Title: Prescription intervals of medications for chronic use: a cohort study

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Supporting information

Table S 1 ATC groupings

ATC code	**Grouping**
A02BC	Proton pump inhibitors
A06A	Laxatives
A12AX	Calcium +/- vitamin D
A12AA	
A11CC04	
A11CC05	
A11CC03	
B01AC04	Antiplatelets (incl. low dose aspirin)
B01AC24	
B01AC22	
B01AC06	
B01AA03	Oral anticoagulants
B01AB10	
B01AB04	
B01AB05	
B01AE07	
B01AF01	
B01AF02	
B01AF03	
B01AB01	
C07AB	Beta blockers
C08CA02	DHP calcium channel blockers +/- diuretics
C08CA05	

ATC code	Grouping
C08CA13	
C08GA02	
C08CA01	
C09CA04	Angiotensin receptor blockers +/- diuretics
C09CA06	
C09DA03	
C09CA07	
C09CA08	
C09CA03	
C09CA01	
C09DA07	
C09DA04	
C09DA01	
C09BA04	ACE inhibitors +/- diuretics
C09AA02	
C09AA04	
C09AA05	
C10AA	Statins
H03AA	Thyroid hormones and derivatives
M01AE52	NSAIDs
M01AE51	
M01AH02	
M01AH01	
M01AG01	
M01AE02	
M01AE01	
M01AB05	
N02BE51	Paracetamol
N02BE01	
N02AJ13	Opioids
N02AX02	
N02AA01	
N02AA05	
N02AA08	
N02AA56	
N02AB03	
N02AA55	
N02AJ06	
N02AA59	
R03DA03	
R05DA04	
N02AE01	
N03AX12	Gabapentinoids

ATC code	Grouping
N03AX16	
N06AX01	Other antidepressants
N06AX02	
N06AX03	
N06AX04	
N06AX05	
N06AX06	
N06AX07	
N06AX08	
N06AX09	
N06AX10	
N06AX11	
N06AX12	
N06AX13	
N06AX14	
N06AX15	
N06AX17	
N06AX18	
N06AX19	
N06AX22	
N06AX23	
N06AX24	
N06AX25	
N06AX26	
N06AX27	
N06AX28	
N06AX29	
N06AX31	
N06AX62	
N06AB03	
N06AB04	SSRIs and SNRIs
N06AB05	
N06AX21	
N06AX16	
N06AB10	
N06AB06	
N05BA01	
N05BA12	Benzodiazepines and associated drugs
N05CD07	
N05CD08	
N05CF02	
N05BA08	
N05BA02	

ATC code	Grouping
N05BA04	
N03AE01	
N05BA09	
N05CF01	
N05BA06	
R03AC	
R03AK07	Inhaled adrenergics
R03AK06	Inhaled adrenergics with corticosteroids and/or anticholinergics
R03BB	
R03AK11	
R03AK08	

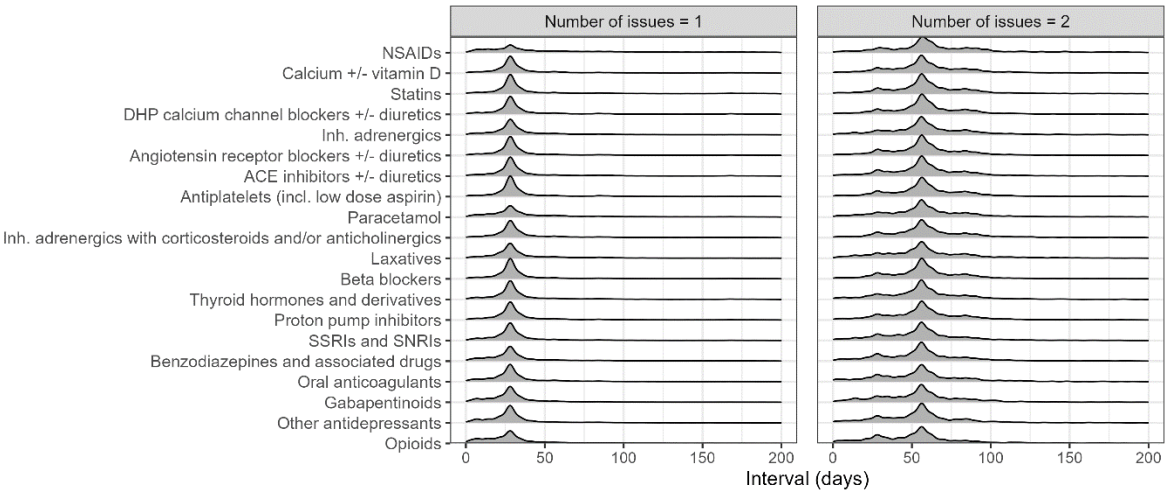

Figure S 2 Marginal empirical interval stratified by drug class and number of prescription repeats.

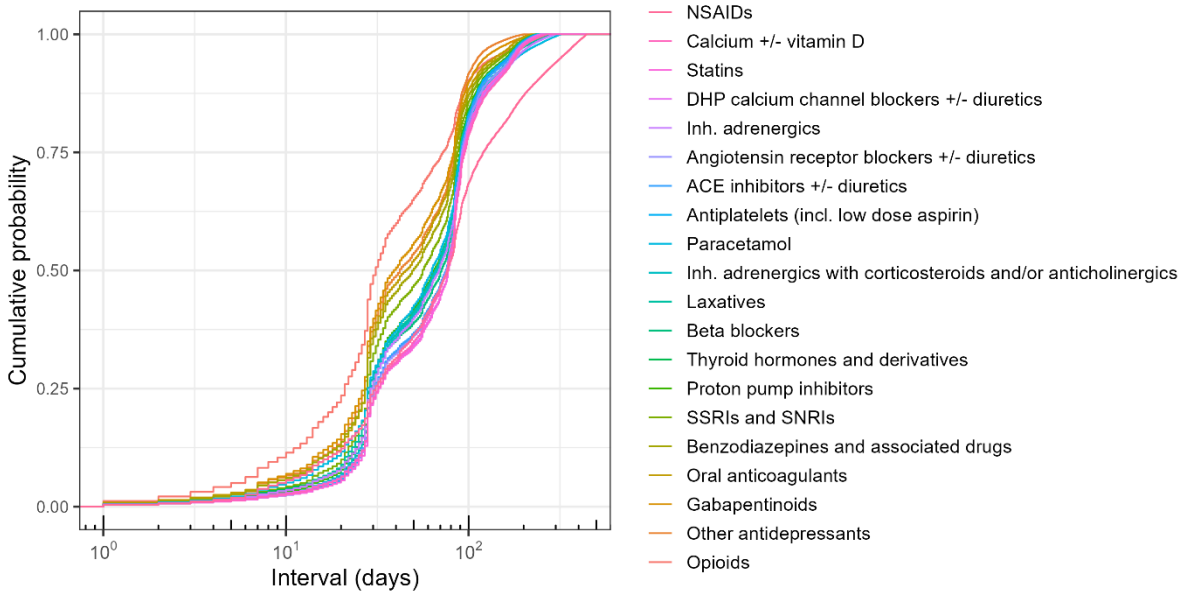

Figure S 3 Marginal empirical distribution functions for each drug class

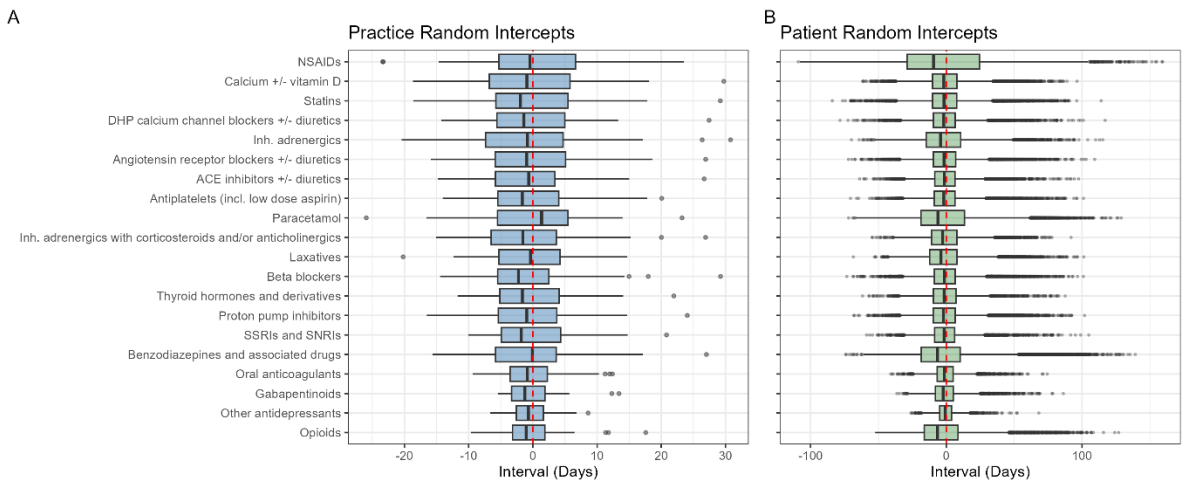

Figure S 4 (a) Boxplot of the distribution of practice-level random intercepts (b) boxplot of the distribution of patient-level random intercepts.

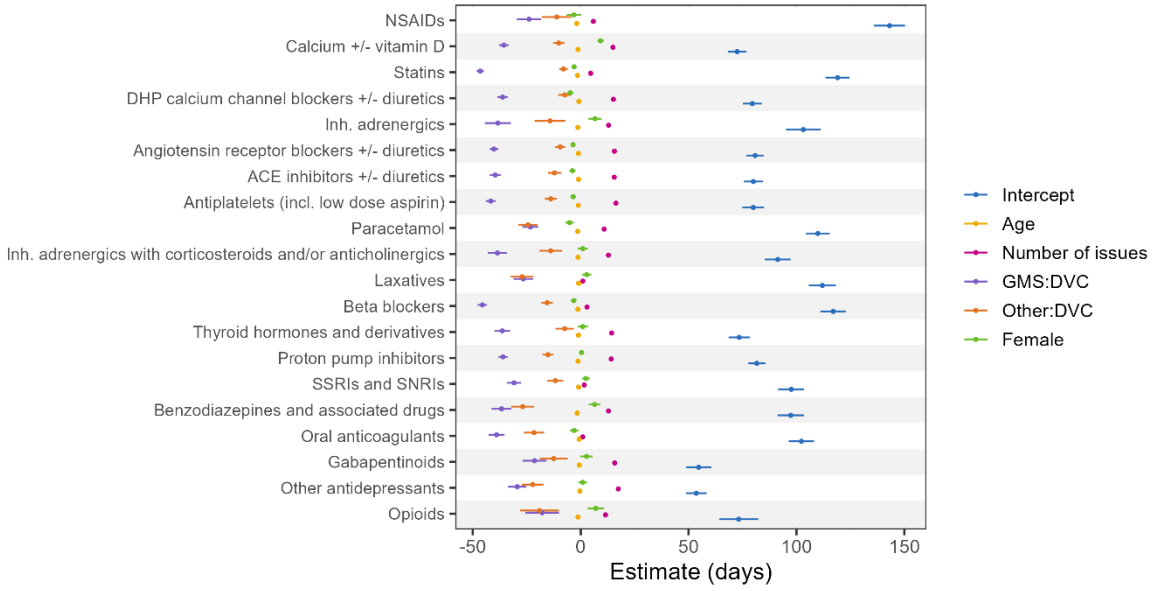

Figure S 5 Fixed effects from the multi-level model without covariate outlier removal.

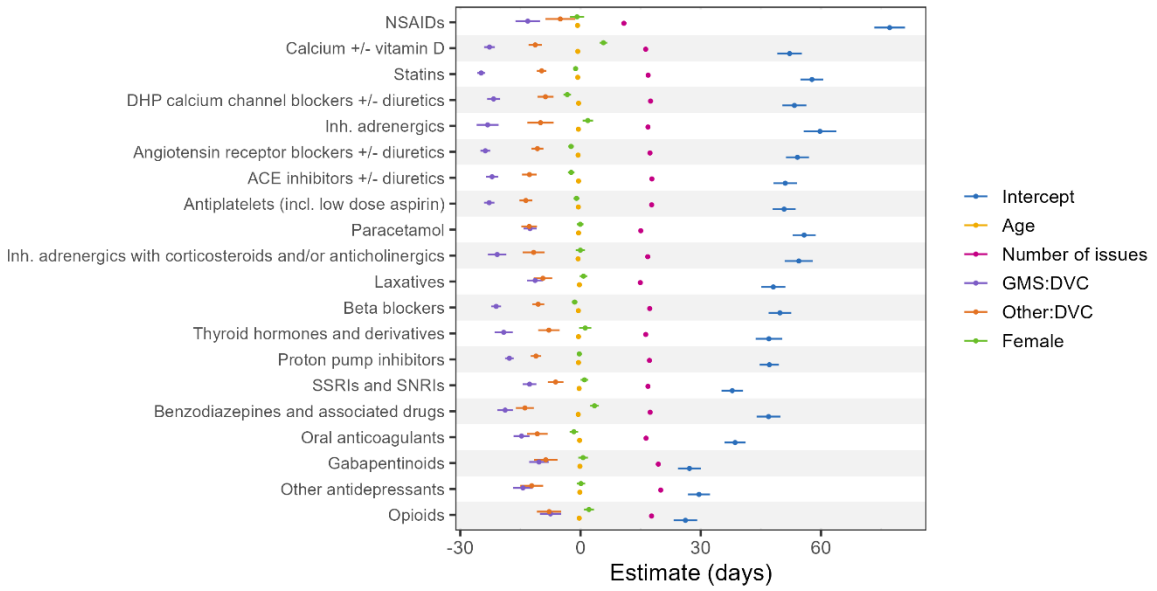

Figure S 6 Fixed effects from the multi-level model with intervals truncated at 270 days.

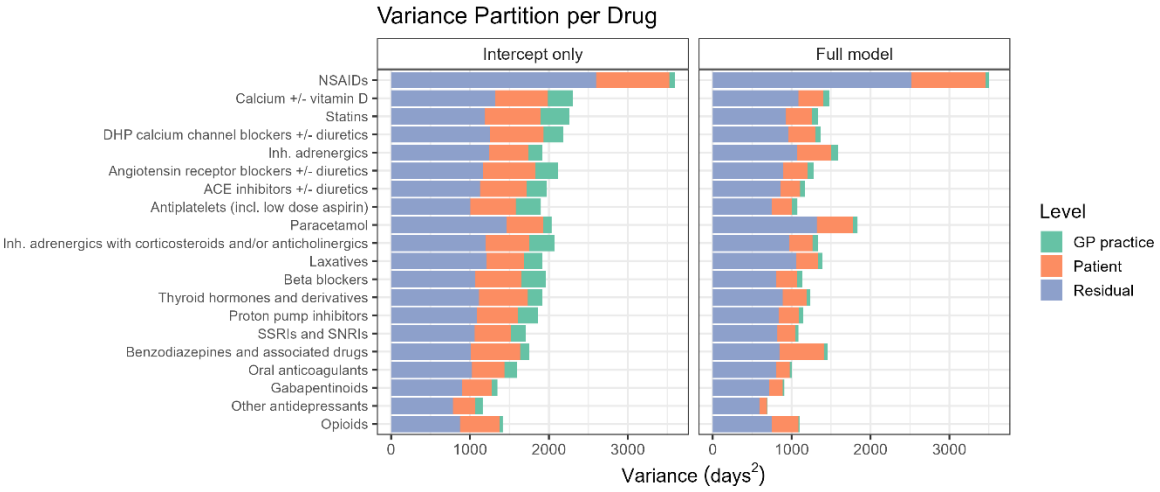

Figure S 7 Variance by level with intervals truncated at 270 days.

Table S 8 Model variance by drug class, model and level.

Drug	Intercept only			Full model		
	Residual	GP level	Patient level	Residual	GP level	Patient level
NSAIDs	6,381.4	2,923.2	121.2	6,346.4	2,834.5	111.9
Calcium +/- vitamin D	1,506.6	849.5	380.8	1,273.3	409.3	88.9
Statins	1,292.4	874.6	429.7	1,026.2	402.3	88.0
DHP calcium channel blockers +/- diuretics	1,357.2	820.7	276.3	1,059.2	406.7	72.3
Inhaled adrenergics	1,796.8	1,000.3	367.2	1,592.9	721.2	123.9
Angiotensin receptor blockers +/- diuretics	1,272.1	837.2	332.1	999.3	385.4	80.9
ACE inhibitors +/- diuretics	1,233.8	753.4	291.8	960.6	325.2	74.9
Antiplatelets (incl. low dose aspirin)	1,092.0	756.4	387.7	832.9	331.5	81.2
Paracetamol	2,264.1	958.9	114.0	2,132.0	1,042.1	83.5
Inhaled adrenergics with corticosteroids and/or anticholinergics	1,410.0	767.5	353.6	1,181.0	421.5	82.5
Laxatives	1,719.9	769.0	239.7	1,569.2	580.3	58.9
Beta blockers	1,148.1	737.2	357.3	880.0	334.5	79.2
Thyroid hormones and derivatives	1,210.7	783.9	196.0	978.2	365.9	55.8
Proton pump inhibitors	1,225.6	713.5	312.7	977.9	357.5	61.3
SSRIs and SNRIs	1,181.7	608.3	212.4	931.6	311.7	52.0
Benzodiazepines and associated drugs	1,280.0	1,061.1	151.0	1,118.8	1,060.5	77.0
Oral anticoagulants	1,139.6	535.7	196.3	908.7	227.4	32.7
Gabapentinoids	1,062.1	476.9	77.8	881.1	292.5	23.8
Other antidepressants	842.1	314.2	98.4	650.0	128.4	14.8
Opioids	1,427.8	1,023.8	53.4	1,308.5	924.5	36.3

WTD model details

The density of the WTD is usually assumed to contain a prevalent component (for renewals of prescriptions) and an incident component (for first time prescriptions). The prevalent component corresponds to a forward (or backward, depending on whether the next or last prescription is used) recurrence density f_{rec} which is a length-biased estimate of the interarrival probability density. The incidence density f_{inc} gives the distribution of new prescriptions and is typically assumed to be constant over the period of interest.

The WTD is parameterised as

$$h(R_i - D) = w\left(\sum_{i=1}^{g} p_i \frac{1 - \int_{-\infty}^{x} f_{IAD,i}}{\mu_i}\right) + \frac{(1-w)}{\Delta}$$

where w is the proportion of prevalent patients, p_i is the prior probability of the waiting time being generated from component $f_{IAD,i}$ and Δ is the width of the time interval of

interest. The waiting time distribution was estimated for each drug class using multiple random index dates. Each index was randomly sampled from a uniform distribution over (t_0, $t_0+\Delta$), where t_0 is the earliest prescription renewal date and Δ was chosen as 365 days. Using multiple random index dates improves the estimate of the FRD by increasing the number of available samples for the optimization. While using random index dates will necessarily induce dependence in the waiting times among samples, the marginal distribution will be unaffected. However, the inclusion of covariates in the WTD model will require consideration as the lack of independence may render the parameter estimates to be biased, and potentially induce further problems in downstream analyses incorporating these estimates (such as biased effect estimates).

The optimal parameters returned by the MLE procedure are known to be dependent on initial conditions due to the presence of nonconvex likelihood surfaces, so we used the best fitting model (in terms of likelihood) from 5 independent runs. The MLE procedure used the *optim* function with the L-BFGS-B optimization method, a quasi-Newton method incorporating box constraints, and a maximum number of 50 iterations was used. We set a lower bound of 0.05 on σ (the standard deviation on the exponential scale) of each interarrival density to prevent spurious fitting to sparse regions, and initialised the distributional parameters using a Gaussian finite mixture model (MClust) of the logarithm of the waiting times. We also regularised σ, w and p using the exponential, softmax and logistic functions respectively. All other parameters were defaults.