]

Other studies have proposed methodological advances aiming to optimize adjustment for underlying for prescribing trends. Notably, early studies utilized the full study exposure window with no limitation in the time interval between index drug and marker drug to calculate crude sequence ratio and null-effect sequence ratio. In 2009, Tsiropoulos et al. proposed an adjustment to the null-effect sequence ratio formula to account for restricted exposure windows.[21] In 2012, Garrison et al. proposed bootstrap resampling methods to adjust crude and null-effect sequence ratios.[24] In 2019, Preiss et al. later developed an alternative method of adjustment for prescribing trends by using normalized smoothing curve fitting to adjust for incident prescriptions in the PSSA visualization.[66]

3.6. Validation of PSSA methods

We identified nine articles which aimed to validate PSSA methodology or provided further context for the validity of the PSSA design and its assumptions. Wahab et al. found the PSSA design to have a sensitivity of 61%, specificity of 93%, positive predictive value of 77%, and negative predictive value of 87% when comparing estimates to gold standard adverse drug events from 120 clinical trials.[61] Others have compared PSSA estimators to estimators from various pharmacoepidemiologic study designs. Corrao et al. found aSRs (e.g., PSSA estimator) to be positively correlated with standardized incidence ratios (e.g., cohort estimator, R = 0.80) and adjusted odds ratios (e.g., nested case-control estimator, R = 0.81).[19] They also saw lower effects from prescription sequence symmetry analysis compared to case-control (a = 0.24) and cohort (a = 0.26) results.[19] Idema et al. later found significant

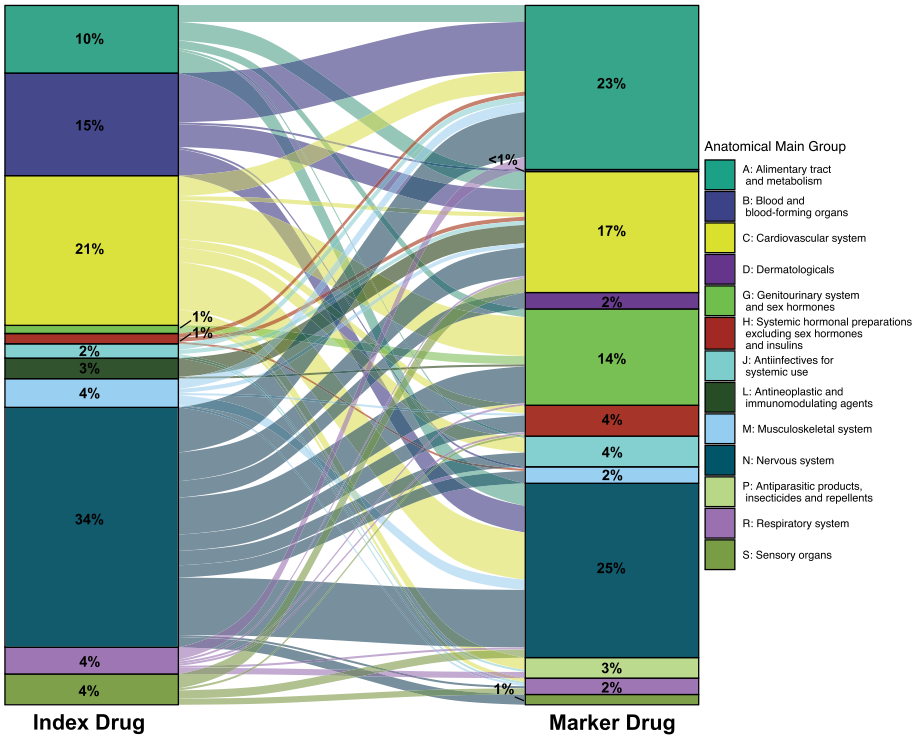

Fig. 6. Index Drug – Marker Drug Combinations, This alluvial graph represents index drug-marker drug combinations stratified by anatomical drug group (e.g., first-level ATC classification) where the width of the linkages between index drug and marker drug group is proportional to the number of unique index drug-marker drug pharmacological class (e.g., fourth-level ATC classification) pairs. Abbreviation: ATC, Anatomical Therapeutic Chemical.

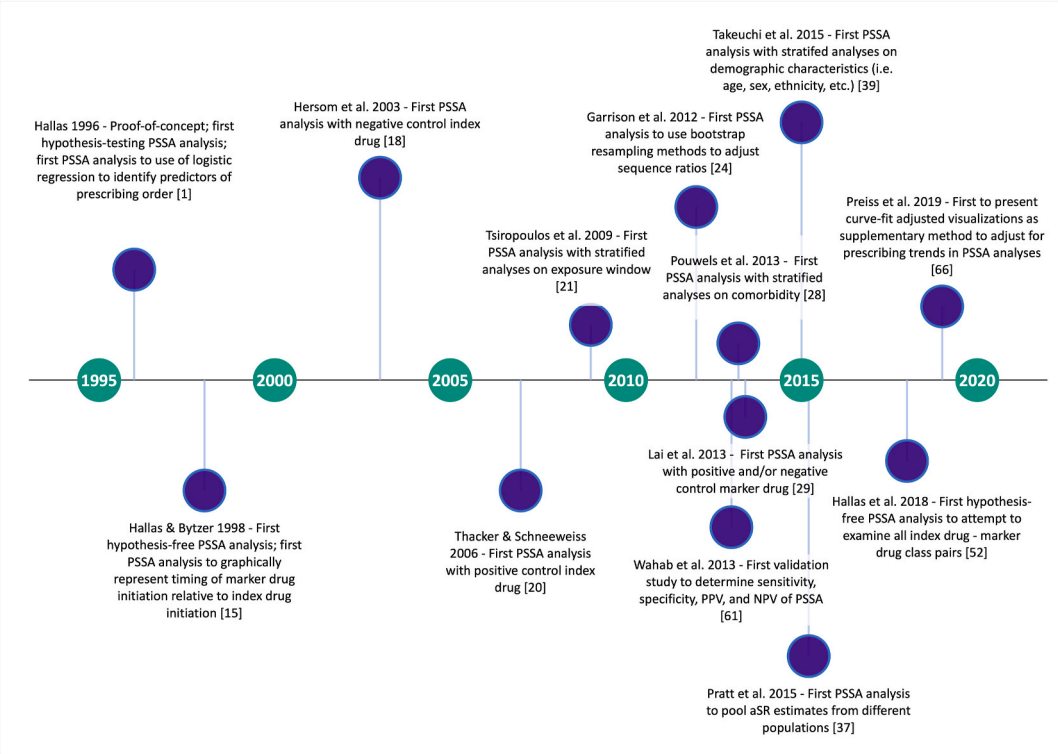

Fig. 7. Timeline of select prescription sequence symmetry analysis methodological advances.

correlation ($p < 0.001$) between PSSA estimates and parallel group designs (cohort and nested case-control designs), but there was considerable dissimilarity between estimates (Bland-Altman plot - 0.20; 70–80% discrepancies).[64] Takeuchi et al. constructed simulated cohorts to compare estimators from three self-controlled methods (self--controlled case series, case-crossover, and PSSA) and found

time-varying confounding produced bias in the self-controlled case series and case-crossover designs. Erroneously long risk periods introduced bias in all three methods, and restriction of follow-up time based on event occurrence produced severe bias in the sequence symmetry analysis estimates.[63] In other words, the PSSA methodology may not be suitable in situations where patients may be censored due to the adverse drug event of interest (i.e., probabilistic censoring).[63] Lastly, Hoang et al. compared PSSA estimates to estimates from newer supervised machine learning (SML) methods and found gradient booster classifier showed 21% higher sensitivity and similar specificity compared to PSSA.[65]

Other validation studies have aimed to investigate different aspects of the PSSA methodology. Pratt et al. found that PSSA produced consistent estimates across separate settings in five countries despite differences in populations and medication utilization patterns.[37] Wahab et al. found both sequence symmetry analysis and disproportionality analysis methods identified adverse drug event signals within one to three years after marketing of the index drug, using rofecoxib-induced myocardial infarction and rosiglitazone-induced heart failure as case studies.[35] Pratt et al. also investigated the validity of PSSA for newly marketed medicines and evaluated the influence of varying uptake trends of index drug using a simulation study.[62] They found that power to detect an association was over 80% in all scenarios except when medicine uptake was gradual and expected effect was weak (aSR = 1.2).[62] The curve-fit method developed by Preiss et al. to adjust for prescribing was shown to have good agreement ($p = 0.999$) with the method used by Tsiropoulos et al.[21,66]

4. Discussion

In this review, we identified a number of PSSA studies which aimed to detect or evaluate prescribing cascades or aimed to investigate the utility of this methodology as a pharmacovigilance tool. Other methods have been used to identify and evaluate prescribing cascades, including cohort studies, cross-sectional studies, and case reports.[67–74] However, the PSSA design has a number of key characteristics that contribute to its utility in detecting and evaluating prescribing cascade signals. Namely, it is relatively simple, has reasonable sensitivity and high specificity, and inherently adjusts for time-invariant confounding.[1,61] Although relatively few PSSA studies explicitly classified their results as prescribing cascade signals, the authors argue that significant positive associations for index drug-marker drug pairs presented in PSSA analyses are often driven by prescribing cascades, particularly in instances where prescription data only is utilized. Importantly, this review required the proxies for exposure and outcome to be medications and/or medication classes and more formally investigate potential prescribing cascades by requiring individuals to be users of both medications of interest. However, it should also be noted that significant signals obtained from PSSA analyses alone cannot establish causality, often require further review from clinical experts, and should ideally be validated using additional study designs and data sources.

We identified over 300 unique prescribing cascade signals in this review. Prescribing cascade signals most commonly arose from index drugs acting on the nervous system, cardiovascular system, or alimentary tract. Marker drugs (and therefore, hypothesized adverse drug events) were mostly commonly related to the nervous system, alimentary tract and metabolism, cardiovascular system, and genitourinary system and sex hormones. Signals representing the anatomical group pairs of nervous system – nervous system, nervous system–alimentary tract and metabolism, cardiovascular system–genitourinary system and sex hormones, and blood and blood forming organs–alimentary tract and metabolism were most common. Although the PSSA methodology was originally intended as a signal detection tool to aid in pharmacovigilance studies, many of the published studies aimed to test specific hypotheses, rather than screen for signals. Therefore, the relative frequency of identified prescribing cascade signals and associated medication class pairs should be interpreted with caution. However, a recent study aiming to predict the frequencies of unknown adverse drug events also found a high frequency of neurologic and psychiatric side effects related to nervous system medications.[75] A recent commentary highlighted the need for more research related to prescribing cascades where cardiovascular medications constitute the index or marker drug.[76] These findings may indicate that medications acting on the nervous system or cardiovascular system are important areas of future prescribing cascade research.

4.1. Methodological considerations and recommendations

In terms of PSSA methodology and reporting, we offer some considerations and recommendations for good practices below based on our review of the current literature.

4.2. Identifying new use of index and marker drugs

When identifying new use of index drug and marker drug, consider including only new users of a particular medication class. If necessary, subgroup analyses for each individual medication within the group of new users of a medication class can be performed. Identification of index drug and marker drug new users may inappropriately include individuals who switched from a medication within the same class when steps are not taken to account for drug switching. This can inadvertently bias the null effect sequence ratio and adjusted sequence ratio by falsely estimating the background prescribing rate of associated medications.[12,77]

4.3. Choice of exposure time window

For PSSA analyses testing a prespecified hypothesis, the choice of primary exposure time window should be informed by the hypothesized time to adverse drug event. For screening studies using PSSA, a one-year window has been most frequently utilized and shown to have good sensitivity.[35] Therefore, PSSA is particularly useful when evaluating prescribing cascades caused by an adverse drug event with a relatively short latency period. Additionally, PSSA is sensitive to within-person time-varying confounders (e.g., disease progression, temporal trends, aging, treatment attrition of the index drug, etc.), all of which become more prominent with longer windows.[1,61] As such, the authors suggest it may be prudent to avoid exposure time windows longer than one year in most situations. Approximately one-third of PSSA studies evaluated multiple exposure windows with one-year, six-month, and three-month windows commonly utilized. Including multiple shorter exposure windows in a PSSA analysis may help reduce within-person time-varying confounding and can provide further context regarding the time to manifestation of hypothesized adverse drug events.[21] However, one should be mindful that this will decrease sample size and precision of estimates when restricting exposure windows.

4.4. Stratified analyses and logistic regression to identify effect modifiers of potential prescribing cascades

In instances where effect modification is suspected, including stratified analyses on key demographic or clinical characteristics of interest (e.g., age, sex, comorbidities, starting dose of index drug, etc.) or constructing a multivariate logistic regression model with prescribing order modeled as a dichotomous dependent variable may aid in identifying effect modifiers of the prescribing cascade of interest.[1,21,28,39] While both methods provide insight into effect modification of PSSA signals, their respective interpretations are slightly different and should be noted. For subgroup analyses on demographic and clinical strata, effect modification is investigated by comparing sequence ratios among stratum levels.[78] In the multivariate logistic regression model, adjusted odds ratios for index drug before marker drug prescribing order among

multiple predictors are simultaneously estimated. Effect modification can be seen when an odds ratio and corresponding CI limit is above or below 1.[1,49] It should be noted that significant effect modifiers identified using these methods within the context of predicting PSSA sequence order should be further explored as any associations that are seen but may be due to differences in disease progression and other time-varying confounders.

4.5. Use of negative and positive controls

When designing a PSSA analysis, incorporating negative control (e.g., absence of a prescribing cascade is well established) and/or positive control (e.g., presence of a prescribing cascade is well established) prescribing cascade dyads in separate analyses may help assess for potential for biases. In studies testing a specific hypothesis, controls should ideally be chosen by identifying index drug – marker drug dyads where 1) the index drug replacement is used in a similar population with mutual indications and similar healthcare follow-up patterns as the study index drug or 2) the marker drug replacement treats a condition/adverse drug event that would likely warrant similar healthcare follow-up patterns to the condition/adverse drug event of interest.[24,79] More specifically, active comparators, in which an index drug comparator is used for a similar indication as the study index drug, should be considered in analyses where the indication is also a risk factor for the outcome of interest, particularly for short-term exposures which are more likely to be time-dependent.[80] Therefore, negative controls may prove to be useful in identifying instances of time-varying bias, protopathic bias, and confounding by indication.[12,29,50]

4.6. Estimating the risk of prescribing cascades

Finally, we recommend reporting the total number of incident users of the index drug in the study exposure window. By reporting the total number index drug new users, measures of the relative incidence of the prescribing cascade can be estimated. The excess risk of prescribing cascade (index drug before marker drug) among those exposed to index drug can be estimated by comparing the excess number of individuals prescribed index drug before marker drug to the total number of index drug new users during the study period.[1,81,82]

$$\textit{Excess risk among exposed} = \frac{n_{index \rightarrow marker} - n_{marker \rightarrow index}}{n_{index}}$$

$$\textit{Excess risk among exposed}_{adjusted} = \frac{n_{index \rightarrow marker} \cdot \frac{(aSR-1)}{aSR}}{n_{index}}$$

Here, $n_{index- > marker}$ is the number of individuals who were prescribed the index drug prior to the marker drug during the study period, $n_{marker- > index}$ is the number of individuals who were prescribed the marker drug prior to the index drug during the study period, and n_{index} is the number of incident users of the index drug during the study period.[1,22,27,81,82] Of note, this formula simply provides an unadjusted estimate of the proportion of individuals who initiated the index drug who presumably entered into a subsequent prescribing cascade; it does not give an estimate of the proportion of individuals with the index adverse drug event who entered into a prescribing cascade. To estimate the frequency of entering a prescribing cascade given an individual developed the adverse drug event, one must divide the incidence above by the assumed proportion of individuals treated with index drug who develop the adverse drug event.[22] Of note, the latter estimate is inversely related to the prevalence of the index adverse drug event.[22]

Additionally, a 'naturalistic' number needed to harm until time *t* ($NNTH_t$) can be calculated which approximates the exposure needed for one additional individual to be harmed.[83,84] In other words, this is the number of index drug initiators needed to treat for one additional individual to initiate the marker drug.[38,49] Notably, $NNTH_t$ is the reciprocal of the excess risk of prescribing cascade (index drug before marker drug) among those exposed to index drug.[83]

$$NNTH_t = \frac{n_{index}}{n_{index \rightarrow marker} \cdot \frac{(aSR-1)}{aSR}}$$

Both measures may be useful in estimating the magnitude of entering a prescribing cascade given incident use of index drug.

4.7. Gaps in the literature

While the PSSA methodology is a useful tool in detecting prescribing cascades, generated signals require significant clinical review due to the potential for false positive and false negative findings. As such, there is a significant amount of systematic and random noise when evaluating signals, particularly when screening for prescribing cascades without prespecified hypotheses. To account for this multiple testing problem, studies have calculated 99% CIs to reduce the number of signals generated by chance.[12,25,29] However, this approach also decreases the likelihood of identifying true signals.[85] Machine learning methods have also been introduced to complement PSSA methods and decrease noise.[65] Additional research is needed to improve the efficiency of PSSA to detect and classify clinically relevant signals.

Our included studies also utilized data throughout Asia, Europe, Australia, and North America to identify prescribing cascades. A few studies have used data from multiple countries to test a single hypothesis, and methods have been developed to obtain pooled estimates and test for heterogeneity across countries.[30,37,40] However, additional research is needed to better understand how regional prescribing practices, ethnic differences in genetic polymorphisms, and environmental and behavioral factors affect heterogeneity of PSSA measures.

Lastly, the current literature has focused on prescribing cascades precipitated by a single index drug. However, little is known about how drug-drug interactions may affect the risk of entering a prescribing cascade, both within the context of PSSA studies as well as other study designs. More research is needed to understand how potential drug-drug interactions may affect the risk of entering a prescribing cascade and any potential utility of the PSSA methodology to explore these differences.

4.8. Strengths and limitations

This review has several notable strengths. We aimed to build on the work of two other reviews that presented the most current PSSA studies at that time and discussed the advantages and pitfalls of this methodology in practice.[11,12] However, this is the first review to our knowledge to comprehensively assess key aspects of the PSSA methodology as well as reporting of results among published studies. We also quantified potential prescribing cascade signals identified through PSSA analyses and categorized signals based on organ system targets. Furthermore, the evidence from this scoping review evaluated the changes and advances of PSSA methodology over time as it has evolved from its inception in 1996 and offered further context regarding the validation of PSSA methods and its key assumptions.

There are also several limitations. First, the search strategy used in this review may have failed to capture the full volume of published literature related to signal detection, signal evaluation, and method validation using PSSA methods. However, we included the four largest repositories of published biomedical literature (PubMed, Embase, Web of Science, Google Scholar) in our search and also cross-referenced relevant articles to identify relevant literature.[86] Furthermore, we consulted a health sciences librarian with extensive expertise in database searching techniques of scientific literature to help develop the search string for this review and believe there is likely negligible selection bias of relevant literature. Second, there is a possibility that some misclassification could have occurred in the data extraction/synthesis of relevant information from included studies. However, data was independently extracted by two reviewers, disagreements were resolved via consensus, and additional checks were employed in an attempt to

ensure consistency and accuracy. Third, we did not attempt to grade the quality of included studies as the aim of this review was more focused on scoping the body of PSSA literature, describing methodological and reporting considerations, and evaluating the evolution of PSSA methodology throughout clinical literature. Fourth, we did not include findings presented in conference abstracts as we could not fully evaluate the necessary methodological and reporting components of these PSSA studies. However, we realize that null findings may never be published in manuscript form. Therefore, we recognize that publication bias may have led to an underestimation of the full breadth of prescribing cascades identified through PSSA analyses. Additionally, the PSSA methodology has been primarily applied to administrative databases of prescription medications, thus limiting the utility of PSSA methods to identify prescribing cascade signals for over-the-counter medications. However, as we aimed to quantify significant index drug – marker drug dyads identified by PSSA methodology, we hope that any underestimation of prescribing cascade signals due to publication bias was minimal.

5. Conclusion

The PSSA methodology has been used as a pharmacovigilance tool to screen for potential prescribing cascades using prescription data. Since its development, over 300 prescribing cascade signals have been detected and/or evaluated. Nevertheless, key considerations should be taken into account when designing a study using the PSSA design with particular attention on sensitivity analyses to evaluate time-varying biases. Furthermore, high-quality reporting of PSSA results is important to provide clinical context for the risk of a given prescribing cascade.

CRediT author statement

Earl J. Morris: Conceptualization, Investigation, Formal Analysis, Writing – Original Draft, Review & Editing, Visualization; Josef Hollmann: Conceptualization, Investigation, Writing – Review & Editing; Ann-Kathrin Hofer: Investigation, Writing – Review & Editing; Hemita Bhagwandass: Investigation, Writing – Review & Editing; Razanne Oueini: Investigation, Writing – Review & Editing; Lauren E. Adkins: Data Curation; Jesper Hallas: Conceptualization, Writing – Review & Editing; Scott M. Vouri: Conceptualization, Writing – Review & Editing.

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Appendix A. PSSA Equations

1) Crude Sequence Ratio (cSR)

$$cSR = \frac{n_{index \rightarrow marker}}{n_{marker \rightarrow index}}$$

where:

$n_{index \rightarrow marker}$ = number of individuals prescribed index drug before marker drug, and
$n_{marker \rightarrow indexr}$ = number of individuals prescribed marker drug before index drug.

2) Overall Average Probability of Marker Drug Prescribed after Index Drug, Given Background Prescribing Trends (P_a)

$$P_a = \frac{\sum_{m=1}^{u}\left[I_m \times \left(\sum_{n=m+1}^{m+d} M_n\right)\right]}{\sum_{m=1}^{u}\left[I_m \times \left(\sum_{n=m-d}^{m-1} M_n + \sum_{n=m+1}^{m+d} M_n\right)\right]}$$

where:

m = a given day within the study period (exposure window).
u = last day of study period.
I_m = number of incident users of index drug on a given day
d = specified number of days within the study period (exposure window).
n = consecutive days of the study period (exposure window).
M_n = number of individuals receiving first marker drug on a given day.

3) Null-effect Sequence Ratio (neSR)

$$neSR = \frac{P_a}{(1 - P_a)}$$

where:

P_a = overall average probability of marker drug prescribed after index drug, given background prescribing trends (calculated above).

4) Adjusted Sequence Ratio (aSR)

$$aSR = \frac{cSR}{neSR}$$

where:

cSR = crude sequence ratio (calculated above).

nesR = null-effect sequence ratio (calculated above).

Appendix B. Search String

PubMed/Medline Search Query	Filters	Results
"prescribing cascade"[tiab] OR (prescribing[tiab] AND cascade[tiab]) OR "medication cascade"[tiab] OR "drug cascade"[tiab] OR "prescription cascade"[tiab] OR "prescription sequence symmetry analysis"[tiab] OR "sequence symmetry analysis"[tiab]	Publication Year: 1990–2020	138
Embase Search Query	Filters	Results
('prescribing cascade':ab,ti OR (prescribing:ab,ti AND cascade:ab,ti) OR 'medication cascade':ab,ti OR 'drug cascade':ab,ti OR 'prescription cascade':ab,ti OR 'prescription sequence symmetry analysis':ab,ti OR 'sequence symmetry analysis':ab,ti)	Publication Year: 1990–2020	239
Web of Science Search Query	Filters	Results
Topic: "prescribing cascade" OR "medication cascade" OR "drug cascade" OR "prescription cascade" OR "prescription sequence symmetry analysis" OR "sequence symmetry analysis"	Publication Year: 1990–2020	184
Google Scholar Search Query	Filters	Results
allintitle: "prescribing cascade" OR "medication cascade" OR "drug cascade" OR "prescription cascade" OR "prescription sequence symmetry analysis" OR "sequence symmetry analysis"	Publication Year: 1990–2020	110

Appendix C. Characteristics of Included PSSA Studies Reporting Original Prescribing Cascade Results I

First Author	Year	Date Range	Country	Signal Detection Method	Index Drug/Class	Marker Drug/Class
Hallas [1]	1996	8/1990–12/1993	Denmark	Hypothesis-testing	Cardiovascular medications	Antidepressants
Hallas [15]	1998	10/1990–1/1995	Denmark	Hypothesis-free	Various medications *Calcium channel blockers, angiotensin-converting enzyme inhibitors, corticosteroids, non-steroidal anti-inflammatory drugs	Proton pump inhibitors, histamine$_2$ receptor blockers, bismuth preparations, and sucralfate
Lindberg [16]	1998	1991–1995	Denmark	Hypothesis-testing	Cholesterol-lowering medications	Antidepressants
Bytzer [17]	2000	10/1990–1/1995	Denmark	Hypothesis-testing	Various medications *Insulin, potassium, digoxin, nitrates, loop diuretics, angiotensin-converting enzyme inhibitors, corticosteroids, antibiotics, non-steroidal anti-inflammatory drugs, opioid analgesics, asthma drugs, methylxanthines	Cisapride, metoclopramide
Hersom [18]	2003	6/1999–3/2000	USA	Hypothesis-testing	Isotretinoin	Antidepressants
Corrao [19]	2005	1997–1999	Italy	Hypothesis-testing	Various antibacterials	Antiarrhythmic drugs
Thacker [20]	2006	1/1997–11/2002	USA	Hypothesis-testing	Acetylcholinesterase inhibitors	Antibacterial + oral corticosteroid
Tsiropoulos [21]	2009	4/1990–12/2006 (for PSSA)	Denmark	Hypothesis-free	Antiepileptic medications	Various medications *Propulsives, laxatives, intestinal antiinfectives, potassium, diuretics, antifungals, chemotherapeutics, corticosteroids, anti-acne medications, pituitary hormones, antibiotics, non-steroidal and anti-rheumatic medications, bone disease medications, opioids, dopaminergic medications, anxiolytics, addiction medications, expectorants, antiinfectives, decongestants and antiallergics
First Author	Year	Date Range	Country	Signal Detection Method	Index Drug/Class	Marker Drug/Class
Vegter [22]	2010	2000–2006	The Netherlands	Hypothesis-testing	Angiotensin-converting enzyme inhibitors	Antitussive agents
Caughey [23]	2010	2003–2006	Australia	Hypothesis-testing	Various medications *Cardiac vasodilators, diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, non-steroidal anti-inflammatory drugs, opioids, antiepileptics, sedatives	Prochlorperazine
Garrison [24]	2012	12/2001–11/2006	Canada	Hypothesis-testing	Long-acting beta2-agonists, diuretics, statins	Quinine
Roughead [25]	2012	2002–2008 (for PSSA)	Australia		Glaucoma eye drops	

(continued on next page)

(*continued*)

First Author	Year	Date Range	Country	Signal Detection Method	Index Drug/Class	Marker Drug/Class
				Hypothesis-testing		Inhaled beta-agonists, inhaled corticosteroids, oral corticosteroids; antidepressants, selective serotonin reuptake inhibitors
van Boven [26]	2013	1994–2011	The Netherlands	Hypothesis-testing	Inhaled corticosteroids	Nystatin, miconazole, methylrosaniline and amphotericin B
Vegter [27]	2013	2000–2011	The Netherlands	Hypothesis-testing	Angiotensin-converting enzyme inhibitors	Antitussives
Pouwels [28]	2013	2006–2011	The Netherlands	Hypothesis-testing	Angiotensin-converting enzyme inhibitors	Nitrofurantoin
Lai [29]	2013	2004–2010	Taiwan	Hypothesis-testing	Antiepileptic medications	Thyroxine
Pratt [30]	2013	1999–2010	USA, Australia, Japan, Taiwan, Sweden, Korea	Hypothesis-testing	Antipsychotics	Insulin
Hachiken [31]	2013	2001–2010	Japan	Hypothesis-testing	Low-dose aspirin	Proton pump inhibitors, histamine2 receptor blockers
First Author	Year	Date Range	Country	Signal Detection Method	Index Drug/Class	Marker Drug/Class
Fujimoto [32]	2014	2005–2011	Japan	Hypothesis-testing	Statins	Mediations for storage lower urinary tract symptoms
Kalisch Ellett [33]	2014	2001–2011	Australia	Hypothesis-testing	Various medications *Prazosin, low-ceiling diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-converting enzyme inhibitors/diuretic combination, estrogens, sedative hypnotics	Oxybutynin
Takada [34]	2014	1/2006–8/2013	Japan (for PSSA)	Hypothesis-testing	Statins	Hypnotic medications
Wahab [35]	2014	2001 - 12/2007 (for PSSA)	Australia	Hypothesis-testing	Rosiglitazone, rofecoxib	Furosemide
Lai [36]	2014	2003–2010	Taiwan	Hypothesis-free	Antipsychotics	Various medications *Stomatological medications, oral corticosteroids, antiarrhythmics, beta-blockers, prolactin inhibitors, quinolones, topical non-steroidal anti-inflammatory drugs, anticholinergic medications
Pratt [37]	2015	1999–2012	USA, Australia, Japan, Taiwan, Korea	Hypothesis-testing	Amiodarone	Thyroxine
Rasmussen [38]	2015	2002–2012	Denmark	Hypothesis-testing	Cardiovascular medications	5-phosphodiesterase inhibitors
Takeuchi [39]	2015	2005 - 12/2013	Japan	Hypothesis-testing	Atypical antipsychotics	Antihyperlipidemic medications
Roughead [40]	2015	1999–2012	Australia, Hong Kong, Japan, Korea, Taiwan, Canada	Hypothesis-testing	Pioglitazone, rosiglitazone, metformin	Furosemide
First Author	Year	Date Range	Country	Signal Detection Method	Index Drug/Class	Marker Drug/Class
Hashimoto [41]	2015	4/2011–3/2012	Japan	Hypothesis-testing	Various medications *Cimetidine, scopolamine, cibenzoline, amezinium metisulfate, cyclophosphamide, morphine, oxycodone, codeine, biperiden, levodopa/bensarazide, amantadine, chlorpromazine, levomepromazine, sulpiride, risperidone, diazepam, paroxetine, fluvoxamine, milnacipran, donepezil, tiotropium	Mediations for lower urinary tract symptoms
Takada [42]	2016	1/2006–5/2014	Japan	Hypothesis-testing	Benzodiazepines	Anti-dementia medications
Pouwels [43]	2016	1999 - 12/2012	Netherlands	Hypothesis-testing	Statins	Antibiotics
Roughead [44]	2016	2001–2013 (Australia); 2009–2013 (Korea); 2001–2012 (Canada); 2008–2012 (Hong Kong); 1996–2014 (Japan)	Australia, Korea, Canada, Taiwan, Japan	Hypothesis-testing	Proton pump inhibitors	Oral vancomycin, metronidazole

(*continued on next page*)

(*continued*)

First Author	Year	Date Range	Country	Signal Detection Method	Index Drug/Class	Marker Drug/Class
Wahab [45]	2016	2002–2011	Australia	Hypothesis-free	Various medications *Ranitidine, famotidine, teriparatide, paracetamol, betahistine, pilocarpine, brinzolamide, latanoprost, lodoxamide	Furosemide
Nisthala [46]	2017	2005–2014	New Zealand	Hypothesis-testing	Amiodarone, lithium, simvastatin, fluticasone, furosemide	Thyroxine/carbimazole (amiodarone), thyroxine (lithium), quinine (simvastatin), nystatin (fluticasone), potassium chloride (furosemide)
First Author	Year	Date Range	Country	Signal Detection Method	Index Drug/Class	Marker Drug/Class
Maura [48]	2018	2013–2015	France	Hypothesis-testing	Direct oral anticoagulants, warfarin	Gastrointestinal medications
Hellfritzsch [49]	2018	4/2011–12/2015	Denmark	Hypothesis-free	Direct oral anticoagulants	Various medications *Proton pump inhibitors, propulsives, laxatives, potassium, iron, digitalis glycosides, antiarrhythmics, loop diuretics, aldosterone, antagonists, topical corticosteroids, non-dihydropyridine calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, opioids, benzodiazepines, selective serotonin reuptake inhibitors
Park [50]	2018	2002–2013	South Korea	Hypothesis-testing	Proton pump inhibitors, histamine2 receptor antagonists	Anti-dementia medications
Park [51]	2018	2002–2013	South Korea	Hypothesis-testing	Benzodiazepines	Anti-dementia medications
Hallas [52]	2018	1995–2012	Denmark	Hypothesis-free	Various medications *All medications classes according to third-level Anatomical Therapeutic Chemical code	Various medications *All medications classes according to third-level Anatomical Therapeutic Chemical code
Sterndorff Winkel [53]	2018	2000–2016	Denmark	Hypothesis-testing	Montelukast	Antidepressants
Adimadhyam [54]	2019	4/2013–12/2015	USA	Hypothesis-testing	Sodium–glucose co-transporter 2 inhibitors	Antifungals
Zhang [55]	2019	1/2017–12/2017	China	Hypothesis-testing	Atorvastatin	Hepatoprotective medications
Ko [56]	2019	7/2001–12/2011	Australia	Hypothesis-testing	Statins	Antistaphylococcal antibiotics
Vouri [57]	2019	2005–2017	USA	Hypothesis-testing	Dihydropyridine calcium channel blockers	Loop diuretics
Yokoyama [58]	2020	2005–2017	Japan	Hypothesis-testing	Antipsychotics	Bisphosphonates
First Author	Year	Date Range	Country	Signal Detection Method	Index Drug/Class	Marker Drug/Class
Yokoyama [59]	2020	2005–2017	Japan	Hypothesis-testing	Anticoagulants	Bisphosphonates
King [60]	2020	2012–2016	Australia	Hypothesis-free	Various medications *Ranitidine, granisetron, fosaprepitant, mesalazine, temozolomide, folinic acid, pemetrexed, fluorouracil, vinblastine, vincristine, bleomycin, pembrolizumab, degarelix, botulinum toxin A, denosumab, sumatriptan, rizatriptan, pizotifen, levetiracetam, benhexol, fluorometholone, brimonidine, brinzolamide, latanoprost, travaprost	Furosemide
Hirano [47]	2020	4/2011–3/2016	Japan	Hypothesis-testing	Anxiolytics, hypnotics, antidepressants, antipsychotics	Antiparkinsonian medications

* Lists drugs/classes associated with significant signals in studies where many various drugs/classes were analyzed.

Appendix D. Characteristics of Included PSSA Studies Reporting Original Prescribing Cascade Results II

First Author	Year	Logistic Regression for Predictors	Stratified Analysis	Negative Control	Positive Control	Number of Incident Index Drug Users Reported	Incidence Reported	NNTH Reported	PSSA Graphics	Mentioned as Prescribing Cascade

(*continued on next page*)

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First Author	Year	Logistic Regression for Predictors	Stratified Analysis	Negative Control	Positive Control	Number of Incident Index Drug Users Reported	Incidence Reported	NNTH Reported	PSSA Graphics	Mentioned as Prescribing Cascade
Hallas [1]	1996	✓				✓	✓			
Hallas [15]	1998	✓				✓			✓	
Lindberg [16]	1998					✓				
Bytzer [17]	2000					✓				
Hersom [18]	2003			✓		✓			✓	
Corrao [19]	2005									
Thacker [20]	2006				✓	✓				
Tsiropoulos [21]	2009					✓				
Vegter [22]	2010	✓				✓			✓	
Caughey [23]	2010									✓
Garrison [24]	2012			✓					✓	✓
Roughead [25]	2012					✓				
van Boven [26]	2013	✓	✓			✓			✓	
Vegter [27]	2013		✓			✓	✓		✓	✓
Pouwels [28]	2013		✓	✓		✓			✓	
Lai [29]	2013		✓	✓	✓	✓			✓	
Pratt [30]	2013		✓						✓	
Hachiken [31]	2013		✓			✓				
Fujimoto [32]	2014		✓			✓				
Kalisch Ellett [33]	2014					✓				✓
Takada [34]	2014					✓				
Wahab [35]	2014		✓							
Lai [36]	2014					✓				
Pratt [37]	2015		✓	✓	✓				✓	
Rasmussen [38]	2015		✓			✓		✓		
Takeuchi [39]	2015		✓						✓	
Roughead [40]	2015		✓	✓						
Hashimoto [41]	2015		✓			✓				
Takada [42]	2016		✓			✓				
Pouwels [43]	2016									
Roughead [44]	2016		✓						✓	
Wahab [45]	2016									
Nisthala [46]	2017			✓	✓				✓	
Maura [48]	2018		✓	✓	✓	✓				
Hellfritzsch [49]	2018	✓				✓		✓		
Park [50]	2018		✓	✓					✓	
Park [51]	2018		✓		✓				✓	
Hallas [52]	2018									
Sterndorff Winkel [53]	2018		✓						✓	
Adimadhyam [54]	2019		✓						✓	
Zhang [55]	2019		✓						✓	
Ko [56]	2019		✓							
Vouri [57]	2019		✓	✓		✓	✓		✓	✓
Yokoyama [58]	2020		✓			✓				
Yokoyama [59]	2020		✓			✓				
King [60]	2020									
Hirano [47]	2020		✓			✓				

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