Supplementary material

Box S1 Analytical approach and assumptions in application of the PROMPT criteria

The HSE-PCRS database records each individual dispensed item as a single observation and these are nested in a hierarchy, within prescriptions, within months and within patients. Therefore a stepwise approach was taken to the application of the PROMPT criteria. Firstly, criteria dependent on presence or strength of a medicine were applied (for example 'Aspirin doses should not exceed 150 mg/day for anti-platelet therapy') as these could be determined by a single dispensing. Then, data were aggregated by prescription to apply criteria dependent on co-prescribing of medicines (for example 'Esomeprazole or omeprazole should not be used in combination with clopidogrel').

Lastly, data were aggregated by month of dispensing and remaining criteria were applied, including those dependent on omission of a medicine, presence of co-morbidity (for example 'Theophylline should not be used as monotherapy for asthma or COPD') and long-term use of a medicine (for example 'Non-steroidal anti-inflammatory drugs (NSAIDs) should not be used long-term (greater than three months)'). Long-term use was classified using the month of dispensing in the HSE-PCRS database to determine dispensing in consecutive months.

For criteria required drug dosage information, for example, 'Proton pump inhibitors should not be prescribed at doses above the recommended maintenance dosage for greater than eight weeks', dosage was evaluated by calculating the Defined Daily Dosages (DDDs) using the strength and prescribed quantity of consecutive prescriptions as follows:

$$\text{Number of DDDs} = \frac{\text{Quantity} \times \text{Strength}}{\text{DDD}}$$

DDDs are a validated statistical measure of drug consumption maintained by the WHO and a DDD is assumed average maintenance dose per day for a drug used for its main indication in adults.

The following assumptions underlay the application of specific criteria:

- Nitrofurantoin was being prescribed in all cases for uncomplicated lower urinary tract infections. (I1)
- Alpha adrenoreceptor blockers were being prescribed in all cases for hypertension. (C1)
- Tricyclic antidepressants (amitriptyline and nortriptyline) at daily doses <75mg were not being prescribed for depression and daily doses of ≥75mg were being prescribed for depression. (CNS2)
- No dispensing of a medicine from the same drug class or with the same indication in the previous two months indicated first-line use. (G1, CNS2)
- Where diagnostic information was not available, dispensing of any medicine indicated for the treatment of a condition in the British National Formulary was used as a proxy for a diagnosis. (CNS3, CNS4)
- 'Strong opioids should not be prescribed without the co-prescribing of laxatives' was analysed by assessing drugs listed as strong opioids in the BNF without the co-prescribing of at least one osmotic or stimulant laxative.

Table S1 Description of data collected during TILDA interview using for adjustment in multivariate regression models

Variable	Format	Description of categories
Age (in years)	Continuous	N/A
Sex	Binary	Male (reference) or Female
Number of regular medicines[a]	Continuous	N/A
Number of reported conditions[b]	Categorical	0 (reference)
		1
		2
		3 or more
Level of educational attainment	Categorical	Primary (reference)
		Secondary
		Tertiary
Number of ED visits at baseline	Continuous	N/A
Number of GP visits at baseline	Continuous	N/A
Depressive symptoms[c]	Categorical	None (reference)
		Sub-clinical
		Clinical
CASP-R12 score at baseline[d]	Continuous	N/A

[a] Number of unique medicines (including all ATC codes and defining a unique medicines based on the level 3 ATC code e.g. C10AA) dispensed in at least three months to a participant during the 12 months of PIP exposure measurement in HSE-PCRS (with an upper bound of 10 or more medicines).

[b] The number of doctor-diagnosed chronic conditions reported by the participants at the TILDA interview from the following list: cardiovascular disease (heart attack, heart failure or angina), cataracts, hypertension, high cholesterol, stroke, diabetes, lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, peptic ulcer, and hip fracture.

[c] Level of symptoms screened by the Centre for Epidemiological Studies Depression scale (CES-D) in the self-completion questionnaire at follow-up. None corresponds to a CES-D score of 0-7, sub-clinical to a score of 8-15, and clinical to a score of >15.

[d] CASP-R12 was included in the self-completion questionnaire rather than in participant interview

Table S2 Sensitivity analysis comparing parameter estimates with 95% CIs by outcome for multivariate regression and marginal structural models (MSMs)

	Unweighted	p	Weighted (MSMs)[a]	p
Any PROMPT PIP (versus none)				
ED visits (IRR (95% CI))	0.95 (0.62, 1.45)	0.801	0.77 (0.47, 1.26)	0.308
GP visits (IRR (95% CI))	0.99 (0.86, 1.14)	0.893	1.02 (0.88, 1.18)	0.834
CASP-R12 score (β coeff (95% CI))	-0.26 (-1.22, 0.69)	0.588	-0.07 (-1.12, 0.98)	0.902

[a] Weighted by product of stabilised inverse probability of exposure and probability of remaining uncensored at follow-up.