The costs incurred by the NHS in England due to the unnecessary prescribing of dependency-forming medications

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Abstract

This cross-sectional study estimates the costs incurred by the National Health Service (NHS) in England as a consequence of the unnecessary prescribing (i.e. non-indicated or dispensable) of dependency-forming medicines (antidepressants, opioids, gabapentinoids, benzodiazepines, Z-drugs). It assesses prescribing in primary care from April 2015-March 2018. Analyses were based upon the following data sets: the number of adults continuously prescribed dependency forming medications and the duration of prescriptions (obtained from Public Health England); the Net Ingredient Cost (NIC) and the dispensing costs for each medicine (obtained from the NHS Business Service Authority [NHSBSA]). Consultation costs were calculated based on guideline recommendations and the number of consultations evidenced in prior research for long-term medication monitoring. Across opioids, gabapentinoids, benzodiazepines, Z-drugs the total estimated unnecessary cost over three years (April 2015-March 2018) was £1,367,661,104 to £1,555,234,627. For antidepressants the total estimated unnecessary cost for one year was £37,321,783 to £45,765,504. The data indicate that the NHS in England may incur a significant estimated mean annual loss of £455,887,035 to £518,411,542 for opioids, gabapentinoids, benzodiazepines, Z-drugs and an estimated annual loss of £37,321,783 to £45,765,504 for antidepressants. Combined this gives an estimated annual loss of £493,208,818 to £564,177,046 as a result of non-indicated or dispensable prescribing of dependency-forming medicines. Estimates are conservative and figures could be higher.

Introduction

Low-value care is defined within the field of health economics as services and interventions that provide little to no benefit to patients, have the potential to cause harm, as well as to incur unnecessary costs and waste limited healthcare resources (Maratt et al., 2019). In recent years, the identification of wasteful health care practices has increasingly become a health care policy priority, with the UK's National Institute for Health and Care Excellence (NICE), the US Preventive Services Task Force, and international initiatives such as the Choosing Wisely Campaign, having jointly advanced nearly 2500 recommendations to reform services considered as wasteful under some circumstances (Miller et al., 2018).

To identify diverse incidences of low-value care, health economists have examined the design, effectiveness and quality of an array of health interventions in different settings. Studies have chartered various forms and outcomes of wasteful practice by using different analytical measures, including patient reports, clinical outcomes, cost-related and the inappropriate or unnecessary use of interventions (Miller et al., 2018). The common focus on inappropriate or unnecessary medication use, including overuse, has been increasingly applied to various patient groups for whom interventions were not indicated or recommended (Miller et al., 2018). For example, such usage has been examined by several studies examining overuse in patients not requiring treatment, such as statins for primary prevention of cardiovascular disease (Byrne et al., 2019); antibiotics for the treatment of viral upper respiratory infections (Jenkins et al., 2013), or acid suppressants for low-risk inpatients with specific conditions (Gupta et al., 2013).

Questions regarding the over-use and unnecessary use of medicines has gained wide attention in the United Kingdom following the British Medical Journal's Too Much Medicine campaign (Godlee, 2019), and a recent UK Government-commissioned review which estimating, on the basis of expert testimony, that 10% of items dispensed in NHS primary care are overprescribed, and are therefore unnecessary (DHSC, 2021). In relation to dependency-forming psychoactive drugs specifically, the issue of unnecessary prescribing has gained particular salience following the publication of Public Health England's (PHE) evidence review of prescribed medicines associated with

dependence and withdrawal (Public Health England, 2019). This review constituted the most comprehensive public evidence review of dependency-forming medicines to date, showing that, in 2017 to 2018, 11.5 million adults in England (26% of the adult population) received one or more prescriptions for a dependency forming medicine (with 'dependency' defined as 'an adaptation to the repeated exposure to a drug', usually being characterised by withdrawal, and sometimes tolerance). The medicines in the review's scope were benzodiazepines, z-drugs, gabapentin and pregabalin (gabapentinoids), opioids for chronic non-cancer pain and antidepressants. The review suggested that there may be significant unnecessary (i.e. non-indicated or dispensable) prescribing of such drugs, as data on duration of use showed substantial prescribing beyond what current guidelines and most recent evidence suggests. Alongside this, the review highlighted significant unmet need concerning healthcare provision for patients adversely affected by prescribed drug dependency and difficulties withdrawing from these drugs.

Severe withdrawal symptoms for all classes of dependency-forming drugs are common and can include muscle spasms, diarrhoea, dizziness, insomnia, nausea, anxiety and agitation, brain zaps, flu-like symptoms, and sudden changes in emotion and mood (Cosci & Chouinard, 2020; Lerner & Klein, 2019). Withdrawal symptoms can be mild and short-lived, but in many cases can last for weeks, months or even years (Lerner & Klein, 2019). When protracted and severe, withdrawal can have a significant negative impact on people's lives with patients describing loss of jobs, loss of homes, loss of friends, and even suicidality (Guy et al., 2020). Evidence suggests that 50% of people who use benzodiazepines for four weeks experience withdrawal reactions, rising to 100% for usage over six months, with 40% reporting withdrawal as moderate or severe (de Las Cuevas et al., 2003; Hood et al., 2014). Antidepressant withdrawal has been found to affect more than half (56%) of people trying to discontinue, with up to 25% reporting withdrawal as severe (Davies & Read, 2019). Opioid dependence can occur within 2-3 weeks and withdrawal can be acute and severe, including insomnia, anxiety, and restlessness (Lerner & Klein, 2019). Gabapentin withdrawal has been found to occur within 12 hours to seven days of drug discontinuation and can include agitation, confusion, disorientation and anxiety (Lerner & Klein, 2019; Mah & Hart, 2013; Mersfelder & Nichols, 2016; Norton, 2001).

Public Health England advanced a series of recommendations to address the absence of dedicated services for people adversely affected by prescribed drug dependence, which included a call for further research into the effects of long-term drug exposure; advanced practitioner training on the effective management of dependency and withdrawal, and consideration for establishing a national helpline and face-to-face support for patients adversely affected. In light of these recommendations, the former Secretary of State for Health, Matt Hancock, announced, in Dec 2019, the UK Government's commitment to consider implementing a 24/7 support helpline (Conservatives, 2019). Subsequently, NHS England & NHS Improvement established a Withdrawal Services Working Group to determine the type and scope of provision required.

Prescribed drug dependency, withdrawal and unnecessary use is not confined to the UK, but is an international issue, being found wherever these medicines are widely prescribed. The increase in the prescription of opioids in the US since the 1990s is well documented, and although prescriptions have fallen since 2011, overdose deaths have risen over the same period, quadrupling since 1999 (WONDER, 2020). The number of benzodiazepine prescriptions have doubled in the US since 2008 (Lembke et al., 2018), mostly linked to longer-term use, while UK primary care prescribing of gabapentioids has risen 88% in the last decade (Sehmi et al., 2019), a trend found in other national contexts (Cairns et al., 2019). Antidepressant prescribing at levels comparable or higher to those found in the UK, have also been reported in Canada, Australia, Portugal and Iceland (OECD, 2019). In the USA antidepressant use has increased from 7.7% of the general population in 1999- 2002 to 12.7% in 2011-2014, a 65% increase, with 25.3% of people who took antidepressants 2011-2014 taking them for 10 years or more (Pratt et al., 2017). Increases in prescriptions and duration of use of all dependency forming drugs may be due to multiple factors including inadequate alternative provision, pharmaceutical sponsorship, withdrawal experiences inhibiting full discontinuation and withdrawal being misdiagnosed as relapse, with drugs being reinstated (Leeuwen et al., 2021).

As the human costs of prescribed drug dependency and withdrawal are now well documented for each class of dependency forming medication (Public Health England, 2019) this study aims to determine the annual low-value care costs of unnecessary prescribing of dependency forming drugs within the NHS in England.

Methods

We aimed to identify and cost annual unnecessary use of dependency forming drugs, a key measure of low-value care. This cross sectional study undertook an 'additive' approach (Miller et al., 2018), which entails first identifying the specific circumstances in which use of the assessed interventions constitutes low-value care (i.e. unnecessary prescribing); measuring levels of inappropriate prescribing, and measuring the costs incurred in such low-value use including unnecessary medicine (Net Ingredient Cost [NIC]), dispensing and consultation costs.

Inclusion and exclusion criteria: We obtained medicine costs and prescribing duration by number of adults prescribed for the following medicines: antidepressants, benzodiazepines, z-drugs, gabapentinoids, and opioids for non-cancer pain (see supplement, Table S2 for the full list of included medicines). Reflecting the criteria used in the PHE report, we included: adults in England (18+ years) and excluded: prescribing for drug misuse and dependence (exclusion of FP10MDA forms for instalment prescribing, opioids prescribed for opioid substitution treatment (OST)); prescribing of opioid medicines for cancer-related pain; prescribing by dentists (FP10-D forms); prescriptions where no NHS number was shown (and therefore linkage was not possible) (Taylor et al., 2019).

Unnecessary prescribing criteria: the criteria for unnecessary prescribing for each medicine class are detailed in Table 1. Unnecessary prescribing is defined here as prescribing that either contravenes current NICE (National Institute for Health and Care Excellence) guidelines (i.e. non-indicated prescribing), or where no evidence for efficacy or continued clinical need exists despite long-term use in the community (i.e. dispensable prescribing). Criteria for what constitutes non-indicated and dispensable prescribing were developed through consultation of the NICE guidelines and peer-reviewed research papers, discussion within the multidisciplinary project team

(academics, psychologists, an economist, a psychiatrist, and persons with lived experience) and consultation with subject experts (primary and secondary care clinicians, academics).

Table 1

Criteria for unnecessary (non-indicated or dispensable) prescribing.

Medicine class	Criteria for unnecessary (non-indicated or dispensable) prescribing	Summary: criteria for unnecessary prescribing	Estimated % of <u>total</u> costs that are unnecessary*
Antidepressants	Guideline recommendations are for antidepressants to be continued from 6 months to 2 years after remission (NICE, 2009). Three studies assessed unnecessary prescribing in long-term antidepressant users (defined variously as ≥ 9 months, > 1.5 years, ≥ 2 years) for the treatment of depression or anxiety (Ambresin et al., 2015; Cruickshank et al., 2008; Eveleigh et al., 2017) (Table S3). Overall 37.2% (weighted mean) were unnecessarily prescribed. 73.7% of antidepressant prescriptions are estimated to be for depression or anxiety (Wong et al., 2016). Therefore 37.2% of the 73.7% of long-term antidepressant users prescribed for depression and/or anxiety (≥ 2 years) may be prescribed these drugs unnecessarily. This means that 27.4% of all ≥ 2 years antidepressant prescriptions for depression or anxiety are dispensable.	27.4% of prescriptions for those prescribed antidepressants for depression or anxiety for ≥ 2 years	7.6-7.9%

Medicine class	Criteria for unnecessary (non-indicated or dispensable) prescribing	Summary: criteria for unnecessary prescribing	Estimated % of <u>total</u> costs that are unnecessary*
	Sensitivity analysis Since there are uncertainties about the evidence base for the long-term efficacy of antidepressants, due to the discontinuation design of randomised trials (Baldessarini & Tondo, 2019; Deshauer et al., 2008; Hengartner, 2020; Recalt & Cohen, 2019), we did a sensitivity analysis involving total costs for everyone prescribed antidepressants for > 2 years		
Benzodiazepines and Z-drugs	Given the risk of adverse reactions and dependence, benzodiazepines and z-drugs are not advised to be prescribed for more than 4 weeks (NICE, n.d., 2010).	Prescriptions for > 4 weeks	Benzodiazepines: 67-72% Z-drugs: 71-76%
Opioids (non-cancer pain)	Opioids are considered effective analgesics for acute pain, cancer pain, palliative care and end of life pain. However, there is little evidence that they are helpful for long term, non-cancer pain, and recent guidelines state they are not effective for > 12 weeks and do not recommend them (NICE, 2021a; Petzke et al., 2020). The Royal College of Anaesthetists'	85% of long-term users (prescribed for > 12 weeks) for non-cancer pain	46-53%

Medicine class	Criteria for unnecessary (non-indicated or dispensable) prescribing	Summary: criteria for unnecessary prescribing	Estimated % of total costs that are unnecessary*
	Faculty of Pain Medicine concur that there is little evidence of efficacy for long term pain, but state that 'a small proportion of people [who] may obtain good pain relief with opioids in the long-term if the dose can be kept low and especially if their use is intermittent' (Faculty of Pain Medicine, n.d.). As no precise figures have been published to indicate what this 'small proportion' constitutes, we estimate, based on expert testimony, that this proportion constitutes 15% of those seeking non-cancer pain relief >12 weeks. Accordingly, 85% of long-term users > 12 weeks for non-cancer pain are classed as subject to unnecessary prescribing.		
Gabapentinoids	Gabapentinoids are recommended for the treatment of neuropathic pain and not for other types of pain (e.g. low back pain, osteoarthritis) due to lack of evidence for efficacy (Mathieson et al., 2020; NICE, 2021a; Wallach & Ross, 2018). A recent large review of UK primary care prescribing showed that 52.0% of gabapentin and 54.8% of pregabalin prescriptions in 2017 were off-label (Montastruc et al.,	Prescriptions for non-neuropathic pain: 41.8% of gabapentin and 31.9% of pregabalin prescriptions Prescriptions for psychiatric	Non-neuropathic pain: 41.8% of gabapentin and 31.9% of pregabalin prescriptions Psychiatric indications: 11.7%-12.6% of

Medicine class	Criteria for unnecessary (non-indicated or dispensable) prescribing	Summary: criteria for unnecessary prescribing	Estimated % of <u>total</u> costs that are unnecessary*
	2018). Of this off-label prescribing, 80.4% of gabapentin and 58.3% of pregabalin were for non-neuropathic pain. Therefore 41.8% of gabapentin and 31.9% of pregabalin prescriptions are dispensable as they are for non-neuropathic pain. Additionally, we have estimated on the basis of expert testimony and evidence (Wettermark et al., 2014) that a further 15% of all long-term >4 weeks gabapentinoid prescribing is also dispensable, as such prescribing is for psychiatric indications where there is no established efficacy beyond 4 weeks (Horowitz et al., 2021).	indications beyond 4 weeks (15% of total)	all gabapentinoid prescriptions

*Based on durational prescribing data from PHE, the range represents the two methods of calculating prescription duration from PHE as shown in Table 2, one-month-two month gap (see 'sample and data' for full description) (Taylor et al., 2019)

Sample and data

Durational data: data on the number of adults continuously prescribed medicines associated with dependence, as well as the duration of use, were obtained from a retrospective analysis reported in the technical annexe of the PHE Report (Appendix C) (Taylor et al., 2019). The PHE analysis used data from the NHS Business Services Authority (NHSBSA) prescriptions database at CCG (Clinical Commissioning Groups)

and GP (primary care physicians) practice level over a three year period (April 2015-March 2018).

The PHE analysis considered everyone in receipt of a prescription dispensed in primary care in March 2018 and then reported the duration of the prescription up to and including that month, back to the start of the prescription or April 2015, whichever was later. We included two methods for calculating the duration of continuous prescribing. **The one-month gap** method considers any prescriptions two months apart as linked – i.e. a single month with no prescriptions submitted would not interrupt a period of continuous prescribing, but it would end when there were two consecutive months without a prescription. **The two-month gap** method considers prescriptions three months apart as linked – two consecutive months without a prescription would not interrupt the period of continuous prescribing, only three consecutive months without a prescription would do so. A summary of this data (estimated duration of and number of adults continuously prescribed medicines associated with dependence) is shown in Table 2. Data using the one month gap method were obtained from the technical annexe of the PHE Report (Appendix C)(Taylor et al., 2019) and for the two month gap method, through a data request to PHE.

Costs: Three **c**osts were reported:

1) Medicine costs - Net Ingredient Cost (NIC) for each medicine for the period between April 2015 and March 2018 were obtained through a data request to the NHSBSA. NIC is the basic cost of a drug (excluding VAT).

2) Medicine costs - total dispensing costs for each medicine reimbursed to doctors and pharmacies for the period between April 2015 and March 2018 were obtained through a data request to the NHSBSA.

3) Consultation costs: these were estimated at £33 per consultation (Curtis & Burns, 2019) with the average consultation lasting 9.22 mins (Curtis & Burns, 2019). While around 1/3 of consultations, including medicine reviews, may be undertaken by advanced nurse practitioners (ANPs) (Lay-Flurrie et al., 2019) research shows that

consultation costs are likely to be the same or slightly more for ANPs (Hollinghurst et al., 2006), perhaps owing to longer consultation lengths (Evans et al., 2020). As guidelines do not give clear recommendations for the frequency of review, either during or after the acute treatment phase, the number of primary care consultations accompanying long-term treatment with benzodiazepines, Z-drugs, opioids or gabapentinoids are based on research indicating the number of consultations reported for the long-term monitoring of antidepressants (Sinclair et al., 2014), excluding >1 year opioid prescribing where at least two reviews are advised annually(Faculty of Pain Medicine, n.d.). This research found the median number of 'antidepressant review consultations' (defined as consultations where any comment about the patient's mental health or antidepressant medication was recorded) for people prescribed antidepressants to be: 5 consultations (in the first year of prescribing), 2 consultations (in the second year), and 1 consultation (in the third year) (median is used due to the data being skewed) (Sinclair et al., 2014).

Data sharing

Data on the duration and number of adults continuously prescribed medicines associated with dependence are available in the Technical Annexe of the PHE Report (Taylor et al., 2019) online here (Appendix C, one-month gap data): https://app.box.com/s/2i61byjuz1bfxeik322iew2q3wpybck5/file/520664470668 All other data are available from the corresponding author on request.

Patient and public involvement

The PHE Review on 'Dependence and Withdrawal Associated with some Prescribed Medicines' emerged from concerns in the service user community about poor acknowledgement of (and provision for) prescribed drug dependency. One co-author of this study is an expert by experience and two co-authors were expert advisors on the PHE Review (Public Health England, 2019).

Table 2

Number estimated to be in receipt of a prescription in March 2018 (retrospective approach) and proportion estimated to have a continuous prescribing period up to that point, by medicine class and method for estimating continuous prescribing (1 month or 2 month gap, reproduced from the Public Health England Report(Public Health England, 2019).

Medicine class	Method	Estimated to be in receipt of a prescription in March 2018	Proportion (%) estimated to have had continuous prescribing up to March 2018 of:				
			At least 3 months	At least 6 months	At least 12 months	At least 24 months	All months *
Antidepressants	One month gap	4,480,468	82.3	68.4	52.1	34.6	24.3
	Two month gap	4,852,276	89.3	79.4	66.0	49.1	38.7
Opioid pain medicines	One month gap	2,344,177	74.8	62.8	50.0	35.6	26.4
	Two month gap	2,522,913	81.3	71.4	60.1	46.7	38.3
Gabapentinoids	One month gap	854,165	83.2	70.1	53.3	34.0	22.5
	Two month gap	908,602	88.6	78.8	64.5	45.9	34.5
Benzodiazepines	One month gap	419,564	69.6	60.0	50.4	39.3	31.5
	Two month gap	444,312	74.8	65.9	57.1	47.1	40.7
Z-drugs	One month gap	364,258	74.5	64.0	53.3	40.4	31.3
	Two month gap	386,246	79.4	69.7	59.9	48.3	40.5

*'All months' here refers to the full period for which the person could be observed. In the case of 'one month gap' this is 35 consecutive months' continuous prescribing and for 'two month gap' it is 34. It should be noted that this will slightly inflate the proportions counted for 'two month gap' compared to 'one month gap'.

Analysis

Unnecessary prescribing criteria are detailed in full in Table 1. All calculations were completed using Microsoft Excel. The methods used to calculate the unnecessary medicine cost are detailed in Table 3, a worked example is provided for opioids in the supplement (Text S2 and Table S1).

We produced two estimates of unnecessary cost for each medicine, using the durational data calculated by the one-month gap and two-month gap method. We used the durational data to estimate unnecessary costs by assuming that for each period of continuous prescribing the cost is evenly spread across the population. We then calculate the proportion (%) of unnecessary cost by discounting the equivalent cost for the indicated period of prescribing.

Table 3: analysis methods used to calculate unnecessary costs: step wise details

Drug type	Based on unnecessary prescribing criteria (Table 1)	
	NIC and Dispensing cost	**Consultation cost (£33 per consultation)**
Antidepressants	In total, 27.4% of people prescribed antidepressants for ≥ 2 years were estimated as not needing them. We followed the following steps to estimate unnecessary costs. Given the durational data spans a 3 year period, the maximum length of unnecessary use and associated costs were limited to one year. . **Step 1:** using the durational data we took 27.4% of the number prescribed for ≥ 2 years. **Step 2:** using this sample (27.4% of the number prescribed for ≥ 2 years), we discounted two years of indicated prescribing for each of the continuous prescribing periods to arrive at a pure estimate of unnecessary cost. **Step 3:** we aggregated the data from step 2. **Step 4:** we calculated the estimated % of unnecessary costs by dividing the total from step 3 by the total number of people prescribed antidepressants over 1 year, i.e. the third year of prescribing (April 2017-March 2018). This equated to 7.6% (one-month gap) to 7.9% (two-month gap) of the 1 year costs for antidepressants estimated to be unnecessary. **Step 5:** we calculated unnecessary cost by applying the % of unnecessary cost (7.6-7.9%) to the one year (April 2017-March 2018) NIC and Dispensing Cost, e.g. for one-month gap we took 7.6% of the 1 year NIC and Dispensing cost.	Costed for year 3 only, as one consultation per person, with 'per person' referring to the 27.4% of people prescribed antidepressants for ≥ 2 years, using the durational data.

	Based on unnecessary prescribing criteria (Table 1)	
Drug type	**NIC and Dispensing cost**	**Consultation cost (£33 per consultation)**
	Sensitivity analysis We conducted a sensitivity analysis involving total costs for everyone prescribed antidepressants for > 2 years **Step 1:** using the durational data we took 73.7% of the number prescribed for ≥ 2 years (73.7% of prescriptions are estimated to be for depression and anxiety). **Steps 2-5:** the analysis method is the same as above.	
Benzodiazepines and Z-drugs	We followed the following steps: **Step 1:** using the durational data we discounted one month of indicated prescribing for each of the continuous prescribing periods in order to arrive at a pure estimate of unnecessary prescribing. **Step 2:** we aggregated the data from step 1. **Step 3:** we calculated the % of unnecessary costs by dividing the figure from step 2 by the total number of people prescribed the drugs over the three year period. For benzodiazepines the percentages ranged between 67-72%, and for z-drugs this was estimated between 71-76% (1-2 month gap respectively). **Step 4:** we calculated total unnecessary cost by applying the % of unnecessary cost (from step 3) to NIC and Dispensing Cost, e.g. for benzodiazepines we took 67% of the 3 year NIC and Dispensing cost (for the 1-month gap calculation).	Calculated as four consultations in year 1 (one consultation was justified given the one month of indicated prescribing), two consultations in year 2 and 1 consultation in year 3. Consultations were evenly split over the years, for example someone prescribed for 12 months would have four consultations costed, someone prescribed for two years would have six consultations costed.
Opioids	We followed the following steps: **Step 1:** to account for the 'small' proportion of people who may obtain good pain relief with opioids in the long-term and have	Calculated for 85% of the durational data sample (to account for the 15% who may obtain good pain relief with opioids).

	Based on unnecessary prescribing criteria (Table 1)	
Drug type	**NIC and Dispensing cost**	**Consultation cost (£33 per consultation)**
	indicated prescribing, we discounted 15% of people prescribed from each continuous prescription period from the durational data. We therefore considered only 85% of the total number of people. **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. **Step 3:** we aggregated the data from step 2. **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 gave 54-62% of unnecessary costs (1-2 month gap respectively). **Step 5:** we calculated unnecessary cost by applying the % of unnecessary costs to 76% of the three year NIC and Dispensing Cost. 76% of the cost is used to deduct the 15% of people who may obtain good pain relief with opioids in the long-term and the 9% of people who were found to be prescribed opioids for cancer pain (see note). **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%	Calculated as three consultations in year 1 (two consultations were justified given the three months of indicated prescribing), 2 consultations in year 2 and two consultations in year 3. Consultations were evenly split over the years, for example someone prescribed for 12 months would have three consultations costed, someone prescribed for two years would have five consultations costed.

	Based on unnecessary prescribing criteria (Table 1)	
Drug type	**NIC and Dispensing cost**	**Consultation cost (£33 per consultation)**
	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).	
Gabapentinoids	The total unnecessary cost consisted of two parts to account for the 15% of people who should be prescribed gabapentinoids for psychiatric indications for no more than one month (part 1) and the 41.8% and 31.9% of dispensable gabapentin and pregabalin prescriptions (for non-neuropathic pain) (part 2), the following steps were taken: **Part 1** **Step 1:** we took 15% of the total number of people prescribed gabapentinoids from the durational data. **Step 2:** using this durational data we discounted one month of indicated prescribing for each of the continuous prescribing periods. **Step 3:** we aggregated the data from step 2. **Step 4:** we calculated the % of unnecessary costs by dividing the total from step 3 by the total number of people from step 1. This gave 78-84% of unnecessary prescriptions for those prescribed gabapentinoids for psychiatric indications (1-2 month gap respectively). **Step 5:** we calculated unnecessary cost by applying the % of unnecessary costs to 15% of the NIC and Dispensing Cost, e.g. for	Calculated using the durational data, on 51.85% of the sample which is the 15% of prescriptions for psychiatric indications and 36.85% (15+36.85=51.85). The 36.85% is the average of the 41.8% of gabapentin and 31.9% of pregabalin prescriptions for non-neuropathic pain. The costs were calculated per person as four consultations in year 1 (one consultation was justified given the one month of indicated prescribing for psychiatric indications and the initial consultation for non-neuropathic pain), two consultations in year 2 and 1 consultation in year 3. Consultations were evenly split over the years, for example someone prescribed for 12 months would have four consultations costed, someone prescribed for two years would have six consultations costed.

Drug type	Based on unnecessary prescribing criteria (Table 1)	
	NIC and Dispensing cost	**Consultation cost (£33 per consultation)**
	the 1 month gap calculation we took 78% of the 3 year NIC and Dispensing cost. **Part 2** We calculated 41.8% + 31.9% of gabapentin and pregabalin NIC and Dispensing cost respectively.	

Note. For all medicine costs the calculations were completed separately for NIC and dispensing cost.

Results

The estimated costs incurred by the NHS in England due to the unnecessary prescribing of dependency-forming medications are detailed in Table 4 and for antidepressants in Table 5. We report the range estimated using the one-month to two-month gap.

Across opioids, gabapentinoids, benzodiazepines, Z-drugs the total estimated unnecessary cost over three years (April 2015-March 2018) was £1,367,661,104 to £1,555,234,627 with a total estimated mean yearly unnecessary cost of £455,887,035 to £518,411,542. For antidepressants the total estimated unnecessary cost for one year was £37,321,783 to £45,765,504.

For benzodiazepines 67-72% of total costs were estimated to be unnecessary with a total unnecessary cost over three years (April 2015-March 2018) of £115,588,439 to £129,870,520 and a mean yearly unnecessary cost of £38,529,480 to £43,290,173.

For z-drugs 71-76% of total costs were estimated to be unnecessary with a total unnecessary cost over three years (April 2015-March 2018) of £75,379,271 to £85,641,915 and a mean yearly unnecessary cost of £25,126,424 to £28,547,305.

For opioids 46-53% of total costs were estimated to be unnecessary with a total unnecessary cost over three years (April 2015-March 2018) of £722,543,759 to £864,201,862 and a mean yearly unnecessary cost of £240,847,920 to £288,067,287.

For gabapentinoids 11.7 to 12.6% of total costs for psychiatric indications, 41.8% of gabapentin and 31.9% of pregabalin prescriptions for non-neuropathic pain were estimated to be unnecessary with a total unnecessary cost over three years (April 2015-March 2018) of £454,149,636 to £475,520,329 and a mean yearly unnecessary cost of £151,383,212 to £158,506,776.

For antidepressants (Table 5) 7.6-7.9% of total costs were estimated to be unnecessary with a total unnecessary cost for one year (April 2017-March 2018) of £37,321,783 to £45,765,504. For the sensitivity analysis (for all costs after 2 years of prescribing)

20.5-21.3% of total costs were estimated to be unnecessary with a total unnecessary cost for one year (April 2017-March 2018) of £62,689,826 to £65,109,069

Table 4

Estimated costs incurred by the NHS in England due to the unnecessary prescribing of dependency-forming medications (benzodiazepines, z-drugs, gabapentinoids, opioid pain medicines), for 3 years (April 2015-March 2018) and 1 year.

Medicine	Total NIC for 3 years	Total dispensing cost for 3 years	Estimated % of total costs that are unnecessary [a]	Unnecessary medicine cost – NIC for 3 years	Unnecessary medicine cost – Dispensing cost for 3 years	Unnecessary consultation cost[b] for 3 years	Total unnecessary cost for 3 years	Mean unnecessary cost for 1 year
One month gap								
Benzodiazepines	£65,333,571	£28,677,577	67%	£43,542,065	£19,112,393	£52,933,980	£115,588,439	£38,529,480
Z-drugs	£16,902,216	£20,880,517	71%	£11,997,770	£14,821,704	£48,559,797	£75,379,271	£25,126,424
Opioid pain medicines	£1,049,970,171	£166,786,453	46%	£432,747,684	£68,741,430	£221,054,645	£722,543,759	£240,847,920
Gabapentinoids for psychiatric indications	£828,055,011	£45,446,996	11.7%[c]	£97,065,628	£5,327,353	-	-	-
Gabapentin	£100,922,354	£22,848,190	41.8%[d]	£42,185,544	£9,550,543	-	-	-
Pregabalin	£727,132,657	£22,598,807	31.9%[d]	£231,955,318	£7,209,019	-	-	-
Total gabapentinoids	£828,055,011	£45,446,996	-	£371,206,490	£22,086,915	£60,856,231	£454,149,636	£151,383,212
Total							**£1,367,661,104**	**£455,887,035**
Two month gap								
Benzodiazepines	See above	See above	72%	£46,766,689	£20,527,813	£62,576,019	£129,870,520	£43,290,173
Z-drugs	See above	See above	76%	£12,784,534	£15,793,650	£57,063,732	£85,641,915	£28,547,305
Opioid pain medicines	See above	See above	53%	£497,762,025	£79,068,877	£287,370,960	£864,201,862	£288,067,287

Medicine	Total NIC for 3 years	Total dispensing cost for 3 years	Estimated % of total costs that are unnecessary [a]	Unnecessary medicine cost – NIC for 3 years	Unnecessary medicine cost – Dispensing cost for 3 years	Unnecessary consultation cost[b] for 3 years	Total unnecessary cost for 3 years	Mean unnecessary cost for 1 year
Gabapentinoids for psychiatric indications	See above	See above	12.6%[c]	103,940,235	5,704,659	-	-	-
Gabapentin	See above	See above	41.8%[d]	42,185,544	9,550,543	-	-	-
Pregabalin	See above	See above	31.9%[d]	231,955,318	7,209,019	-	-	-
Total gabapentinoids	See above	See above	-	£378,081,097	£22,464,222	£74,975,011	£475,520,329	£158,506,776
Total							**£1,555,234,627**	**£518,411,542**

NIC: Net Ingredient Cost; a. For comparability, these percentages are all a % of the whole durational data sample. Therefore for gabapentinoids and opioids they differ from the % used to calculate the unnecessary cost, as the latter were calculated on a proportion of the durational data sample, e.g. 85% for opioids; b. total consultation cost is not included as these were calculated as £33 per consultation (instead of a proportion of total cost); c. % of unnecessary cost for psychiatric indications for gabapentinoids; c. Non-neuropathic pain: 41.8% of gabapentin and 31.9% of pregabalin prescriptions

Table 5

Estimated costs incurred by the NHS in England due to the unnecessary prescribing of antidepressants, for 1 year (April 2017-March 2018).

Antidepressants	Total NIC for 1 year	Total dispensing cost for 1 year	Estimated % of total 1 year costs that are unnecessary	Unnecessary medicine cost – NIC for 1 year	Unnecessary medicine cost – Dispensing cost for 1 year	Unnecessary consultation cost[b] for 1 year	Total unnecessary cost for <u>1 year</u>
One month gap	£215,664,724	£89,995,548	7.6%	£16,444,484	£6,862,181	£14,015,118	**£37,321,783**
Two month gap	As above	As above	7.9%	£17,079,088	£7,126,997	£21,559,419	**£45,765,504**
Sensitivity analysis							
One month gap	As above	As above	20.5%	£44,232,062	£18,457,764	-	£62,689,826
Two month gap	As above	As above	21.3%	£45,939,007	£19,170,062	-	£65,109,069

Discussion

This is the first study to identify and cost the annual unnecessary prescribing of dependency forming medicines in the NHS in England. Across opioids, gabapentinoids, benzodiazepines, Z-drugs the total estimated unnecessary cost over three years (April 2015-March 2018) was £1,367,661,104 to £1,555,234,627 with a total estimated mean yearly unnecessary cost of £455,887,035 to £518,411,542. For antidepressants the total estimated unnecessary cost for one year was £37,321,783 to £45,765,504.

These figures indicate significant low-value care in the utilisation of dependency forming medications in the NHS in England. This raises evident policy questions regarding what value-driven strategies should be designed and implemented to reduce or eliminate inefficient prescribing practices, and to further redirect wasted resources to fund underused alternative innovative services. A vital first step of moving from low-to high-value care is advancing a data-driven understanding of the nature and extent of low-value care in the current health care system (Miller et al., 2018), as this study has aimed to do.

While this study has uncovered significant low-value care in England's current health care system, its estimates may still be conservative for a number of reasons. Firstly, this study does not estimate other systemic costs, such as follow-up costs incurred via additional medical examinations for medically unexplained symptoms in people on long-term dependence-inducing medications or for complications of long-term use such as falls associated with benzodiazepines in the elderly. Secondly, underestimation of consultation costs may follow from the number of primary care consultations accompanying long-term benzodiazepines, Z-drugs, opioid and gabapentinoid treatment being based on the number of consultations derived for the long-term monitoring of antidepressants (Sinclair et al., 2014) (excluding >1 year opioid prescribing where at least two reviews are advised annually (Faculty of Pain Medicine, n.d.)). The number of consultations for opioids, gabapentinoids and most benzodiazepines and Z-drugs may be higher as they are controlled drugs with addictive and abuse potential and so should not be dispensed on repeat prescription (NICE, 2021b) potentially leading to more frequent contact with surgeries. Also, as the cost of each consultation is based on the average length of a GP consultation (9.22mins (Curtis

& Burns, 2019)), costs may be underestimated as medicine reviews are often of longer duration. Further, as this analysis is based on GP or nurse consultations only, any additional online, face-to-face or telephone consultations with clinical pharmacists or specialist services have not been costed, neither have reviews and monitoring conducted through secondary care (addiction or psychiatric services).

A further limitation is that minor fluctuations in prescribing rates since 2017-18 may impact our costing estimates, as prescriptions for benzodiazepines and Z-drugs have slightly decreased since 2017-18 while prescriptions for antidepressants and gabapentinoids have increased (Sehmi et al., 2019). Additionally, as future fluctuations in the cost of the medicines, distribution and consultations covered may occur, estimates capture an economic scenario liable to variation. For example, as NICE (March 2021) recently updated its guidelines to advise against opioid treatment for chronic non-cancer primary pain, recommending instead antidepressants, changes to unnecessary prescribing trends will follow, with potential reductions in unnecessary opioid prescribing and potential increases in antidepressant use.

Our assumptions as to what constitutes non-indicated prescribing will also have a cost implication for each class of drug. In the case of antidepressants, the analysis of nonindicated prescribing does not include prescribing for indications where there is no established efficacy (e.g. for off-label or mild depression indications). As such prescribing may be common, for example, one study shows 69% (Coupland et al., 2011) of diagnosed depression was of mild severity, and another shows that of those taking antidepressants, 26.4% reported mild depressive symptoms (Shim et al., 2011) therefore, our antidepressant costs are likely to be a significant underestimation. To address this we performed a scenario analysis taking the NIC cost alone as an example to estimate the unnecessary antidepressant costs for mild depression in a range of scenarios (from 10%-40% of overall prescriptions). Considering the NIC costs alone would result in an annual extra unnecessary costs (not included in our final results) ranging between £14,733,364 to £58,933,459 (Table S4).

Opioid costs are higher. This is due to multiple factors, high overall prescribing rates, more unnecessary use, the overprescribing of strong opioids for chronic pain (Ashaye et

al., 2018) the prescribing of more expensive opioid formulations being preferred (de Lima et al., 2018) and overall, higher NIC costs. We've assumed that the 9% of opioid prescriptions for cancer pain do not exceed 9% of overall opioid costs. This is based on a review of primary care opioid prescribing, where the mean annual days of supply per patient was longer for patients in the non-cancer group (130.6 ± 124.2 days) than in the cancer group (88.9 ± 95.8 days), and the mean number of annual prescriptions per patient was slightly higher in the non-cancer group, as was the mean annual defined daily dose for all four strong opioids (Zin et al., 2014). A further limitation is that an estimated 20% of all palliative care treatment in England is for non-cancer pain (Faculty of Pain Medicine, n.d.) about 30,000 patients, of which an unspecified amount may be receiving palliative treatment for >3 months. This cohort has not been excluded from our estimates, but as it may only constitute 0.5% of opioid users, it will exert a very minor impact on our overall estimates. With respect to gabapentinoids, our costing analysis assumes that the proportion of prescribing for non-neuropathic pain and psychiatric indications remains broadly stable relative to other indications over the year assessed. Research on indication prescribing trends broadly supports this assumption (Wettermark et al., 2014).

Furthermore, the analysis also assumes that the prescription costs are not 'time-sensitive', meaning that there is no significant differences in the initial and subsequent periods of prescribing. This was confirmed using the data relating to a sample cohort of NHSBSA patient data for 2018. Furthermore, the analysis also assumes that the prescription costs are not 'time-sensitive', meaning that there is no significant differences in the initial and subsequent periods of prescribing. This was tested using the data relating to a sample cohort of NHSBSA patient data for 2018. We did not see notable differences between the initial and subsequent prescriptions. The consultation cost analysis is based on the assumption that consultations will comprise a medication review. Although we acknowledge that such consultations may also entail other forms of patient care and review, given the length of the consultation that is included as the basis for the cost analysis we think this is not an overestimation of the consultation cost. Finally, as this analysis takes a healthcare system's approach, our results do not account for other costs absorbed by the economy as a consequence of unnecessary prescribing,

such as adverse effects impacting productivity, disability payments, tax revenues, absenteeism.

Conclusion and clinical implications

We found across opioids, gabapentinoids, benzodiazepines, Z-drugs the total estimated unnecessary cost over three years (April 2015-March 2018) was £1,367,661,104 to £1,555,234,627 with a total estimated mean yearly unnecessary cost of £455,887,035 to £518,411,542. For antidepressants the total estimated unnecessary cost for one year was £37,321,783 to £45,765,504.

Given the significant annual costs unnecessarily incurred, it is important that programmes are developed to reduce waste incurred by low-value care. One current initiative that may support this agenda, is NHSE&I national Structured Medication Review (SMR) programme, which is designed to address unnecessary poly-pharmacy and which has recently estimated that around 10% of poly-pharmacy related prescriptions are unnecessary (DHSC, 2021). While this review will help identify many patients subject to unnecessary prescribing, and resultant low-value care, its newly published guidance (Group, 2021) does not address the problems associated with withdrawing from, tapering or deprescribing dependency forming medicines. Nor does it mention that there is almost no dedicated NHS provision to support people suffering from prescribed dependency and withdrawal; adversities that will impede any successful deprescribing programme, vital to reducing patient harm and economic waste.

Despite PHE in 2013 recommending that services for prescribed drug dependence be commissioned (Public Health England, 2013), as of 2018 less than 3% of the UK population had access to such services (Guy & Davies, 2018). In response to PHE's recommendations, NHSE&I are currently drafting a new commissioning framework for local withdrawal services, due for publication in April 2022, yet it remains to be seen whether Integrated Care Systems (or current CCGs) will support such services without additional central funding.

In addition to curtailing the harms associated with prescribed drug dependency and withdrawal, the potential savings (up to £564,177,046 annually) from reducing such low-value care may enable resource diversification and some investment in supporting patients to withdraw safely and effectively. Until dedicated local NHS face-to-face provision is provided to assist those in serious need, the implementation of other resources (e.g. a national helpline, digital and website resources) could provide a lifeline for those currently suffering from dependency and withdrawal issues without any dedicated NHS help.

Ethical approval

Ethical approval was not required.

Declaration of Interest

RC is a Board Member of the International Institute for Psychiatric Drug Withdrawal (IIPDW) and JD an associate member. JD and LM are secretariat members of the All-Party Parliamentary Group for Prescribed Drug Dependence and founding members of the Council for Evidence based Psychiatry. JM is co-chairperson of the Critical Psychiatry Network, a board member of the Council for Evidence-Based Psychiatry, chief investigator on the RADAR study of antipsychotic reduction funded by the UK government s National Institute of Health Research (NIHR) and co-investigator on the REDUCE study of antidepressant discontinuation also funded by the NIHR. TR & MP have no disclosures to declare.

Acknowledgements

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