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Spatiotemporal modelling of pregabalin prescribing in England with effect of deprivation

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ABSTRACT

Objective This paper aims to understand spatial and temporal trends in pregabalin prescribing and the relationship with deprivation across England at both general practice and clinical commissioning group (CCG) levels.
Design A set of 207 independent generalised additive models are employed to model the spatiotemporal trend of pregabalin prescribed and dispensed per 1000 population, adjusting for deprivation. The response variable is pregabalin prescribed in milligrams, with weighted Index of Multiple Deprivation (IMD), geographical location and time as predictors. The set of active prescribing facilities grouped within CCG is the unit of analysis.
Setting National Health Service open prescribing data; all general practices in England, UK between January 2015 and June 2017.
Population All patients registered to general practices in England, UK.
Results Adjusting for deprivation, a North–South divide is shown in terms of prescribing trends, with the North of England showing increasing prescribing rates during the study period on average, while in the South of England rates are on average decreasing. Approximately 60% of general practices showed increasing prescribing rate, with the highest being 4.03 (1.75 for the most decreasing). There were no apparent spatial patterns in baseline prescription rates at the CCG level. Weighted IMD score proved to be statistically significant in 138 of 207 CCGs. Two-thirds of CCGs showed more pregabalin prescribed in areas of greater deprivation. Whether the prescribing rate is high due to high baseline prescription rate or increasing rates needs to be specifically looked at.
Conclusions The spatial temporal modelling demonstrated that the North of England has a significantly higher chance to see increase in pregablin prescriptions compared with the South, adjusted for weighted IMD. Weighted IMD has shown positive impact on pregabalin prescriptions for 138 CCGs.

Strengths and limitations of this study

- ► This study presents how appropriate modelling of National Health Service open prescribing data can be used to address the concern on misuse of pregabalin.
- ► The use of generalised additive mixed models allowed faster approach in each clinical commissioning group (CCG) at the general practice level, accounting for both spatiotemporal effects and deprivation.
- ► The independence assumption between models for each CCG is likely to be validated in reality.
- ► Weighted Index of Multiple Deprivation scores are not standardised, which makes comparisons across CCGs hard.

INTRODUCTION

This study takes place amid wide concern over misuse of pregabalin/Lyrica for recreational use and a global increase in prescribing rates at the UK level.

Pregabalin is a gabapentinoid and is a close analogue of the neurotransmitter γ-aminobutyric acid (GABA). It does not work by directly binding to GABA receptors, but it is capable of crossing the blood–brain barrier and potentiates GABA effects. It was developed as a successor to gabapentin and eventually made it to market in 2004 with Pfizer. They held the initial patent, but generic versions are now available in the UK while it remains under patent in the USA.

In the UK pregabalin is currently indicated for peripheral and central neuropathic pain, as an adjunct of therapy for focal seizures in epilepsy, and for generalised anxiety disorder. Pregabalin is recommended by the National Institute for Health and Care Excellence as a first-line treatment option for peripheral neuropathic pain alongside amitriptyline, gabapentin and duloxetine.[1] It has been noted that the use of pregabalin has extended beyond its licence into other chronic pain conditions.[2] A recent systematic review and meta-analysis of the use of gabapentinoids in chronic low back pain has highlighted that there is very limited evidence of effectiveness, while significant risks of adverse effects have been demonstrated.[3]

In the UK, prescribing of pregabalin has risen steeply, with an increase from 476102 prescriptions in 2006 to 554756 in 2017 (https://openprescribing.net/chemical/

0408010AE/). Clearly this rise has had financial implications, with a significant increase in associated prescribing costs. However, along with the other gabapentinoid, gabapentin, there has been increasing concern about misuse of pregabalin and its potential for abuse. Typically abuse will involve taking large doses, well above therapeutic levels, to achieve a euphoria effect.

Initial reports of problems with pregabalin and gabapentin were anecdotal.[4–6] More detailed evidence of problems is now emerging. A systematic review of the abuse and misuse of pregabalin and gabapentin[7] found that increasing numbers of patients are using these medications and taking them to achieve euphoric highs. In the general population prevalence of abuse was estimated at 1.6%, but among populations such as opioid abusers the prevalence has ranged from 3% to 68%.[7] The systematic review also highlights evidence that the gabapentinoids are being identified in postmortem toxicology analyses and are playing a role in overdose deaths. In the UK there were 4 deaths linked to pregabalin in 2012, but this rose to 111 deaths in 2016.[8]

In October 2017, 88% and 83% higher spending on pregabalin prescriptions can be seen in North East and North West England, respectively, compared with London (data can be obtained from https://openprescribing.net/analyse/). The reasons for this North–South divide are not known, but there are well-known socioeconomic inequities and differences in health outcomes along this axis.[9]

In the UK, the Advisory Council on the Misuse of Drugs recommended in January 2016 that pregabalin and gabapentin should be reclassified as class C drugs with tighter legal controls over their prescribing.[10] Such concern of misuse occurs not only in the UK; examples covering other regions are given in this paragraph. A cross-sectional study in Southern Germany[11] showed that out of 56% of 253 participating patients who have used pregabalin at least once, 92% had acquired it at least once from illegal source. The study addressed the concern over the development of dependency due to misuse of pregabalin in Southern Germany. In Australia, misuse-related ambulance attendance rate increased from 0.28 per 100 000 population to 3.32 per 100 000 between January 2012 and December 2017.[12] The rate also showed strong positive correlation with prescription rates in Australia. The Swedish and French pharmacovigilance centres and the European Monitoring Centre for Drugs and Drug Addiction[13] have seen approximately 30 cases of dependence, abuse or withdrawn symptoms attributed to pregabalin in 2011. Jordan,[14] USA[15] and Turkey[16] also had reported cases to alert the clinical community of the potential pregabalin abuses.

Using the National Health Service (NHS) open data, it has been demonstrated that it is possible to map prescribing at various healthcare levels down to individual general practices (GP).[17] The ability to map pregabalin prescribing, taking into account deprivation and other potential covariates, in order to analyse prescribing trends is useful for setting prescribing policies. In this article we seek to address the following research questions: (1) What are the temporal trends in prescription rates at the GP level? (2) How do prescription trends vary across the country at the practice level and at the clinical commissioning group (CCG) level? (3) Which areas in the UK are prescribing more pregabalin compared with the national average? (4) What is the nature of the relationship between the prescribing of pregabalin and deprivation?

METHODS

Patient and public involvement

The relevant data used in this paper are from NHS open prescribing data (more details can be seen in the Data sources section). The data are longitudinal and cover the period between January 2015 and June 2017. There are no patients or public involved in this study.

Data sources

The monthly amount of pregabalin prescribed at the GP level is freely available from data.gov.uk and can be extracted from the files available from the GP Practice Prescribing Data website (https://data.gov.uk/dataset/prescribing-by-gp-practice-presentation-level). Data on the number of people registered at each GP are also available from this source and are broken down geographically into the number of patients registered to the practice by the 2011 Lower Layer Super Output Areas (LSOAs; available from https://data.gov.uk/dataset/lower_layer_super_output_area_lsoa_boundaries). This breakdown is updated on a quarterly basis. CCG boundaries for April 2017 were obtained from the Open Geography portal of the Office for National Statistics (http://geoportal.statistics.gov.uk/datasets/clinical-commissioning-groups-april-2017-full-clipped-boundaries-in-england-v4). The map tiles are by Stamen Design under Creative Commons License CC By 3.0. The data are by OpenStreetMap under Open Database License. The English Indices of Deprivation 2015 are available from gov.uk (https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015). Information on deprivation can be obtained from File 1 Index of Multiple Deprivation (IMD); this provides a set of relative measures of deprivation for small areas across England. The score is combined using the following weights to produce an overall score of IMD: income deprivation (22.5%), employment deprivation (22.5%), education, skills and training deprivation (13.5%), health deprivation and disability (13.5%), crime (9.3%), barriers to housing and services (9.3%), and living environment deprivation (9.3%).

This paper focuses on the number of milligrams prescribed per registered population as unit using the British National Formulary code 0408010AE (BNF 74, 2017) to identify prescriptions of relevance. Note that oral solutions are not considered in this paper, but these only account for a small percentage of prescriptions (less than 1% on average).

Weighted IMD score

In order to explore the relationship between deprivation and prescribing rates for pregabalin, a method for assigning a deprivation score to each GP was required. One option for this could be to use the IMD score for the LSOAs in which each GP is located. However this method may not be a good reflection of the deprivation of patients registered at that practice.

Practices typically accept patients from a relatively small number of LSOAs. Each LSOA has a unique IMD and is covered by other GPs. Thus a fraction showing the weight of contribution from each GP to the IMD of LSOA roughly can be obtained. Using the IMD of each of those LSOAs and the fraction of the total practice list from each LSOA, a simple weighted IMD score is constructed in this paper which attempts to capture the IMD of patients who attend each practice.

Statistical methods

In order to answer the research questions, Gaussian generalised additive models (GAM)[18] with fixed and random effects are used. The outcome was the square root of the number of milligrams prescribed per population. The square root transform is used because it produces more normal-shaped data to fit assumptions (see the equation) and the model fit was significantly improved (according to the restricted maximum likelihood (REML) score; eg, REML score improved from 2216.309 to 3134.627 in Cumbria CCG). Note that the log transformation may show better REML score in different CCGs (not for the Cumbria case 2767.1) but was not chosen as there are zero prescriptions for certain GPs and doing so would require artificially altering the prescription to positive.

The analyses are conducted on different CCGs separately. Within each CCG, an intercept and weighted IMD (defined in the Weighted IMD score section) are included as fixed effects and a random slope with respect to time at the GP level is also included. In addition, this model allows for spatial correlation in prescribing rates between practices by including a spatial random effect which was modelled using a two-dimensional spline surface.

Let P_{ijt} denote the number of milligrams of pregabalin prescribed for GP i in CCG j in month t, where GP has coordinates in the British National Grid (Open Scene Gragh Binary (OSGB)) projection (x_{ijt}, y_{ijt}). The model assumed the following form:

$$\sqrt{\mathrm{P}_{\mathrm{ijt}}} \sim \mathrm{N}\left(\mu_{\mathrm{ijt}}, \sigma^2_{\mathrm{ijt}}\right)$$

$$\mu_{\mathrm{ijt}} = \mathrm{X}_{\mathrm{ij}}\beta_{\mathrm{j}} + \mathrm{a}_{\mathrm{ij}}\mathrm{t} + \mathrm{S}\left(\mathrm{x}_{\mathrm{ijt}}, \mathrm{y}_{\mathrm{ijt}}\right)$$

$$\sigma^2_{\mathrm{ijt}} \propto 1/\mathrm{n}_{\mathrm{ijt}}$$

Here, X_{ij} includes the fixed effects for GP i in CCG j, a_{ij} captures the temporal trend in prescriptions for each GP within the CCG, $S(x_{ijt}, y_{ijt})$ is the spatial effect and n_{ijt} is the number of patients registered to GP i in CCG j at time t.

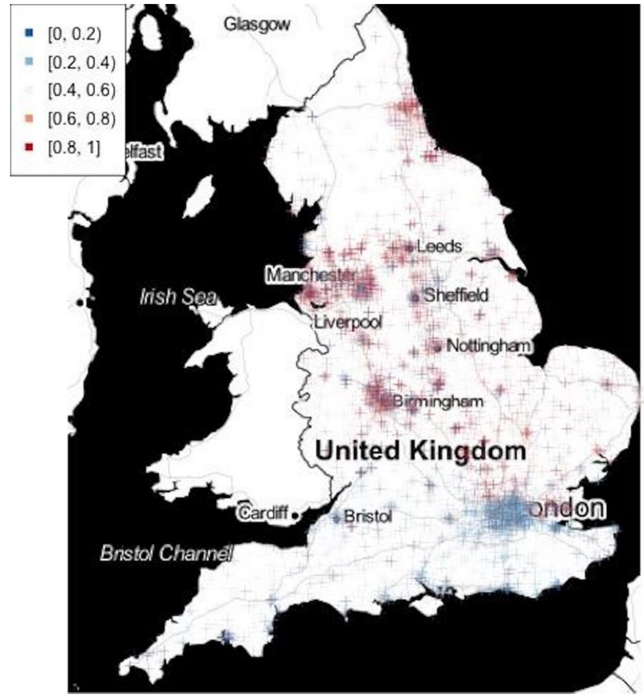

Figure 1 Probability of an increasing pregabalin prescription rate for each individual general practice surgery.

Models with subsets of the domains and subdomains of the IMD (identified through backward selection) as predictors have also been considered, but they proved difficult to interpret, both from an epidemiological perspective and also because the domains and subdomains are themselves highly correlated.

The inclusion of the spatial effects was justified on the basis that their inclusion significantly improves model fit for all CCGs apart from NHS Crawley CCG, NHS Eastbourne CCG, NHS Isle of Wight CCG and NHS North Hampshire CCG.

RESULTS

Temporal trends in prescribing

The temporal trends in prescriptions from the models (the a_{ij}) capture whether prescriptions are increasing over time. Bayesian inference provides posterior probability distributions as outcomes; this means that there is an associated uncertainty in our estimates of each of these trends. Thus, rather than mapping these trends directly, which would ignore the uncertainty, the probabilities of the trends being positive are mapped instead.

Accordingly, when interpreting figure 1, the following should be borne in mind. The closer the mapped value is to 1, the more likely the prescription rates are to be increasing with time; values close to 0.5 are surgeries where the prescription rates do not change significantly with time; and values close to 0 represent surgeries with decreasing prescription rates over time.

Figure 1 shows the probability of increasing prescription rates at each of the GP surgeries in the UK. Careful examination of this plot suggests a North–South divide,

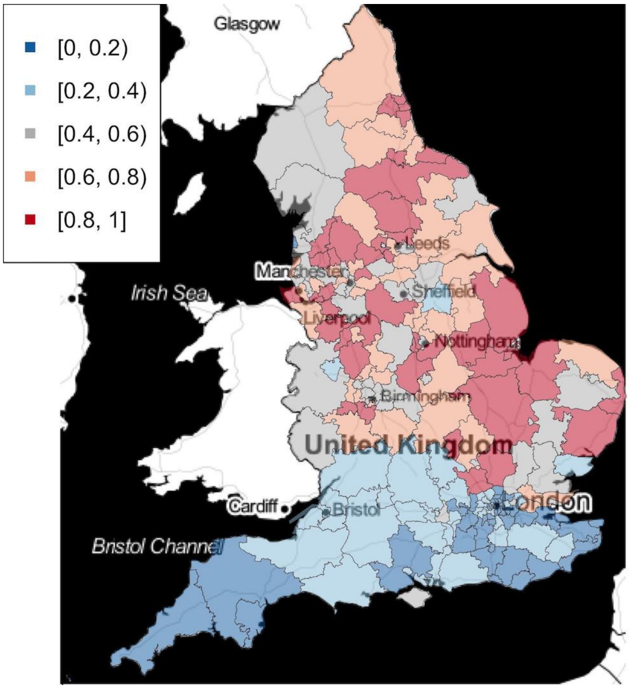

Figure 2 Average probability of increasing pregabalin prescription rates within each clinical commissioning group: England and Wales.

with surgeries in the North tending to have an increasing rate of prescriptions, whereas prescription rates seem to be falling in the South. In order to make these trends clearer, these probabilities are averaged by CCG and mapped in figure 2. Grey areas represent flat prescription

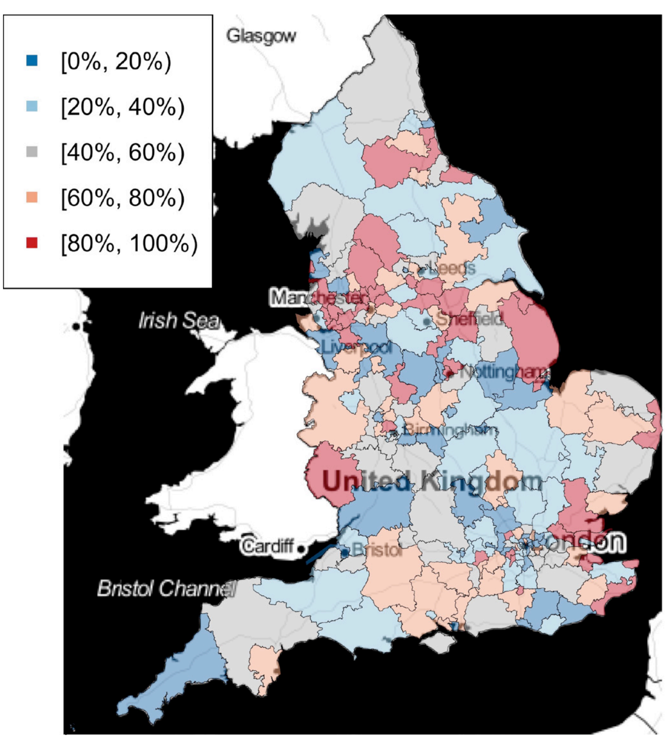

Figure 4 IMD-adjusted baseline prescription rates in percentiles for each clinical commissioning group: England and Wales. IMD, Index of Multiple Deprivation.

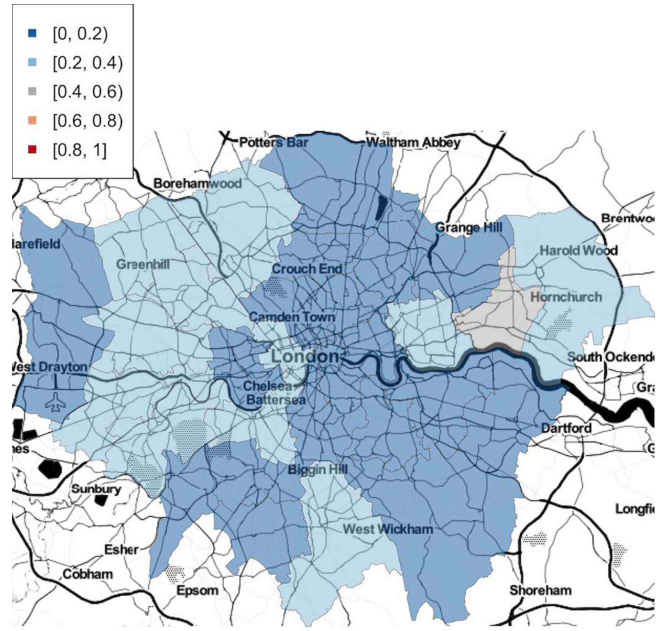

Figure 3 Average probability of increasing pregabalin prescription rates within each clinical commissioning group: London (zoned in).

rates and blue areas refer to decreasing rates. The interpretation of this latter figure is similar to that for figure 1.

Averaging by CCGs makes the North–South divide visually clearer; North CCGs in general show increasing prescription rates compared with the South. A more detailed map for London CCGs is shown in figure 3.

The estimated IMD-adjusted baseline prescription rates from these models (the intercepts) are shown in figure 4, with a detailed map for London in figure 5. Rather than plotting the raw rates, which would be difficult to interpret, the percentiles are illustrated here.

Table 1 shows the CCGs in which the top 10 GPs with the highest increasing rates were seen. The rate of increase should be looked at combining with the baseline estimates. For example, the top 2 CCGs (NHS Bristol CCG and NHS Isle of Wight CCG) both had very low baseline estimates. It is more likely that the increasing prescription rates occur purely due to the very low prescription at the beginning.

Relationship with deprivation

The coefficient of weighted IMD in our model shows how, within each CCG, the relationship between pregabalin prescription rates and deprivation varies. A positive coefficient means that as deprivation increases, pregabalin prescription rates also increase, whereas a negative coefficient means that as deprivation increases pregabalin prescription rates decrease. Since there is uncertainty involved in the estimates of the effect of deprivation on pregabalin prescription rates, the probability that the coefficient is positive is again mapped in figure 6. Details for London can be seen in figure 7.

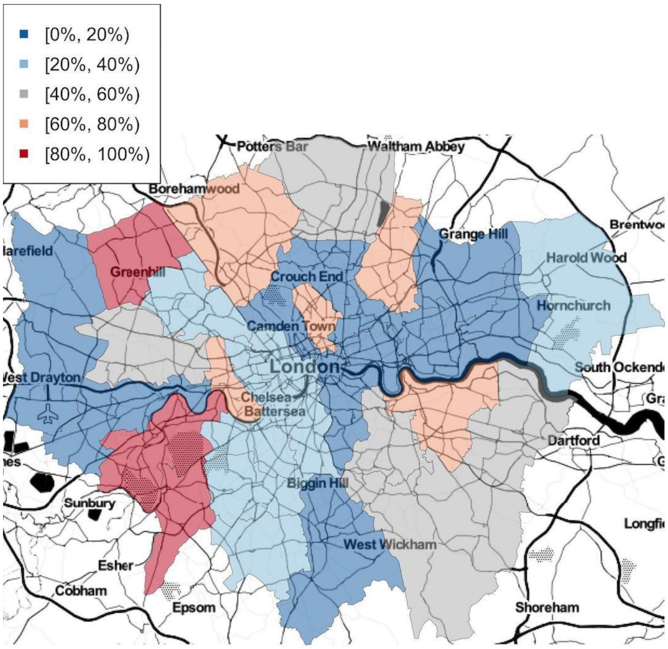

Figure 5 IMD-adjusted baseline prescription rates in percentiles for each clinical commissioning group: London (zoned in). IMD, Index of Multiple Deprivation.

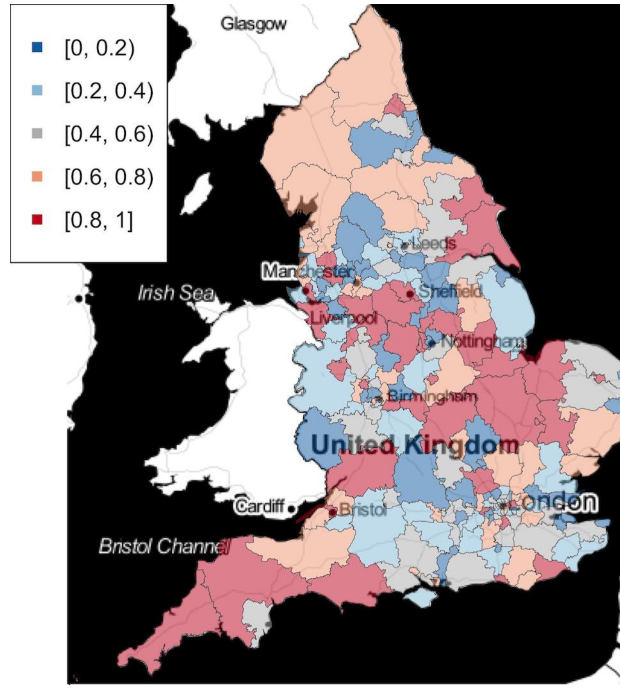

Figure 6 Map of probability of the relationship between weighted IMD and pregabalin prescription rates being positive for each clinical commissioning group: England and Wales. IMD, Index of Multiple Deprivation.

Two-thirds of CCGs (138 of 207) showed a positive impact of deprivation on milligrams of pregabalin prescribed by each GP.

Table 2 shows the coefficient of weighted IMD on prescriptions of pregabalin for the top 10 average prescribers, together with their p values in brackets and adjusted R-squared statistic (a measure of model fit).

DISCUSSION

This article brings attention to how the prescription of pregabalin behaves spatially and temporally at the GP level. The models supported the existence of the North and South divide with deprivation taken into account. An overall increasing trend across the UK between January 2015 and June 2017 is also shown in the models. Around 60% of GP surgeries were estimated to have an increasing trend in pregabalin prescriptions, most of which are to the North of London (see figures 1–3). Such results agree with what have been shown in previous studies; the highest prescribing CCGs are in the northern and eastern regions of England.[19] Additionally, the models employed in this paper suggested that such clear North–South divide in time trends is not a result of higher deprivation index in the North compared with the South as the weighted IMD

Table 1 CCGs which the GPs with the highest estimated temporal slopes lie in (with 95% CI) and the baseline estimate for the CCG

Rank	CCG which the GP lies in	Estimated increasing rate (slope), wrt time	95% CI	Estimated baseline (intercept)
1	NHS Bristol CCG	4.03	3.851 to 4.206	1.86
2	NHS Isle of Wight CCG	3.35	2.837 to 3.873	0.86
3	NHS Haringey CCG	1.99	1.628 to 2.353	10.73
4	NHS Stoke on Trent CCG	1.87	1.797 to 1.942	16.82
5	NHS Eastern Cheshire CCG	1.77	1.621 to 1.929	–8.46
6	NHS Sunderland CCG	1.67	1.618 to 1.728	5.70
7	NHS North Kirklees CCG	1.44	1356 to 1.515	5.72
8	NHS Gloucestershire CCG	1.20	1.081 to 1.328	4.67
9	NHS Southern Derbyshire CCG	1.09	0.992 to 1.190	5.27
10	NHS East and North Hertfordshire CCG	0.99	0.948 to 1.029	4.89

CCG, clinical commissioning group; GP, general practice; NHS, National Health Service; wrt, with respect to.

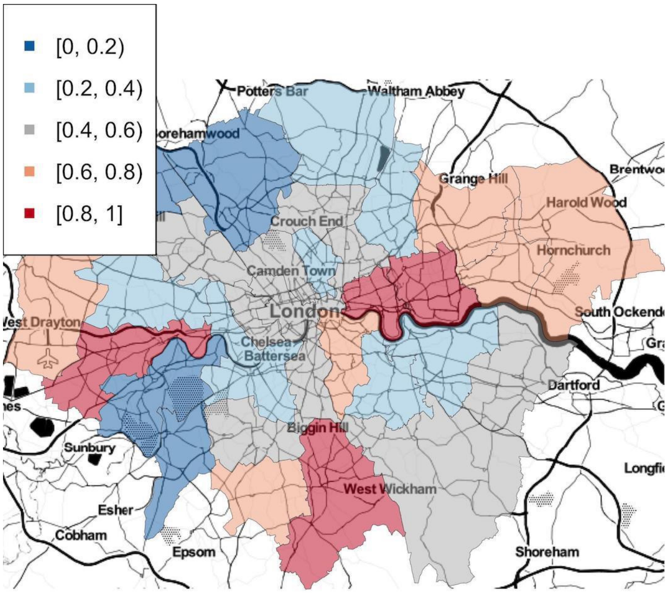

Figure 7 Map of probability of the relationship between weighted IMD and pregabalin prescription rates being positive for each clinical commissioning group: London (zoned in). IMD, Index of Multiple Deprivation.

has been accounted for. There are some more underlying causes which remain unknown and require further study. The models however have the limitation of assumption of independence between CCGs. This can potentially be avoided using GAM for the whole of England at the GP level; it is extremely computationally time-consuming. Further studies on both individual-level and regional-level data on whether the prevalence of chronic pain increased, for example, should also be done to be able to draw conclusions over the misuse or abuse potentials of pregabalin prescriptions.

Over half (0.589) of the GPs showed increasing estimates in pregabalin prescription rates over the period of January 2015 and June 2017. The mean estimate within England is approximately 0.011. That is to say the pregabalin prescription rates showed an overall increasing trend in England at a small rate. Such increasing prescription rate over time may indicate potential overprescribing in pregabalin. This upward trend falls in line with what has been claimed in the raw data and most literatures from different countries. India has seen an almost four times increase in dosage in pregabalin between 2012 and 2017.[20] The USA has also shown a rather plateaued trend in pregabalin use after 2008,[21 22] different from what was seen in reports in India,[20] Japan[23] and the UK.[4 24] However, nearly twice the increase was found later between 2012 and 2016 in the USA.[25] This could be due to the restrictions on pregabalin in the USA, which then leads to relative flat prescription trend afterwards, as the most commonly used gabapentinoid from 2002 to 2015 was gabapentin, as reported by Johansen.[21] Firm conclusions over the temporal trends which may suggest abuse and misuse will need analyses with more data on pregabalin doses from non-prescribers, for example.

A novel approach on how deprivation is related to pregabalin prescription in this article is presented. There are 138 CCGs estimated to have positive correlations between weighted IMD scores and pregabalin prescriptions. That is saying that for GP surgeries in these CCGs, the more deprived the areas are, the more pregabalin is likely to be prescribed. The reason behind this could be that people in more deprived areas are likely to suffer lower living standard and thus develop more medical problems. An indication of higher chance of overprescribing and deprivation is shown in a study in Sweden; lower income group is likely to be at higher risk of being prescribed higher than the maximum allowed dose of pregabalin.[26] The findings validate what was concluded by Green, O'Dowd and Watt *et al*, where they stated that prescribing trends were associated with GP deprivation quintile.[19] This may be a consequence of the CCGs being treated independently in this paper. As

Table 2 Model estimates for CCGs with the highest average pregabalin prescriptions per population between January 2015 and June 2017

CCG	Population weighted IMD	Global intercept	R-squared (adjusted)
NHS Doncaster CCG	−0.0521 (0.037)	10.011 (<0.001)	0.705
NHS Scarborough and Ryedale CCG	0.844 (<0.001)	−13.008 (<0.001)	0.866
NHS Wirral CCG	−0.005 (<0.001)	7.326 (<0.001)	0.722
NHS Canterbury and Coastal CCG	0.170 (0.061)	4.8796 (<0.002)	0.879
NHS Vale of York CCG	0.08 (0.028)	5.904 (<0.001)	0.724
NHS Nottingham West CCG	0.264 (<0.001)	2.389 (0.003)	0.668
NHS Morecambe Bay CCG	0.078 (<0.001)	5.131 (<0.001)	0.756
NHS West Hampshire CCG	0.068 (0.018)	6.045 (<0.001)	0.287
NHS North East Lincolnshire CCG	−0.075 (0.689)	8.299 (<0.001)	0.901
NHS Northern, Eastern and Western Devon CCG	0.135 (<0.001)	−5.123 (<0.001)	0.522

P values are shown in brackets.
CCG, clinical commissioning group; IMD, Index of Multiple Deprivation; NHS, National Health Service.

an overall trend, more GPs showed positive correlation between prescription and deprivation. However, a firm conclusion on this matter for the study requires more data, such as prevalence of neuropathic pain, both at the regional and individual levels. It is not clear what the patterns are for these estimates on map, but the highly positive areas are mostly located in Cornwall, Devon, Midlands and North Yorkshire, with a few CCGs shown in London. Unfortunately, the weighted IMD scores are not standardised; it is thus hard to make comparisons across the country between CCGs.

Another drawback of this paper is that extreme care needs to be shown when interpreting the time trend. It merely describes what the data for each individual GP surgery represent. The message across is to draw attention to the pattern for policy makers but not to reflect in any sense the quality of performance on their prescriptions. That is to say, an increasing trend in GP surgery does not mean that the GP surgery is performing poorly in terms of pregabalin prescriptions. Even with weighted IMD being adjusted for, there are still other factors which may result in increasing pregabalin prescriptions. For instance, a change in the nature of population of GP surgeries can result in higher pregabalin prescription rates. These estimates are also only useful at describing the temporal trend shown in pregabalin prescriptions for each individual GP surgery. They are not suitable for interpretation of the pregabalin quantities prescribed. The estimates should be looked at combined with the estimated baseline prescription rates. For example, Blackpool CCG showed neutral probability of increasing prescription (see figure 2). It however is in the top 20% for baseline prescription rates (see figure 6). Cautions should be particularly drawn when the baseline prescriptions are high and associated with high increasing rate of prescriptions.

To what extent should one raise alert for further investigation for CCGs or GP surgeries with high estimated increasing rate shall be combined with the baseline prescription rates (shown in figures 4 and 5)? For instance, baseline prescriptions which are in the top 20% can be seen in CCGs across Yorkshire, Nottinghamshire and Lincolnshire. More highlights also lie in the northwestern part of the country, mainly Blackpool, Lancashire and CCGs to the north of Manchester. Other northern CCGs with high starting rate are around Durham and Newcastle. Down in South, the high starting prescriptions mostly concentrate around CCGs near Essex and Kent, together with some CCGs in Herefordshire. Two of the London CCGs also appeared in the top 20 baseline prescription rates.

With these borne in mind, table 1 only shows the CCGs in which the GP surgeries with the highest estimated increasing rate in prescriptions lie; it does not conclude any performance quality related to these regions. Eight out of these listed regions are located to the North of London, which is in line with the results seen in figures 1–3. The top 2 southern CCGs showed very low baseline estimates. The raw data for the top 10 GPs showed higher pregabalin prescription rates than the national 90th percentile calculated for all years considered in the study, apart from the ones in Isle of Wight and Haringey CCGs, which are above the national average based on June 2017 data and below the 10th percentile for all years, respectively. Temporal trends on raw prescription data for these practices have shown at least moderate incline in the time period considered. Although most of these 10 GP surgeries lie within the CCGs with baseline prescriptions above the national average, causes for such increasing behaviours in each of these GP surgeries however remain uncovered and require further studies.

Overall, this study demonstrated how the prescription of pregabalin behaves regionally and temporally at the GP level. The models supported the existence of the North and South divide with deprivation taken into account. It also showed an overall increasing trend across the UK between January 2015 and June 2017. The models however have the limitation of assumption of independence in between CCGs when applied. This may be avoided using GAM for the whole of England at the GP level, which is extremely computationally time-consuming. Further studies at both individual-level and regional-level data on whether the prevalence of chronic pain increased, for example, should also be done to be able to draw conclusions over the misuse or abuse potentials of pregabalin prescriptions.

Contributors This is a joint work by ZZ, BT, BR and EL. EL provided medical comments and background. BT, BR and ZZ proposed the statistical approach to the study. ZZ practised the statistical modelling, data analyses and interpretations of the results. All authors were involved in the proposal and open discussion over the subject. All authors contributed to critical revision of the manuscript.

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