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PHARMACO-EPIDEMIOLOGY

Sequence symmetry analysis in pharmacovigilance and pharmacoepidemiologic studies

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Abstract Sequence symmetry analysis (SSA) is a method for detecting adverse drug events by utilizing computerized claims data. The method has been increasingly used to investigate safety concerns of medications and as a pharmacovigilance tool to identify unsuspected side effects. Validation studies have indicated that SSA has moderate sensitivity and high specificity and has robust performance. In this review we present the conceptual framework of SSA and discuss advantages and potential pitfalls of the method in practice. SSA is based on analyzing the sequences of medications; if one medication (drug B) is more often initiated after another medication (drug A) than before, it may be an indication of an adverse effect of drug A. The main advantage of the method is that it requires a minimal dataset and is computationally efficient. By design, SSA controls time-constant confounders. However, the validity of SSA may be affected by time-varying confounders, as well as by time trends in the occurrence of exposure or outcome events. Trend effects may be adjusted by modeling the expected sequence ratio in the absence of a true association. There is a potential for false positive or negative results and careful consideration should be given to potential sources of bias when interpreting the results of SSA studies.

Keywords Sequence symmetry analysis · Self-control method · Case-based design · Signal detection · Pharmacoepidemiology · Pharmacovigilance

Introduction

While clinical trials usually have sufficient sample size to demonstrate efficacy, few are powered to detect rare adverse events or adverse events that occur after long term exposure. As a result, pharmacovigilance and pharmacoepidemiologic studies using spontaneous reporting (SR) adverse drug reaction (ADR) databases, electronic health records, or medical encounter claims data are critical to

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monitor the safety of newly marketed medications [1, 2]. The rapid growth in computing power and the development of large administrative datasets provide an opportunity for researchers and regulatory agencies to conduct active post-marketing surveillance of medications.

Petri et al. [3] introduced 'prescription sequence analysis' as a new and fast cohort crossover approach for detection of safety issues associated with use of medications in 1988. Thereafter, a more general term, sequence symmetry analysis (SSA), was proposed by Hallas and used to identify whether there was an association between the initiation of cardiovascular medications and the onset of depression in 1996 [4]. The method was first used to identify whether there was an association between the initiation of cardiovascular medications and the onset of depression. Since its initial application, the use of SSA has been increasing, both as a method of studying specific side effects of medication use and as a data mining tool to detect unknown and unsuspected safety issues [5–7]. A validation study of the method indicated that SSA has moderate sensitivity and high specificity in detecting heart failure as an adverse event [8]; however the new signals identified by the paper have yet to be confirmed. SSA has also been found to have robust performance when the same association is analyzed across several different databases [9, 10]. Additionally, SSA may result in more rapid detection of safety issues as it requires only a minimal dataset and is computationally efficient [9, 10]. More recently SSA has been applied as a signal generation tool and has the potential to provide a complementary approach to adverse event detection alongside routine PV using spontaneous reports [8].

A common limitation in observational studies is the potential for confounding [2]. The advantage of SSA is that it is robust to confounders that are stable over time, e.g., gender, and genetic factors [4, 11, 12]. In this review article, we explain the theoretical and conceptual framework of SSA and discuss the strengths and advantages of SSA based on currently available literature. We also highlight the challenges and pitfalls in applying SSA. Finally, we summarize the application of SSA in practice.

Theoretical and conceptual framework of sequence symmetry analysis

Sequence symmetry analysis is based on examining the sequence of events in relation to initiating a medication [4]. If a medication (referred to as an index medication) is suspected of causing an adverse event, it may be more often followed by the initiation of a medication commonly used to counteract or treat the adverse event (referred to as an outcome medication). For example, if a particular medication is associated with diarrhea we would notice more people initiating anti-diarrheal medication after initiating the index medication than before the index medication. Initially, Hallas [4] described the method to include all sequences of events irrespective of their proximity, however, Tsiropolous [7] published a variation to the method in which a limit was placed on the time window between events.

The statistic of interest in SSA is the sequence ratio (SR), which is a measure of asymmetry of sequences. The SR is calculated by dividing the number of people for whom the outcome medication was initiated after the index medication with the number of people for whom the outcome medication was initiated before the index medication. As such, the SR could also be regarded as an estimate of the incidence rate ratio of the outcome in the exposed period versus that of the non-exposed period [4, 6].

$$\text{Sequence ratio} = \frac{\text{Number of people using index medication} \rightarrow \text{outcome medication}}{\text{Number of people using outcome medication} \rightarrow \text{index medication}}$$

In the absence of an association, one would expect a symmetrical pattern in the distribution of initiation of the outcome medication before and after the initiation of the index medication.

To illustrate the calculation of the sequence ratio, consider the scenario of medication induced hypothyroidism. Amiodarone, an anti-arrhythmic drug, is known to induce hypothyroidism. Therefore we would expect a higher chance of a person receiving thyroid hormone supplement, in the form of thyroxin, after initiating amiodarone [13, 14] (Fig. 1a). In the absence of an association, we would expect the pattern to be symmetrical as represented by the volume of patients in blue in Fig. 1b. The relative excess volume of patients in red (Fig. 1b) may be due to the side effect which is calculated by the SR (Fig. 1a).

SSA requires the identification of new users of both the index and outcome medications. An efficient graphical approach to the identification of incident users is the waiting time distribution method, also proposed by Hallas [4, 15]. The waiting time distribution method graphs a group of medication users by the time of their first prescription within a specified time window. Those patients who have their first prescription at the beginning of the

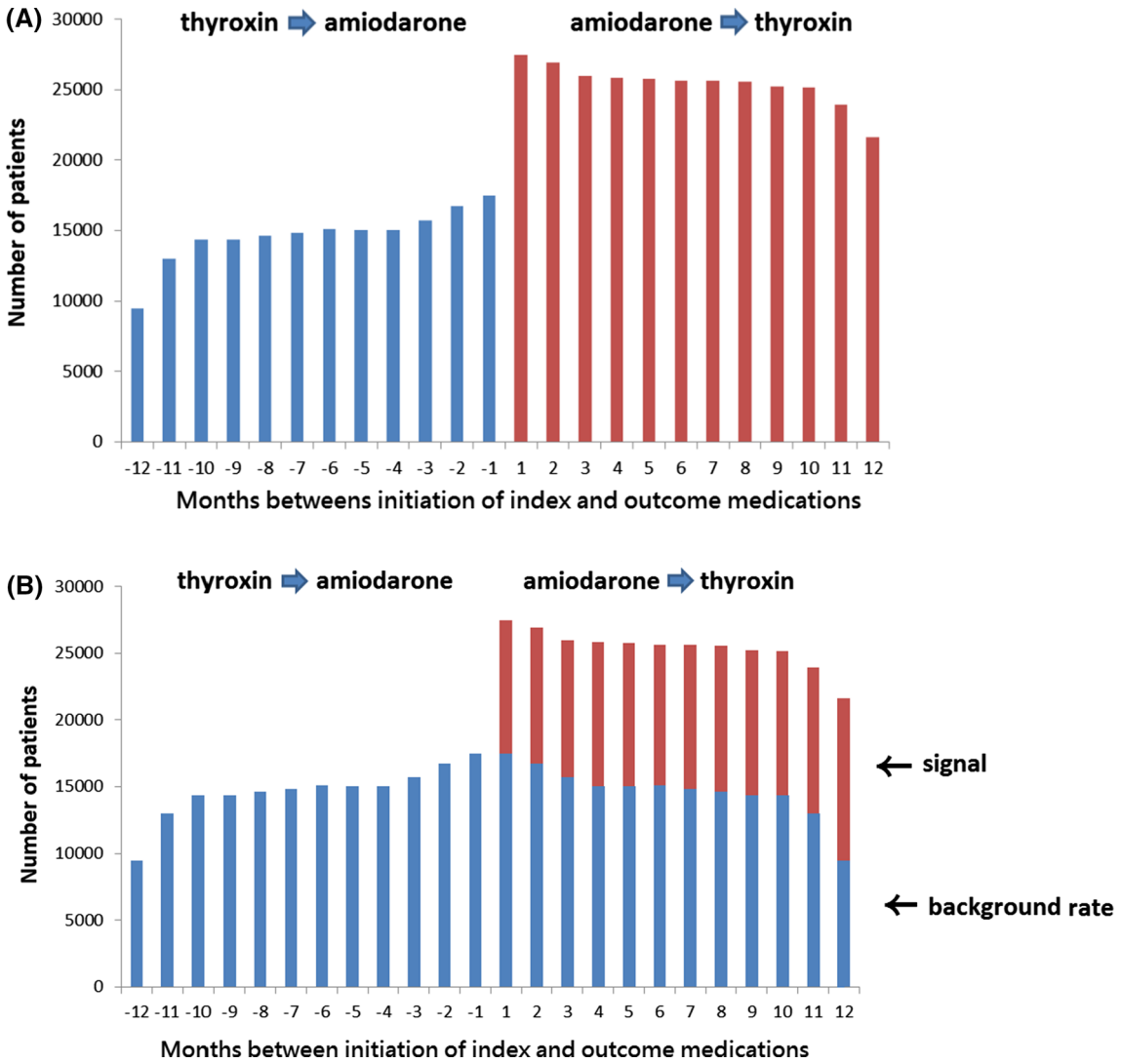

Fig. 1 Theoretical and conceptual framework of SSA. **a** Asymmetrical prescribing pattern of potential causal relationship. **b** Estimation of background rate of natural occurrence from non-causal sequence. Background rate indicates a group of patients received thyroxin before amiodarone due to chance, instead of the pharmacological effects of amiodarone

window may be prevalent users and are excluded from the analysis. After a specified waiting time, the number of medication users could be constant over time and the graph will be dominated by incident users. As a result, we are able to efficiently select incident users after the waiting window. This graphical approach strengthens the efficiency of large scale surveillance across multiple datasets [6, 7] (Fig. 2).

The choice of outcome has been described as a medication initiated that has the potential to be used to treat the occurrence of an adverse event (e.g., thyroxin for amiodarone induced hypothyroidism). If data are available, it is also possible to use diagnosis events as outcomes. For example, Caughey et al. [16] used hospitalization for hip fracture as an outcome and performed SSA to test the association between prochlorperazine and hip fracture. It is also possible to investigate symmetry between two events, for example Cole et al. [17] evaluated the association between hysterectomy and the risk of irritable bowel syndrome. We provide examples of index and outcome drugs or events in Table 1.

The validity of SSA is dependent on the availability of a good indicator for the outcome of interest. Whether a medication or a hospitalization event is used, the specificity of the outcome measure as an indicator of the adverse event is important. The use of non-specific drug indicators requires an additional level of interpretation. Further, when the adverse event in question only constitutes a smaller proportion of the use of the outcome drug in question, associations might be attenuated. Since SSA relies on medication indicators, associations may be underestimated if patients who experience side effects discontinue the

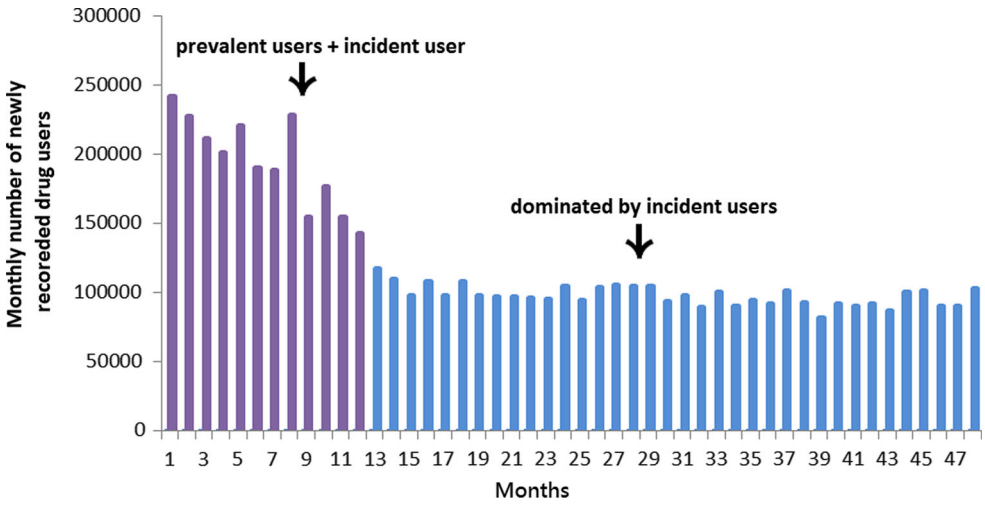

Fig. 2 Hypothetical waiting time distribution method to capture incident drug users. The waiting time distribution provides a graphical representation of a group of medication users by the time of their first prescription within a specified time window, with most past users captured at the beginning of the window (*purple bar*). After a specified waiting time (12 months), the number of medication users will be constant over time and the graph will be dominated by incident users (*blue bar*). (Color figure online)

suspected medication, are not treated with a medicine for the side effect or use an over-the-counter (OTC) medication that is not recorded in the dataset. As a result the drug → outcome sequences that would otherwise have occurred will not be included in the analysis and the signal may be attenuated. This will only be a problem to the extent that the adverse drug effect is commonly known or suspected, which will lead some clinicians to discontinue the offending drug rather than just treating the outcome symptom. The SSA can thus be expected to work best with unsuspected associations.

Strengths and advantages of sequence symmetry analysis

SSA is a case-only design, as it includes only those patients who have the outcome of interest [18]. Additionally it only includes those patients who have the exposure or medication of interest. SSA has been shown to capture signal even when the adverse event is rare [12]. For example, Lai et al. [6] found a significant signal of hyperprolactinemia among patients receiving sulpiride and amisulpride who were later dispensed prolactine inhibitor treatment, even though the incidence rate of hyperprolactinemia in the population was relatively low. As another example, Tsiropoulos et al. [7] detected an association between use of antiepileptic drugs and use of antibiotics with only a few users of both medications.

SSA has been shown to have high specificity but moderate sensitivity. A validation study by Wahab et al. [8] found SSA to have a specificity of 93% (95% CI 0.87–0.96), a sensitivity of 61% and a positive predictive value of 77% (95% CI 0.61–0.88) when tested against adverse events identified in 120 clinical trials for 19 medications. Additional research has demonstrated that when applied to administrative data sources, SSA can be a complementary tool to traditional pharmacovigilance methods. The rates of detected events increased 21% after supplementary use of the SSA beyond traditional methods and different signals were detected using the different methods [19, 20].

SSA inherently controls for time-constant patient-specific confounders such as genetic or environmental factors [4]. Traditional methodologies for evaluating exposure-outcome associations, such as cohort or case–control studies, require data on a large number of confounders to produce unbiased risk estimates. SSA has the advantage that it only requires three variables, a patient identifier, medication code and medication dispensed date. Data for other potential confounders are not required as the design controls for them implicitly [10]. This ensures computational efficiency, which is an important feature of the SSA method [7]. An additional benefit of the limited data set is that it is very suitable for distributed network analyses, i.e., when structured queries are sent to data owners and applied locally, and where summary results of those queries are returned to a coordinating centers for collation. Since this obviates the need for exchange of raw data, the method aids in preserving the confidentiality and privacy of patients [10, 13, 21, 22]. SSA has become one of the routine methodological approaches for the Asian Pharmacoepidemiology Network (AsPEN) [13], a multinational research network established to support pharmacoepidemiology research among several Asian countries [23].

Lastly, a graphical output of SSA can be generated to aid in the interpretation of generated signals. The premise behind SSA is the concept of symmetry. While the SR is the statistic used to summarize potential asymmetry, a visual representation of the sequence of events can help to understand the temporality of the association (Fig. 1). Review of the SSA graphs and temporality of the

Table 1 Published studies using sequence symmetry analysis from 1996–2016

Year	Authors	Index drug/event (A)	Outcome drug (with the indication)/ event (B)	Main findings
Proof-of-concept study				
1996	Hallas [4]	**Rx.** cardiovascular drugs	**Rx.** antidepressant (depression)	Cardiovascular drugs associated with initiation of antidepressants: Angiotensin-converting enzyme inhibitors (466 pairs; adjusted sequence ratio [ASR], 1.29; 95% CI 1.08–1.56) Calcium channel blockers (814 pairs; ASR = 1.31; 95% CI 1.14–1.51)
Signal evaluation (with specific hypotheses)				
1998	Lindberg et al. [31]	**Rx.** cholesterol lowering medication	**Rx.** antidepressant (depression)	No association between cholesterol lowering medication and initiation of antidepressants (184 pairs; ASR, 0.90; 95% CI 0.68–1.22)
2000	Cher [32].	**Dx.** myocardial infarction	**Dx.** acute cholecystitis	Hospitalization for myocardial infarction may increase the risk for subsequent hospitalization for acute cholecystitis (718 pairs; ASR, 1.45; 95% CI 1.28–1.64)
2000	Bytzer et al. [33]	**Rx.** pre-defined list of 32 medications	**Rx.** cisapride and metoclopramide (functional dyspepsia and nausea)	Medicines associated with initiation of cisapride: Non-steroidal anti-inflammatory drugs (211 pairs; adjusted SR, 1.33; 95% CI 1.02–1.77) Methylxanthines (17 pairs adjusted SR 2.36, 95% CI 1.00–8.44) 14 of 32 medicines associated with metoclopramide initiation
2003	Hersom et al.	**Rx.** isotretinoin	**Rx.** antidepressant (depression)	No association between isotretinoin and any antidepressant use (2821 pairs; ASR, 0.97; 95% CI 0.92–1.02)
2004	Corrao et al. [34]	**Rx.** antibacterial agents	**Rx.** antiarrhythmic drugs (arrhythmia)	Antibacterial agents associated with arrhythmia medicines, ciprofloxacin (870 pairs; ASR, 1.17; 95% CI 1.02–1.33) and erythromycin (73 pairs; ASR, 1.78; 95% CI 1.09–2.89)
2006	Thacker. et al. [35]	**Rx.** acetylcholinesterase inhibitors	**Dx.** chronic airways disorders 1. Emergency room visits 2. Hospitalizations 3. Physician visits **Rx.** antibacterial plus oral corticosteroid on the same day (chronic airways disorders)	Analysis included 922 initiators of acetylcholinesterase inhibitors. No association was found between acetylcholinesterase inhibitor use and chronic airways disorders. Adjusted SRs ranged from 1.00 (95% CI 0.61–1.62) for physician visits to 1.64 (95% CI 0.55–4.89) for emergency room visits
2006	Silwer et al. [36]	**Rx.** statins	**Rx.** non-steroidal anti-inflammatory drugs (muscle pain)	No association between initiation of statins and NSAIDs (1321 pairs; ASR, 0.94; 95% CI 0.85–1.05)
2007	Cole et al. [17]	**Px.** hysterectomy	**Dx.** irritable bowel syndrome	No association between hysterectomy and irritable bowel syndrome (726 pairs; ASR, 1.0; 95% CI 0.9–1.2)
2010	Caughey et al. [16]	**Rx.** medicines that may be associated with dizziness **Rx.** prochlorperazine	**Rx.** prochlorperazine (dizziness) **Dx.** hip fracture	Associations found with cardiovascular drugs, non-steroidal anti-inflammatory drugs, opioids and sedatives and the subsequent initiation of prochlorperazine that ranged from 1.07 (3845pairs; 95% CI 1.01–1.14) for diuretics to 1.50 (3411 pairs; 95% CI 1.40–1.61) for statins. Initiation of prochlorperazine was associated with hospitalization for hip fracture (327 pairs,; ASR, 1.49; 95% CI 1.19–1.86)

Table 1 continued

Year	Authors	Index drug/event (A)	Outcome drug (with the indication)/ event (B)	Main findings
2010	Vegter et al. [37]	**Rx.** angiotensin-converting enzyme inhibitors	**Rx.** antitussives (dry cough)	Angiotensin-converting enzyme inhibitors was associated with initiation of antitussive agents (1054 pairs; adjusted SR, 2.2; 95% CI 1.9–2.4)
2011	Caughey et al. [38]	**Rx.** non-steroidal anti-inflammatory drugs	**Dx.** stroke	Initiation of non-steroidal anti-inflammatory drugs (NSAIDs) was associated with hospitalization for stroke with ASRs ranging from 1.44 (333 pairs; 95% CI 1.16–1.80) for indomethacin to 2.04 (114 pairs; 95% CI 1.36–3.04) for piroxicam
2012	Garrison et al. [24]	**Rx.** diuretics, statins, and inhaled long-acting beta2-agonists (LABAs)	**Rx.** quinine (nocturnal leg cramps)	Diuretics, statin, and LABAs were associated with initiation of quinine: Diuretics: 1590 pairs; ASR, 1.47; 95% CI 1.33–1.63. Statins: 1326 pairs; ASR, 1.16; 95% CI 1.04–1.29. LABAs: 576 pairs; ASR, 2.42; 95% CI 2.02–2.89
2013	Lai et al. [14]	**Rx.** antiepileptic drugs	**Rx.** thyroxine (hypothyroidism)	Antiepileptic drug was associated with initiation of thyroxine (16,200 pairs; ASR, 1.13; 95% CI 1.09–1.18)
2013	Vegter et al. [39]	**Rx.** angiotensin-converting enzyme inhibitors	**Rx.** antitussives (dry cough)	Angiotensin-converting enzyme inhibitors was associated with initiation of antitussive agents (1898 pairs; adjusted SR, 2.2; 95% CI 1.8–2.2)
2013	Pouwels et al. [40]	**Rx.** angiotensin-converting enzyme inhibitors	**Rx.** nitrofurantoin (urinary tract infections)	Angiotensin-converting enzyme inhibitors was associated with initiation of nitrofurantoin (161 pairs; ASR, 1.68; 95% CI 1.21–2.36)
2013	Pratt et al. [10]	**Rx.** antipsychotics	**Rx.** insulin (hyperglycemia)	Olanzapine was associated with initiation of insulin USA-Public database: 20,234 pairs; ASR, 1.14; 95% CI 1.10–1.17 Sweden database: 177 pairs; ASR, 1.53; 95% CI 1.13–2.06
2013	van Boven et al. [41]	**Rx.** inhaled corticosteroids	**Rx.** nystatin, miconazole, methylrosaniline and amphotericin B (oral candidiasis)	Inhaled corticosteroids was associated with initiation of medicines for oral candidiasis (1062 pairs; ASR, 1.94; 95% CI 1.71–2.21)
2013	Fujimoto et al. [42]	**Rx.** statin use	**Rx.** solifenacin, flavoxate, oxybutynin (lower urinary tract symptoms)	Statins use was associated with initiation of medicines for lower urinary tract symptoms (ASR, 1.17; 95% CI 1.05–1.30)
2014	Kalisch Ellett [43]	**Rx.** medication reported to be associated with urinary incontinence	**Rx.** oxybutynin (urinary incontinence)	Drugs associated with initiation of oxybutynin Calcium channel blockers (2230 pairs; adjusted SR, 1.45; 95% CI 1.33–1.57) Angiotensin-converting enzyme inhibitors (2616 pairs; ASR, 1.28; 95% CI 1.19–1.39) Angiotensin receptor blockers (2040 pairs; ASR, 1.42; 95% CI 1.30–1.55) Hypnotic-sedatives (3326 pairs; adjusted SR, 1.10; 95% CI 1.03–1.18) Hormone replacement therapy (2446 pairs; ASR, 1.54; 95% CI 1.42–1.67)
2014	Takada et al. [44]	**Rx.** aspirin	**Rx.** H2-receptor antagonists and proton pump inhibitors (gastrointestinal complications) **Dx.** ulcer, gastritis and duodenitis, and melena	Enteric-coated low-dose aspirin was associated with diagnosis of gastrointestinal ulcers (ASR, 1.39; 95% CI 1.13–1.73) and diagnosis of melena (ASR, 20.80; 95% CI 3.33–863.25)

Table 1 continued

Year	Authors	Index drug/event (A)	Outcome drug (with the indication)/ event (B)	Main findings
2014	Takada et al. [45, 46]	**Rx.** statin	**Rx.** hypnotic drug (sleep disturbances)	Statin use was associated initiation of hypnotic drugs (12,053 pairs; ASR, 1.18; 95% CI 1.11–1.25)
2014	Wahab et al. [19]	**Rx.** rofecoxib and rosiglitazone	**Dx.** myocardial infarction **Rx.** diuretic (myocardial infarction and heart failure)	Rofecoxib was associated with hospitalization for myocardial infarction (1014 pairs; ASR, 1.55 95% CI 1.31–1.84); rosiglitazone was associated with hospitalization for heart failure (101 pairs; ASR, 2.10, 95% CI 1.22–3.62) and initiation of frusemide (422 pairs; ASR, 1.73; 95% CI 1.34–2.24)
2015	Fujimoto et al. [46]	**Rx.** statins	**Dx.** malignant neoplasm	Statin was associated with diagnosis of colorectal cancer (1575 pairs; ASR, 1.20; 95% CI 1.08–1.34) lung cancer (818 pairs; ASR, 1.32; 95% CI 1.13–1.53) and pancreatic cancer (804 pairs; ASR, 1.31; 95% CI 1.13–1.53)
2015	Rasmussen et al. [47]	**Rx.** cardiovascular drugs	**Rx.** 5-phosphodiesterase inhibitor (erectile dysfunction)	Cardiovascular drugs associated with initiation of medicines for erectile dysfunction: Thiazides (3118 pairs; ASR, 1.28; 95% CI 1.20–1.38) b-Adrenoceptor blockers (2511 pairs; ASR, 1.18; 95% CI 1.09–1.28) Calcium channel blockers (3379 pairs; ASR, 1.29, 95% CI 1.21–1.38) ACE inhibitors (4182 pairs; ASR, 1.29, 95% CI 1.21–1.37) Angiotensin II receptor agonists (2082 pairs; ASR, 1.16, 95% CI 1.06–1.26)
2015	Takeuchi et al. [48]	**Rx.** atypical antipsychotics	**Rx.** anti-hyperlipidemic drugs (hyperlipidemia)	Olanzapine was associated with initiation of hyperlipidemia medicine (336 pairs; ASR, 1.56; 95% CI 1.25–1.95). No significant risk for risperidone, perospirone, blonanserin, quetiapine, and aripiprazole
2015	Roughead et al. [22]	**Rx.** rosiglitazone and pioglitazone	**Dx.** heart failure **Rx.** frusemide (heart failure)	Pioglitazone (ASR, 1.47; 95% CI 1.14–1.91) and rosiglitazone (ASR 1.65; 95% CI 1.58–1.72) was associated with the furosemide initiation in the Caucasian populations. Pooled risk estimates were lower (ASR, 1.11; 95% CI 0.93–1.32 and ASR, 1.21; 95% CI 1.01–1.45 for pioglitazone and rosiglitazone, respectively) in the Asian populations. Association between pioglitazone and hospitalization for heart failure in Caucasian population only (ASR, 1.88, 95% CI 1.01–3.5)
2016	Pouwels et al. [49]	**Rx.** statin	**Rx.** antibiotics (infection)	Statins are associated with a reduced risk of infections among patients with drug-treated type 2 diabetes (4684 pairs; adjusted SR, 0.86; 95% CI 0.81–0.91)
2016	Takada et al. [50]	**Rx.** sodium channel blocking antiepileptic drugs (phenytonin, carbamazepine, lamotrigine, topiramate, valproic acid, ethotoin)	**Dx.** malignant neoplasm	Sodium channel blocking antiepileptic drugs was inversely associated with diagnoses of Colorectal cancer (513 pairs; ASR, 0.72; 95% CI 0.60–0.86) Lung cancer (317 pairs; ASR, 0.65; 95% CI 0.51–0.81) Gastric cancer (390 pairs; ASR, 0.80; 95% CI 0.65–0.98) Hematological malignancies (225 pairs; ASR, 0.50; 95% CI 0.37–0.66)

Table 1 continued

Year	Authors	Index drug/event (A)	Outcome drug (with the indication)/ event (B)	Main findings
Signal detection (without specific hypotheses)				
1998	Hallas et al. [11]	**Rx.** non-ulcer drugs	**Rx.** H2 blocker and proton pump inhibitors, bismuth preparation and sulcralfate (dyspepsia)	Analysis included 31,232 incident users of ulcer drugs. Drugs induced dyspepsia included: Non-steroidal antiinflammatory drugs (1814 pairs, ASR, 1.80; 95% CI 1.64–1.99), Calcium blockers (539 pairs, ASR, 1.40; 95% CI 1.18–1.67), Corticosteroids (1044 ASR, 1.15; 95% CI 1.02–1.30), Angiotensin converting enzyme inhibitors (335 pairs, ASR, 1.38; 95% CI 1.12–1.73) Methylxanthines (121 pairs, ASR, 1.49; 95% CI 1.05–2.19)
2009	Tsiropoulos et al. [7]	**Rx.** antiepileptic drugs	**Rx. and Dx.** for adverse drug reactions)	Analysis included 24,882 incident anti-epileptic drug users. Previously unrecognized signals included: Topiramate → initiation of dopaminergic agent medicines (12 pairs, ASR, 10.4; 95% CI 1.5–448) Gabapentin → hospitalization for glaucoma (9 pairs, ASR, 8.0; 95% CI 1.1–355) Valproic acid → hypothyroidism (9 pairs, adjusted SR, 8.0; 95% CI 1.1–355)
2012	Roughead et al. [29]	**Rx. and Dx.** all potential drugs or disease diagnoses.	**Rx.** glaucoma eye-drop (glaucoma)	Analysis included 25,984 veterans. Drugs associated with initiating timolol eye drops Inhaled beta-agonists, (786 pairs; ASR, 1.48; 99% CI 1.22–1.78 Inhaled corticosteroids (494 pairs; ASR, 1.43; 99% CI 1.13–1.81) Antidepressants (1253 pairs; ASR, 1.24; 99% CI 1.07–1.43) Selective serotonin reuptake inhibitors (791 pairs; ASR 1.30 95% CI 1.08–1.56) Drugs associated with initiating latanoprost eye drops Inhaled beta-agonist (2251 pairs; A SR, 1.24; 99% CI 1.11–1.38) Antidepressants (1871 pairs; ASR, 1.16; 99% CI 1.03–1.31) Selective serotonin reuptake inhibitors (1155 pairs ASZR 1.20 95% CI 1.03–1.39) Hospitalizations associated with timolol eye drops Bradycardia (74 pairs ASR 2.22; 99% CI 1.15–4.31)

Table 1 continued

Year	Authors	Index drug/event (A)	Outcome drug (with the indication)/ event (B)	Main findings
2014	Lai et al. [6]	**Rx.** sulpiride	**Rx.** for possible adverse drug reactions	Analysis included 1680 sulpiride users. Drugs associated with initiating sulpiride: Corticosteroids for local oral treatment (59 pairs; ASR, 1.71; 95% CI 1.00–2.91) Emollient softeners laxatives (219 pairs; ASR, 1.55; 95% CI 1.18–2.04) Non-selective beta blocking agents (304 pairs; ASR, 1.61; 95% CI 1.28–2.03) Corticosteroids (57 pairs; ASR, 2.18; 95% CI 1.21–3.92) Fluoroquinolone antibacterials (55 pairs; ASR, 1.81; 95% CI 1.03–3.17), Topical non-steroid anti-inflammatory drugs (173 pairs, ASR, 1.36; 95% CI 1.01–1.84).
2015	Hashimoto et al. [51]	**Rx.** medication reported to be associated with lower urinary tract symptoms	**Rx.** for lower urinary tract symptoms (LUTS)	Analysis included 17,824 patients with LUTS. Drugs associated with LUTS included: Donepezil (ASR, 1.98; 95% CI 1.57–2.50) Intestinal lavage solution (ASR, 1.86; 95% CI 1.65–2.10) Cyclophosphamide (ASR, 1.52; 95% CI 1.14–2.04) Amantadine (ASR, 1.53; 95% CI 1.12–2.09) Levodopa/benserazide (ASR, 1.82; 95% CI 1.18–2.81) Paroxetine (ASR, 1.77; 95% CI 1.33–2.36) Milnacipran (ASR, 2.10; 95% CI 1.28–3.45) Diazepam (ASR, 1.44; 95% CI 1.28–1.63) Risperidone (ASR, 1.55; 95% CI 1.34–1.79) Levomepromazine (ASR, 2.20; 95% CI 1.34–1.79) Sulpiride (ASR, 1.32; 95% CI 1.01–1.72) Cimetidine (ASR, 1.99; 95% CI 1.24–3.20) Scopolamine butylbromide (ASR, 1.72; 95% CI 1.55–1.92) Tiotropium bromide (ASR, 1.75; 95% CI 1.42–2.16) Cibenzoline (ASR, 2.97; 95% CI 1.92–4.59) Amezinium metilsufate (ASR, 1.89; 95% CI 1.10–3.26) Morphine (ASR, 1.29; 95% CI 1.14–1.45) Oxycodone (ASR, 1.20; 95% CI 1.03–1.41)

Table 1 continued

Year	Authors	Index drug/event (A)	Outcome drug (with the indication)/ event (B)	Main findings
2016	Kalisch Ellett et al. [52]	**Rx.** all potential drugs	**Dx.** hospital admission for dehydration or heat-related illness	Analysis included 6700 veterans with incident hospital admission for dehydration or heat-related illness. Drugs associated with the event included: Diuretics (ASR, 1.83; 95% CI 1.58–2.11) Angiotensin-converting enzyme inhibitor (ASR, 1.59; 95% CI 1.31–1.90) Beta-blockers (ASR, 1.56; 95% CI 1.30–1.84) Non-steroidal anti-inflammatory drug (ASR, 1.51; 95% CI 1.22–1.83) Anticoagulant (ASR, 1.50; 95% CI 1.31–1.71) Nitrates (ASR, 1.45; 95% CI 1.19–1.75) Angiotensin 2 receptor blocker (ASR, 1.43; 95% CI 1.12–1.79) Calcium channel blockers (ASR, 1.36; 95% CI 1.06–1.69) Anticholinergic agent (ASR, 1.30; 95% CI 1.13–1.48) Antidepressant (ASR, 1.21; 95% CI 1.05–1.37) Antipsychotics (ASR, 1.20; 95% CI 1.04–1.36) Selective serotonin reuptake inhibitor (ASR, 1.17; 95% CI 1.01–1.35) Hypnotics (ASR, 1.16; 95% CI 1.00–1.32)
2016	Wahab et al. [53]	**Rx.** all potential drugs	**Dx.** heart failure hospitalization, and **Rx.** frusemide	Analysis included 250,000 veterans. Drugs associated with hospitalization for heart failure or incident frusemide dispensing included: *Heart failure hospitalization* Betahistine (ASR, 2.67; 95% CI 1.47–4.21) Travoprost (ASR, 1.98; 95% CI 1.24–2.84) Bimatoprost (ASR, 1.83; 95% CI 1.25-2.51) Sulfasalazine (ASR, 1.70; 95% CI 1.01–2.55) Fexofenadine (ASR, 1.36; 95% CI 1.14–1.60) Latanoprost (ASR, 1.34; 95% CI 1.12–1.58) Glucosamine (ASR, 1.33; 95% CI 1.01–1.69) Tobramycin (ASR, 1.32; 95% CI 1.13–1.53) Erbinafine (ASR, 1.32; 95% CI 1.10–1.56) Loratadine(ASR, 1.23; 95% CI 1.09–1.37) Mupirocin (ASR, 1.22; 95% CI 1.11–1.34) Paracetamol (ASR, 1.09; 95% CI 1.03–1.16) *Frusemide dispensing* Teriparatide (ASR, 5.02; 95% CI 1.07–23.7) Iodoxamide (ASR, 2.50; 95% CI 1.06–5.91) Famotidine (ASR, 1.69; 95% CI 1.38–2.08) Latanoprost (ASR, 1.48; 95% CI 1.38–1.59)

Table 1 continued

Year	Authors	Index drug/event (A)	Outcome drug (with the indication)/event (B)	Main findings
				Pilocarpine(ASR, 1.43; 95% CI 1.16–1.77)
				Brinzolamide (ASR, 1.37; 95% CI 1.16–1.62)
				Betahistine (ASR, 1.31; 95% CI 1.07–1.62)
				Ranitidine (ASR, 1.24; 95% CI 1.17–1.31)
				Paracetamol (ASR, 1.06; 95% CI 1.04–1.09)
Validation of SSA				
2013	Wahab et al. [8]	To determine the validity of SSA to detect adverse drug reactions from an administrative claims database. (sensitivity, specificity, positive and negative predictive values)		
2013	Wahab et al. [19]	To test the time to signal detection of quantitative adverse drug events signaling methods in a health claims database (SSA) and in a spontaneous reporting database (ROR, PRR, Bayesian confidence propagation neural network)		
2014	Pratt et al. [25]	To evaluate the validity of SSA as a signal detection tool for newly marketed medications and the adjustment for underlying medication utilization patterns		
2015	Pratt et al. [13]	To determine the consistency of SSA results for detecting positive and negative control adverse drug events across different settings		

association may help to further validate the plausibility of an identified signal.

Challenges and pitfalls of sequence symmetry analysis

While there are advantages to the use of SSA, there are potential challenges and pitfalls. As described in the previous section SSA utilizes a non-symmetrical pattern of treatment orders as evidence of a potential adverse effect of the medication of interest. There may be other reasons, apart from a true effect, that could create such asymmetry, and these are discussed below.

Prescribing trends

The SSA may be affected by prescribing trends over time which may possibly lead to a biased effect estimate [4]. For example, an excess of index medications → outcome sequences could occur if the use of the outcome medication is increasing, e.g., because of changes in reimbursement or other drivers in utilization. This would result in the SR overestimating the true incidence rate ratio. To remedy such bias, a null-effect SR can be calculated which adjusts the SR for the background rate of the medications under study. As described by Hallas [4], the null-effect SR takes the prescription trends in the background population into account, by computing an expected SR based on the probability of the sequence of initiation of outcome drugs after index drugs in the absence of any causal association. The calculation of null-effect SR has been described by Hallas and revised by Tsiropolous et al. [7] who placed a restriction on the exposure window between sequences. The null-effect SR is derived from the calculation of the probability, P, of each incident index drug user being exposed to an outcome drug within the specified exposure window after the day the index drug was initiated.

$$\mathrm{P} = \frac{\sum_{\mathrm{n=x+1}}^{\mathrm{x+d}} \mathrm{M_n}}{\sum_{\mathrm{n=x-d}}^{\mathrm{x-1}} \mathrm{M_n} + \sum_{\mathrm{n=x+1}}^{\mathrm{x+d}} \mathrm{M_n}}$$

Here, P indicates the probability of each incident index drug user will have his first prescription for a drug after day x inside a time window, n indicates consecutive days of the study period, M_n indicates the number of persons receiving their first outcome drug on the date, and d is the specified number of days for observation time window (e.g., 365 days to capture the pairs of index and outcome drugs).

The overall average probability, P_a, is then calculated by weighting the number of incident users of an index drug on each day of the study and averaging for all days [7], as:

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

Here, Pa indicates the overall average probability that the outcome drug will be prescribed after the index drug, with the given prescription pattern in the background population taken into consideration. It is calculated by weighting the number of incident users of an index drug on consecutive m days of the study and averaging for all days. n indicates consecutive days of the study period, u indicates the last day of the study period, M_n indicates the number of persons receiving their first outcome drug on the date, I_m indicates the number of persons receiving their first index drug on that day, and d is the specified number of days for observation time window (e.g., 365 days to capture the pairs of index and outcome drugs).

Finally, a null-effect SR is calculated as $P_a/(1 - P_a)$. The adjusted sequence ratio is then calculated as the crude SR divided by the null-effect SR [4].

$$\text{Adjusted SR} = \text{crude SR}/\text{Null-effect SR}$$

The limitations of the method described to adjust for the underlying trends in medication use and their effect on the calculation of the SR are that individual level data on initiation of new drugs for the entire population is required and that it can be computationally demanding. Other approaches for adjustment, such as bootstrap resampling methods, have been described by Garrison et al. [24]. A simulation has tested a limited set of potential utilization patterns of the underlying trends and found that adjustment of the crude SR by the null-effect SR effectively removes bias related to changes in underlying utilization trends [25]. However, more work is required to study potential bias in other scenarios.

Inappropriate identification of new use

As discussed in the theoretical background to SSA, the method requires the identification of initiation of the medication of interest and of the outcome medication. The reason for this is that adverse events are more likely to occur soon after treatment initiation and that the initiation of the outcome medication is more likely to reflect treatment for the onset of an adverse event rather than treatment for an ongoing condition. When employing SSA, the medication of interest may be a specific medication or a medication class. When examining use by specific medication, new users of a medication may include patients who have switched to that medication from a medication in the same class. Exclusion of switchers from study cohorts or censoring the switchers at the time of switching is the

simplest solution to overcome potential bias from existing use of the medicine class. In SSA, switching medications might affect the estimation of the background rate from the non-causal sequences. For example, first generation antipsychotics such as haloperidol have a higher risk of extrapyramidal symptom (EPS) and therefore patients may be switched to second generation antipsychotics such as olanzapine when EPS is suspected [6, 26]. This results in a switch to olanzapine, a second generation antipsychotic, shortly after a diagnosis of EPS has been registered. Analysis of this sequence without the recognition of prior first generation antipsychotic use would lead to an apparent inverse association between use of olanzapine and risk of EPS. A solution to this problem is to include only new users of a medication class. In the example of EPS discussed above, patients would only be selected for inclusion in SSA at the time of initiating their first antipsychotic in the class.

Time-variant variables and selection of study periods

SSA may be affected by bias due to within-person confounding [27] such as fluctuations in disease severity, dietary or other behavioral changes which mat influence the order of prescribing of the index and outcome medicines. The effect of time-varying confounding on the results of SSA may be influenced by the length of the exposure window. Limiting the study period, for example to 12 months, can help to reduce potential bias due to time-varying covariates, however, the trade-off is the potential to miss adverse reactions that develop only after a long-term exposure [6–8].

There is no standard exposure time window for SSA, and the best strategy to determine the appropriate time window is to consider the likely time course of the development of the adverse effect under study. For signal detection studies without specific hypotheses, a 1-year time window might be optimal for achieving acceptable sensitivity and positive predictive value. A study by Wahab et al. [19]. found the restriction to a shorter exposure window reduced the sensitivity of SSA but this may be due to small sample sizes. However, Wahab et al. [19] assessed SSA only for acute events and the restricted time window may be insufficient for detecting adverse events that may take longer to manifest.

There is no formal computational method to adjust for known time-variant confounders in the SSA, as opposed to the case-crossover and self-controlled case series analyses that allow for adjustments of time-varying covariates, e.g., by incorporating time-dependent covariates in a conditional logistic or poisson regression model.

Inverse causality and protopathic bias

One of the assumptions of SSA is that the occurrence of the outcome will not affect the probability of exposure. Violation of this assumption may result in an effect known as inverse causation. For example, if a non-symmetrical distribution of a sequences is found with SR below 1.0, this could be explained by either the index drug reducing the risk of using the outcome drug or the outcome drug increasing the risk of using the index drug. It is not possible from these data alone to know which is correct.

Protopathic bias is also a potential problem when employing SSA. Protopathic bias occurs when the index medication is used to treat the underlying symptoms of an outcome before the outcome is diagnosed [28]. This might lead to a false conclusion that the index medication induces the outcome event. Inverse causality and protopathic bias highlight the importance of including sensitivity analyses to test the robustness of SSA results.

Tradeoff-signal versus noise

SSA may be used for hypothesis generation. Two recurrent discussions in such activity are how to address the problem of multiple testing and the related problem of how to define a signal. A signal generated by SSA may be defined as a SR in which the lower limit of the 95% confidence interval is greater than 1. Published studies have used variations of this, for example, Tsiropoulos considered a result to be a signal if there was sufficient power (highest number of sequence pairs) or the most significant associations (highest SR) [7]. Other studies have calculated 99% confidence intervals to identify the significant signals when investigating outcomes for a medication class, e.g., potential safety signals associated with the use of glaucoma eye drops [29] and antiepileptic drugs [14]. Lowering the significance level may not be the ultimate solution to the signal to noise tradeoff [30]. Using a lower alpha value threshold, e.g., 0.01 rather than 0.05, will reduce the number of non-causal signals generated purely by chance, but it will also reduce the number of causal signals to the same extent, since fewer of the true associations will reach statistical significance. Thereby, the signal/noise ratio is virtually unchanged by a lower p value threshold. The chosen alpha level, therefore, should be determined by a careful consideration of sensitivity and specificity, and the implications of false positive or false negative findings.

Detection bias and confounding by indication

As with many other observational study designs, detection bias may play a role in SSA because patients might be

more likely to receive a particular treatment after they start another because they are now in the health system [10, 14]. For example developing a health condition such as diabetes may trigger a patient to be more actively seeking treatment for other health conditions. A study investigating the risk of antipsychotic induced hyperglycemia identified a seemingly protective association between antipsychotics and initiating insulin (the indicator of hyperglycemia), however, the authors noted that it was possible that entry into the health system through diagnosis of diabetes may have prompted the diagnosis of a psychiatric condition [10]. Hallas pointed out several possible causes of asymmetrical patterns, such as confounding by indication [4]. For example, the relationship between a cardiovascular medication and depression may be confounded when cardiovascular disease itself may lead to depression [4].

Application of sequence symmetry analysis in practice

Examples of the use of SSA are listed in Table 1. We classified all the SSA studies into three groups by purpose of the studies, i.e., signal evaluation with a specific study hypothesis, signal generation studies where the aim was to detect new signals associated with treatment or methodological studies which evaluated the validity of SSA. Although SSA was originally considered as a signal detection tool for drug safety, most of the SSA studies undertaken to date have aimed to test known hypotheses or to prove clinical phenomena and evaluate the risk signal, with only a limited number focused on generating hypotheses or detecting unknown, unsuspected risks [6, 7, 29]. Further research is required to determine the utility of SSA as a potential tool for large scale data-mining in claims data.

Execution of sequence symmetry analysis

The execution of SSA requires a dataset that includes (1) a unique patient identifier; (2) a variable to identify the medication dispensed and (3) a variable to identify the date of medication supply. An analytical SAS or R program is available from the authors upon request. It contains the following sections:

1. Selection of new use of index and outcome medication.
2. Identifying patients with new use of either medication.
3. Ordering sequences according to which came first.
4. Crude SR calculation.
5. Null-effect SR calculation.
6. Adjusted SR calculated as the ratio of the crude SR and the null-effect SR.
7. Confidence interval calculation.

Conclusion

Sequence symmetry analysis has been increasingly applied in pharmacoepidemiology studies. Its advantages are that it provides efficient computation, moderate sensitivity but high specificity and is robust towards time constant confounding factors. Its minimal data requirement means that it is suitable when only dispensing data are available. However, there is a potential for false positive or negative results and careful consideration should be given to potential sources of bias when interpreting the results of SSA studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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