SUPPLEMENTARY INFORMATION

Investigating potential prescribing cascades resulting in prochlorperazine prescription: an exploratory analysis of antihypertensives and NSAIDs

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Supplementary Information 1 - Null-effect sequence ratio and trend-adjusted sequence difference calculations

Null-effect sequence ratio calculation

To adjust for temporal trends in marker medication prescribing, we calculated a null-effect sequence ratios (SR_o) based on method described by Tsiropoulos et al (1) and adapted by Doherty et al (2):

$$p = \frac{\sum_{t=1}^{T}(X_t \sum_{i=t+1}^{t+u} Y_i)}{\sum_{t=1}^{T}\left(X_t(\sum_{i=t-u}^{t-1} Y_i + \sum_{i=t+1}^{t+u} Y_i)\right)}$$

$$SR_0 = \frac{p}{1-p}$$

Whereby t is a given day in the chosen study period, T the total number of days in the study period, and u the number of days in the observation window. X_t denotes the number of initiators of the index medication on day t and Y_i the number of initiators of the marker medication on day i.

For simplicity, these have been reduced to the following:

$$SR_0 = \frac{\sum_{t=1}^{T}(X_t \sum_{i=t+1}^{t+u} Y_i)}{\sum_{t=1}^{T}(X_t \sum_{i=t-u}^{t-1} Y_i)}$$

Originally, it is recommended to use the marginal number of index medication initiators for X_t, i.e., all initiators of the index medication on day t, regardless of outcome status. We used the number of initiators of the index medication in the study population as X_t, i.e., the number of initiators of the medication who also were prescribed the marker medication during the observation window on day t. We utilised this method consistent with Doherty et al and which deviated from that described by Tsiropoulous et al, as temporal trends in use of the marker medication e differ in the marginal population from the trend among those in the study population.

Sequence difference and adjusted sequence difference calculation

The sequence difference (the observed differences in the numbers of both sequence orders) was also adjusted for potential bias of the null-effect sequence ratio as recommended by Rahbek et al (3):

The observed difference is represented as:

$$\Delta = N \cdot p - N(1 - p)$$

Where N is the total number of observed sequences and p the proportion which are exposure first.

To adjust for the background prescribing trend, p is adjusted for the null-effect to become p_0, which is obtained from the null-effect SR_0 as follows:

$$p_0 = \frac{\mathrm{SR}_0}{1 + \mathrm{SR}_0}$$

Thus, the trend-adjusted sequence difference (Δ_0) can then be obtained from:

$$\Delta_0 = N \cdot p_0 - N(1 - p_0)$$

References

1. Tsiropoulos I, Andersen M, Hallas J. Adverse events with use of antiepileptic drugs: a prescription and event symmetry analysis. Pharmacoepidemiol Drug Saf. 2009;18(6):483–91.
2. Doherty AS, Lund LC, Moriarty F, Boland F, Clyne B, Fahey T, et al. Prescribing Cascades Among Older Community-Dwelling Adults: Application of Prescription Sequence Symmetry Analysis to a National Database in Ireland. Ann Fam Med 2025.
3. Rahbek MT, Hallas J, Lund LC. Trend adjustment of the sequence difference when performing sequence symmetry analyses. Pharmacoepidemiol Drug Saf. 2024;33(1):e5723.

Table S1: Stratified PSSA of the cardiac alpha adrenoceptor blockers* to prochlorperazine prescribing cascade (2018-2020) with a 365 day run in period (2017)

	Incident users: index (n)	Incident users: both (n)	Index first (n)	Marker first (n)	Prevalence (%)	Crude SR[a] (95% CI[b])	SR_o[c]	Adjusted SR (95% CI)	Δ_0[d]
365 day window									
Overall	8,483	201	117	84	1.38	**1.39 (1.05, 1.85)**	0.87	**1.60 (1.21, 2.12)**	46
Negative control	8,483	63	24	39	0.28	0.62 (0.37, 1.02)	0.95	0.65 (0.39, 1.07)	-13
180 day window	8,483	203	110	93	1.30	1.18 (0.90, 1.56)	0.92	1.28 (0.97, 1.69)	25
60 day window	8,483	115	65	50	0.77	1.30 (0.90, 1.88)	0.96	1.35 (0.93, 1.95)	17

[a] sequence ratio
[b] confidence interval
[c] null effect sequence ratio
[d] trend-adjusted sequence difference
[e] significant aSRs in bold
*Medications included: C02CA01 - prazosin; C02CA02 - indoramin; C02CA03 - trimazosin; C02CA04 - doxazosin; C02CA06 - urapidil

Table S2: Stratified PSSA of the urological alpha adrenoceptor blockers to prochlorperazine prescribing cascade (2018-2020) with a 365 day run in period (2017)

	Incident users: index (n)	Incident users: both (n)	Index first (n)	Marker first (n)	Prevalence (%)	Crude SR[a] (95% CI[b])	SR_o[c]	Adjusted SR (95% CI)	Δ_0[d]
365 day window									
Overall	25,972	441	270	171	1.04	**1.58 (1.30, 1.91)**	0.87	**1.81 (1.49, 2.19)**	127
Negative control	25,972	144	62	82	0.24	0.76 (0.54, 1.05)	0.94	0.80 (0.58, 1.11)	-16
180 day window	25,972	472	275	197	1.06	**1.40 (1.16, 1.68)**	0.93	**1.50 (1.25, 1.80)**	94
60 day window	25,972	245	143	102	0.55	**1.40 (1.09, 1.81)**	0.96	**1.46 (1.13, 1.88)**	46

[a] sequence ratio
[b] confidence interval
[c] null effect sequence ratio
[d] trend-adjusted sequence difference
[e] significant aSRs in bold
*Medications included: G04CA01 – Alfuzosin; G04CA02 – Tamsulosin; G04CA03 – Terazosin; G04CA04 – Silodosin; G04CA51 – Alfuzosin and finasteride; G04CA52 – Tamsulosin and dutasteride; G04CA53 – Tamsulosin and solifenacin; G04CA54 – Tamsulosin and tadalafil; G04CA55 – Doxazosin and finasteride

Table S3: Stratified PSSA of the beta blocker to prochlorperazine prescribing cascade (2018-2020) with a 365 day run in period (2017)

	Incident users: index (n)	Incident users: both (n)	Index first (n)	Marker first (n)	Prevalence (%)	Crude SR[a] (95% CI[b])	SR_0[c]	Adjusted SR (95% CI)	Δ_0[d]
365 day window									
Overall	58,793	1,295	754	541	1.28	**1.39 (1.25, 1.56)**	0.87	**1.60 (1.43, 1.78)**	299
Male	29,384	437	275	162	0.94	**1.70 (1.40, 2.06)**	0.87	**1.94 (1.60, 2.36)**	140
Female	29,409	858	479	379	1.63	**1.26 (1.10, 1.45)**	0.87	**1.45 (1.27, 1.66)**	158
Bisoprolol	43,918	957	538	419	1.23	**1.28 (1.13, 1.46)**	0.87	**1.47 (1.30, 1.67)**	182
Nebivolol	4,688	97	60	37	1.28	**1.62 (1.08, 2.46)**	0.87	**1.86 (1.24, 2.82)**	29
Atenolol	3,277	58	42	16	1.28	**2.62 (1.50, 4.76)**	0.88	**3.00 (1.71, 5.43)**	29
Metoprolol	2,406	53	40	13	1.66	**3.08 (1.68, 5.90)**	0.87	**3.52 (1.93, 6.74)**	30
Propranolol	2,279	72	39	33	1.71	1.18 (0.74, 1.88)	0.87	1.35 (0.85, 2.16)	11
Negative control	58,793	462	208	254	0.35	0.82 (0.68, 0.98)	0.95	0.86 (0.72, 1.03)	-35
180 day window	58,793	1,432	863	569	1.47	**1.52 (1.36, 1.69)**	0.92	**1.64 (1.48, 1.82)**	347
60 day window	58,793	830	493	337	0.84	**1.46 (1.27, 1.68)**	0.96	**1.52 (1.32, 1.74)**	171

[a] sequence ratio
[b] confidence interval
[c] null effect sequence ratio
[d] trend-adjusted sequence difference
[e] significant aSRs in bold

Table S4: Stratified PSSA of the calcium channel blocker to prochlorperazine prescribing cascade (2018-2020) with a 365 day run in period (2017)

	Incident users: index (n)	Incident users: both (n)	Index first (n)	Marker first (n)	Prevalence (%)	Crude SR[a] (95% CI[b])	SR_o[c]	Adjusted SR (95% CI)	Δ_0[d]
365 day window									
Overall	66,884	1,440	822	618	1.23	**1.33 (1.20, 1.48)**	0.87	**1.52 (1.37, 1.69)**	297
Male	28,341	407	243	164	0.86	**1.48 (1.22, 1.81)**	0.87	**1.70 (1.39, 2.07)**	106
Female	38,543	1,033	579	454	1.50	**1.28 (1.13, 1.44)**	0.87	**1.46 (1.29, 1.65)**	193
Amlodipine	39,827	862	482	380	1.21	**1.27 (1.11, 1.45)**	0.87	**1.45 (1.27, 1.66)**	158
Lercanidipine	23,346	505	293	212	1.26	**1.38 (1.16, 1.65)**	0.87	**1.58 (1.33, 1.89)**	114
Negative control	66,884	578	215	363	0.32	0.59 (0.50, 0.70)	0.95	0.62 (0.52, 0.73)	-136
180 day window	66,884	1,559	869	690	1.30	**1.26 (1.14, 1.39)**	0.93	**1.36 (1.23, 1.50)**	238
60 day window	66,884	890	488	402	0.73	**1.21 (1.06, 1.39)**	0.96	**1.26 (1.11, 1.44)**	102

[a] sequence ratio
[b] confidence interval
[c] null effect sequence ratio
[d] trend-adjusted sequence difference
[e] significant aSRs in bold

Table S5: Stratified PSSA of the diuretic to prochlorperazine prescribing cascade (2018-2020) with a 365 day run in period (2017)

	Incident users: index (n)	Incident users: both (n)	Index first (n)	Marker first (n)	Prevalence (%)	Crude SR[a] (95% CI[b])	SR_o[c]	Adjusted SR (95% CI)	Δ_0[d]
365 day window									
Overall	66,172	1,663	876	787	1.32	**1.11 (1.01, 1.23)**	0.87	**1.27 (1.16, 1.40)**	198
Male	29,158	526	283	243	0.97	1.16 (0.98, 1.38)	0.87	**1.33 (1.12, 1.58)**	74
Female	37,014	1,137	593	544	1.60	1.09 (0.97, 1.22)	0.87	**1.25 (1.11, 1.40)**	126
Furosemide	40,282	1,041	537	504	1.33	1.07 (0.94, 1.20)	0.87	**1.22 (1.08, 1.38)**	103
Bumetanide	5,673	120	66	54	1.16	1.22 (0.85, 1.75)	0.88	1.40 (0.98, 2.00)	20
Furosemide + Potassium-sparing	5,150	165	93	72	1.81	1.29 (0.95, 1.76)	0.87	**1.48 (1.09, 2.01)**	32
Indapamide	4,598	117	61	56	1.33	1.09 (0.76, 1.57)	0.87	1.25 (0.87, 1.79)	13
Bendroflumethiazide	3,448	66	39	27	1.13	1.44 (0.89, 2.37)	0.87	**1.66 (1.02, 2.72)**	16
Bendroflumethiazide + Potassium	2,292	38	23	15	1.00	1.53 (0.81, 2.97)	0.88	1.75 (0.92, 3.39)	10
Spironolactone	2,155	62	29	33	1.35	0.88 (0.53, 1.45)	0.87	1.01 (0.61, 1.66)	0
Hydrochlorothiazide	1,483	35	15	20	1.01	0.75 (0.38, 1.46)	0.87	0.86 (0.44, 1.68)	-3
Negative control	66,172	667	237	430	0.36	0.55 (0.47, 0.65)	0.95	0.58 (0.50, 0.68)	-177
180 day window	66,172	1,835	966	869	1.46	**1.11 (1.01, 1.22)**	0.92	**1.20 (1.10, 1.32)**	167
60 day window	66,172	1,000	536	464	0.81	**1.16 (1.02, 1.31)**	0.96	**1.20 (1.06, 1.36)**	91

[a] sequence ratio
[b] confidence interval
[c] null effect sequence ratio
[d] trend-adjusted sequence difference
[e] significant aSRs in bold

Table S6: Stratified PSSA of the angiotensin receptor blocker to prochlorperazine prescribing cascade (2018-2020) with a 365 day run in period (2017)

	Incident users: index (n)	Incident users: both (n)	Index first (n)	Marker first (n)	Prevalence (%)	Crude SR[a] (95% CI[b])	SR_0[c]	Adjusted SR (95% CI)	Δ_0[d]
365 day window									
Overall	36,850	887	472	415	1.28	**1.14 (1.00, 1.30)**	0.87	**1.30 (1.14, 1.49)**	116
Male	15,015	256	132	124	0.88	1.06 (0.83, 1.36)	0.87	1.22 (0.95, 1.56)	25
Female	21,835	631	340	291	1.56	**1.17 (1.00, 1.37)**	0.87	**1.34 (1.14, 1.56)**	92
Losartan	6,322	146	74	72	1.17	1.03 (0.74, 1.42)	0.87	1.18 (0.85, 1.63)	12
Valsartan	9,825	219	126	93	1.28	**1.35 (1.04, 1.77)**	0.87	**1.55 (1.19, 2.03)**	47
Candesartan	4,284	116	60	56	1.40	1.07 (0.74, 1.54)	0.87	1.23 (0.85, 1.77)	12
Telmisartan	5,899	149	76	73	1.29	1.04 (0.76, 1.44)	0.87	1.19 (0.87, 1.65)	13
Olmesartan medoxomil	9,218	228	116	112	1.26	1.04 (0.80, 1.34)	0.87	1.18 (0.91, 1.54)	19
Negative control	36,850	351	136	215	0.37	0.63 (0.51, 0.78)	0.95	0.67 (0.54, 0.83)	-69
180 day window	36,850	914	502	412	1.36	**1.22 (1.07, 1.39)**	0.93	**1.32 (1.16, 1.50)**	126
60 day window	36,850	516	247	269	0.67	0.92 (0.77, 1.09)	0.96	0.95 (0.80, 1.13)	-13

[a] sequence ratio
[b] confidence interval
[c] null effect sequence ratio
[d] trend-adjusted sequence difference
[e] significant aSRs in bold

Table S7: Stratified PSSA of the angiotensin-converting enzyme inhibitor to prochlorperazine prescribing cascade (2018-2020) with a 365 day run in period (2017)

	Incident users: index (n)	Incident users: both (n)	Index first (n)	Marker first (n)	Prevalence (%)	Crude SR[a] (95% CI[b])	SR_0[c]	Adjusted SR (95% CI)	Δ_0[d]
365 day window									
Overall	45,867	996	580	416	1.26	**1.39 (1.23, 1.58)**	0.87	**1.60 (1.41, 1.81)**	230
Male	22,987	344	211	133	0.92	**1.59 (1.28, 1.97)**	0.87	**1.81 (1.46, 2.26)**	99
Female	22,880	652	369	283	1.61	**1.30 (1.12, 1.52)**	0.87	**1.49 (1.28, 1.74)**	128
Lisinopril	3,036	52	33	19	1.09	**1.74 (1.00, 3.09)**	0.87	**1.99 (1.14, 3.54)**	17
Perindopril	12,771	257	157	100	1.23	**1.57 (1.22, 2.02)**	0.87	**1.80 (1.40, 2.32)**	73
Ramipril	28,333	646	363	283	1.28	**1.28 (1.10, 1.50)**	0.87	**1.47 (1.26, 1.71)**	123
Negative control	45,867	397	159	238	0.35	0.67 (0.55, 0.82)	0.95	0.70 (0.57, 0.86)	-70
180 day window	45,867	1,026	570	456	1.24	**1.25 (1.11, 1.41)**	0.93	**1.35 (1.19, 1.52)**	153
60 day window	45,867	600	316	284	0.69	1.11 (0.95, 1.31)	0.96	1.15 (0.98, 1.35)	42

[a] sequence ratio
[b] confidence interval
[c] null effect sequence ratio
[d] trend-adjusted sequence difference
[e] significant aSRs in bold

Table S8: Stratified PSSA of NSAIDs to prochlorperazine prescribing cascade (2018-2020) with a 365 day run in period (2017)

	Incident users: index (n)	Incident users: both (n)	Index first (n)	Marker first (n)	Prevalence (%)	Crude SR[a] (95% CI[b])	SR_o[c]	Adjusted SR (95% CI)	Δ_0[d]
365 day window									
Overall	143,452	3,028	1,662	1,366	1.16	**1.22 (1.13, 1.31)**	0.87	**1.39 (1.30, 1.49)**	494
Male	60,968	873	453	420	0.74	1.08 (0.94, 1.23)	0.87	**1.23 (1.08, 1.41)**	90
Female	82,484	2,155	1,209	946	1.47	**1.28 (1.17, 1.39)**	0.87	**1.46 (1.34, 1.59)**	403
Ibuprofen	27,690	646	325	321	1.17	1.01 (0.87, 1.18)	0.87	1.16 (0.99, 1.35)	48
Naproxen	6,842	151	84	67	1.23	1.25 (0.91, 1.73)	0.87	**1.43 (1.04, 1.98)**	27
Dexketoprofen	5,123	136	68	68	1.33	1.00 (0.71, 1.40)	0.87	1.14 (0.82, 1.60)	9
Diclofenac	23,367	422	227	195	0.97	1.16 (0.96, 1.41)	0.87	**1.33 (1.10, 1.61)**	60
Aceclofenac	6,233	147	78	69	1.25	1.13 (0.82, 1.56)	0.88	1.29 (0.93, 1.79)	19
Diclofenac, combinations	1,120	18	11	7	0.98	1.57 (0.62, 4.16)	0.88	1.79 (0.71, 4.73)	5
Celecoxib	3,598	69	33	36	0.92	0.92 (0.57, 1.47)	0.87	1.05 (0.65, 1.68)	2
Etoricoxib	16,081	330	197	133	1.23	**1.48 (1.19, 1.85)**	0.87	**1.69 (1.36, 2.11)**	85
Meloxicam	2,738	75	51	24	1.86	**2.12 (1.32, 3.49)**	0.88	**2.42 (1.51, 3.98)**	31
Negative control	143,452	1,941	401	1,540	0.28	0.26 (0.23, 0.29)	0.95	0.27 (0.25, 0.31)	-1116
180 day window	143,452	3,324	1,788	1,536	1.25	**1.16 (1.09, 1.25)**	0.93	**1.26 (1.17, 1.35)**	382
60 day window	143,452	1,784	1,010	774	0.70	**1.30 (1.19, 1.43)**	0.96	**1.35 (1.23, 1.49)**	266

[a] sequence ratio
[b] confidence interval
[c] null effect sequence ratio
[d] trend-adjusted sequence difference
[e] significant aSRs in bold

Table S9: Sensitivity analyses examining medication dyads with a 365-day observation window and a six-month run in period (1st January 2017 - 30th June 2017)[a]

	Incident users: index (n)	Incident users: both (n)	Index first (n)	Marker first (n)	Prevalence (%)	Crude SR[b] (95% CI[c])	SR_0[d]	Adjusted SR (95% CI)	Δ_0[e]
Alpha-1 receptor blocker (cardiac) to prochlorperazine	9,900	295	165	130	1.95	**1.27 (1.01, 1.60)**	0.86	**1.48 (1.17, 1.86)**	57
Alpha-1 receptor blocker (urologic) to prochlorperazine	30,778	686	396	290	1.52	**1.37 (1.17, 1.59)**	0.86	**1.59 (1.37, 1.85)**	156
Beta blockers to prochlorperazine	68,462	1,944	1,114	830	1.89	**1.34 (1.23, 1.47)**	0.86	**1.57 (1.43, 1.71)**	431
CCB[f] to prochlorperazine	77,631	2,187	1,200	987	1.79	**1.22 (1.12, 1.32)**	0.86	**1.42 (1.30, 1.54)**	380
Diuretic to prochlorperazine	78,495	2,533	1,313	1,220	1.98	**1.08 (1.00, 1.16)**	0.86	**1.26 (1.16, 1.36)**	291
ARB[g] to prochlorperazine	42,424	1,313	679	634	1.84	1.07 (0.96, 1.19)	0.86	**1.25 (1.12, 1.39)**	146
ACEI[h] to prochlorperazine	53,453	1,497	845	652	1.84	**1.30 (1.17, 1.44)**	0.86	**1.51 (1.36, 1.67)**	304
NSAID[i] to prochlorperazine	160,643	3,892	2,108	1,784	1.47	**1.18 (1.11, 1.26)**	0.87	**1.36 (1.28, 1.45)**	594

[a] run-in period is 1st January 2017 to 30th September 2017 (272 days) for NSAID to prochlorperazine
[b] sequence ratio
[c] confidence interval
[d] null effect sequence ratio
[e] trend-adjusted sequence difference
[f] calcium channel blocker
[g] angiotensin II receptor blocker
[h] angiotensin-converting enzyme inhibitor
[i] non-steroidal anti-inflammatory drug
[j] significant aSRs in bold