Supplement

Text S1

We have assumed that the 9% of opioid prescriptions for cancer pain, equate to 9% of the overall costs. This is based on a review of primary care opioid prescribing, which showed that the mean annual days of supply per patient during the study period was longer for patients in the non-cancer group (130.6 ± 124.2 days) than in the cancer group (88.9 ± 95.8 days) (Zin et al., 2014). Also, the mean number of prescriptions issued per patient per year was slightly higher in the non-cancer group (from 6.0 in 2000 to 9.5 in 2010) than in the cancer group (from 4.6 to 8.8), as was the mean annual defined daily dose in the non-cancer group than in the cancer group for all four strong opioids, that is, morphine (0.73 ± 0.28 vs. 0.12 ± 0.04), fentanyl (0.46 ± 0.29 vs. 0.06 ± 0.24), oxycodone (0.24 ± 0.19 vs. 0.038 ± 0.028) and buprenorphine (0.23 ± 0.15 vs. 0.008 ± 0.006) (Zin et al., 2014). End of life care: most of this is excluded by excluding the 9% of costs for cancer pain and excluding prescriptions for those who are on these drugs for < 3 months.

Text S2

Opioids worked example of unnecessary medicine cost using 5 months of data and 1 month gap method (Table S1). As the first 3 months of prescribing is indicated the calculation begins at month 4.

Table S1

Five months of prescribing data for opioids, November 2017-March 2018

Number of months prescribed (1)	**Total people prescribed (2)**	**85% of people prescribed (3)**	**Number unnecessarily prescribed (4)**
1	448018	380815	-
2	143641	122095	-
3	121533	103303	-
4	82932	70492	17623
5	76745	65233	26093
Total	872869	741939	43716

Step 1: to account for the 'small' proportion of people who may obtain good pain relief with opioids in the long-term and have indicated prescribing. we discounted 15% of people prescribed from each continuous prescription period from the durational data. We therefore considered 85% of the total sample. **This is shown in column 3 of Table S1.**

Step 2: using this sample (85% of the total number) we discounted three months of indicated prescribing for each of the continuous prescribing periods to arrive at a pure estimate of unnecessary prescribing. **This is shown in column 4 of Table S1. For example, if 65233 people were prescribed for 5 months, the number of unnecessary prescriptions (i.e. discounting the indicated prescribing period) would be =65233 – ((65233÷ 5)*3)=26093.**

Step 3: we aggregated the data from step 2. **In Table S1 this is the total of column 4 = 43716.**

Step 4: we calculated the estimated % of unnecessary costs by dividing the total from step 3 by the total number of people from step 1. **This is 43716 ÷ 741939=6%**

Step 5: we calculated unnecessary cost by applying the % of unnecessary costs to 76% of the three year NIC and Dispensing Cost (see note below for explanation of why we take 76% of the costs). **The worked example takes a 5 month sample, therefore if we consider 5 months of costs for opioids they will be:**

76% of 5 months Net Ingredient Cost (NIC) for Opioids = £95,535,509

Unnecessary medicine cost for 5 months = 6% of £95,535,509= £5,732,131

Note. We take 85% of the sample from the durational data (step 1) and 76% of the cost (step 5). Both have 15% deducted to account for the 'small' proportion of people who may obtain good pain relief with opioids. The difference between the deductions is because the durational data has already excluded opioid prescribing for cancer pain but it was not possible for the NHSBSA to exclude the costs for cancer prescribing from the NIC and dispensing cost, which, based on the 9% of people prescribed opioids for cancer pain, we estimate as 9% of costs. Therefore 76% of the cost is taken (15+9% deducted). We have assumed that the 9% of opioid prescriptions for cancer pain (Taylor et al., 2019), equate to 9% of the overall costs (see Text S1 in the supplement for justification for this assumption).

Table S2: chemical substance and BNF code (British National Formulary) included within each medicine class (obtained from the Technical Annexe of the Public Health England Report: dependence and withdrawal associated with some prescribed medicines) (Taylor et al., 2019)

Chemical name	BNF paragraph	Medicine class
Agomelatine	40304	Antidepressants
Amitriptyline	40301	Antidepressants
Amoxapine	40301	Antidepressants
Citalopram	40303	Antidepressants
Clomipramine	40301	Antidepressants
Dosulepin	40301	Antidepressants
Doxepin	40301	Antidepressants
Duloxetine	40304	Antidepressants
Escitalopram	40303	Antidepressants
Fluoxetine	40303	Antidepressants
Flupentixol	40304	Antidepressants
Flupentixol dihydrochloride	40304	Antidepressants
Fluvoxamine	40303	Antidepressants
Imipramine	40301	Antidepressants
Isocarboxazid	40302	Antidepressants
Lofepramine	40301	Antidepressants
Maprotiline	40301	Antidepressants
Mianserin	40301	Antidepressants
Mirtazapine	40304	Antidepressants
Moclobemide	40302	Antidepressants
Nefazodone	40304	Antidepressants
Nortriptyline	40301	Antidepressants
Oxitriptan	40304	Antidepressants
Paroxetine	40303	Antidepressants
Phenelzine	40302	Antidepressants

Chemical name	BNF paragraph	Medicine class
Protriptyline	40301	Antidepressants
Reboxetine	40304	Antidepressants
Sertraline	40303	Antidepressants
Tranylcypromine	40302	Antidepressants
Trazodone	40301	Antidepressants
Trimipramine	40301	Antidepressants
Tryptophan	40304	Antidepressants
Venlafaxine	40304	Antidepressants
Vortioxetine	40304	Antidepressants
Buprenorphine	40702	Opioid pain medicines
Co-codamol	40701	Opioid pain medicines
Codeine	40702	Opioid pain medicines
Co-dydramol	40701	Opioid pain medicines
Cyclizine + Dipipanone	40702	Opioid pain medicines
Cyclizine + Morphine	40702	Opioid pain medicines
Dextromoramide	40702	Opioid pain medicines
Diamorphine	40702	Opioid pain medicines
Dihydrocodeine	40702	Opioid pain medicines
Dihydrocodeine + Paracetamol	40701	Opioid pain medicines
Dipipanone + Cyclizine	40702	Opioid pain medicines
Fentanyl	40702	Opioid pain medicines
Hydromorphone	40702	Opioid pain medicines
Meptazinol	40702	Opioid pain medicines
Methadone	40702	Opioid pain medicines
Morphine	40702	Opioid pain medicines
Morphine + Cyclizine	40702	Opioid pain medicines
Naloxone + Oxycodone	40702	Opioid pain medicines
Oxycodone	40702	Opioid pain medicines
Oxycodone + Naloxone	40702	Opioid pain medicines
Papaveretum	40702	Opioid pain medicines

Chemical name	BNF paragraph	Medicine class
Paracetamol + Dihydrocodeine	40701	Opioid pain medicines
Paracetamol + Tramadol	40702	Opioid pain medicines
Pentazocine	40702	Opioid pain medicines
Pethidine	40702	Opioid pain medicines
Tapentadol	40702	Opioid pain medicines
Tramadol	40702	Opioid pain medicines
Tramadol + Paracetamol	40702	Opioid pain medicines
Gabapentin	40801	Gabapentinoids
Pregabalin	40801	Gabapentinoids
Chlordiazepoxide	40102	Benzodiazepines
Diazepam	40102	Benzodiazepines
Flurazepam	40101	Benzodiazepines
Loprazolam	40101	Benzodiazepines
Lorazepam	40102	Benzodiazepines
Lormetazepam	40101	Benzodiazepines
Nitrazepam	40101	Benzodiazepines
Oxazepam	40102	Benzodiazepines
Temazepam	40101	Benzodiazepines
Zaleplon	40101	Z-drugs
Zolpidem	40101	Z-drugs
Zopiclone	40101	Z-drugs

Table S3

Studies used for developing the criteria for unnecessary antidepressant prescribing which assess long-term antidepressant prescribing for people with depression, depressive symptoms, or anxiety disorders and whether continued use of antidepressants is indicated.

Study	**Overview**	**Result**
Cruickshank et al., (2008) UK	Reviewed 83 patients across 12 GP practices who had been prescribed an antidepressant for depression for > 1.5 years.	31% (26/83) had no clear clinical reason for continued use.
Ambresin et al., (2015) Australia	Out of 787 patients with depressive symptoms, 145 were prescribed antidepressants for ≥ 2 years.	32% (47/145) reported no episode of major depression for the last year – which could suggest that stopping antidepressants could be considered
Eveleigh et al., (2017) Netherlands	Long-term users (with a depressive or anxiety disorder) were defined as being prescribed antidepressants for ≥ 9 months: 6442 long-term users were identified.	37**%** (2411/6442) were deemed eligible for an antidepressant withdrawal study, by their GP.
Weighted mean	-	**Over these 3 studies 37.2% (2484/6670) of long-term antidepressant users may be unnecessarily prescribed.**

Table S4: Sensitivity analysis of prescription costs for mild depression (10%-40%)

Year	2015-16	2016-17	2017-18
10%	£14,733,364.95	£13,713,919.05	£11,818,426.85
12%	£17,680,037.94	£16,456,702.87	£14,182,112.22
14%	£20,626,710.93	£19,199,486.68	£16,545,797.59
16%	£23,573,383.92	£21,942,270.49	£18,909,482.96
18%	£26,520,056.92	£24,685,054.30	£21,273,168.33
20%	£29,466,729.91	£27,427,838.11	£23,636,853.71
22%	£32,413,402.90	£30,170,621.92	£26,000,539.08
24%	£35,360,075.89	£32,913,405.73	£28,364,224.45
26%	£38,306,748.88	£35,656,189.54	£30,727,909.82
28%	£41,253,421.87	£38,398,973.35	£33,091,595.19
30%	£44,200,094.86	£41,141,757.16	£35,455,280.56
30%	£44,200,094.86	£41,141,757.16	£35,455,280.56
32%	£47,146,767.85	£43,884,540.98	£37,818,965.93
34%	£50,093,440.84	£46,627,324.79	£40,182,651.30
36%	£53,040,113.83	£49,370,108.60	£42,546,336.67
38%	£55,986,786.82	£52,112,892.41	£44,910,022.04
40%	£58,933,459.81	£54,855,676.22	£47,273,707.41

References

Ambresin, G., Palmer, V., Densley, K., Dowrick, C., Gilchrist, G., & Gunn, J. M. (2015). What factors influence long-term antidepressant use in primary care? Findings from the Australian diamond cohort study. *Journal of Affective Disorders*, *176*, 125–132. https://doi.org/10.1016/j.jad.2015.01.055

Cruickshank, G., MacGillivray, S., Bruce, D., Mather, A., Matthews, K., & Williams, B. (2008). Cross-sectional survey of patients in receipt of long-term repeat prescriptions for antidepressant drugs in primary care. *Mental Health in Family Medicine*, *5*(2), 105–109.

Eveleigh, R., Muskens, E., Lucassen, P., Verhaak, P., Spijker, J., van Weel, C., Voshaar, R. O., & Speckens, A. (2018). Withdrawal of unnecessary antidepressant medication: A randomised controlled trial in primary care. *BJGP Open*, *1*(4), 1–11. https://doi.org/10.3399/bjgpopen17X101265

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