


ORIGINAL ARTICLE

Quality and use of unlicensed vitamin D preparations in primary care in England: Retrospective review of national prescription data and laboratory analysis

Mandy Wan^{1,2}  | Anish Patel² | Jignesh P. Patel^{2,3} | Greta Rait⁴ |
Stuart A. Jones² | Rukshana Shroff⁵

¹Pharmacy Department, Guy's and St Thomas' NHS Foundation Trust, Evelina London Children's Hospital, London, UK

²Institute of Pharmaceutical Science, King's College London, London, UK

³Department of Haematological Medicine, King's College Hospital Foundation NHS Trust, London, UK

⁴Research Department of Primary Care and Population Health, University of College London, London, UK

⁵Renal Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Correspondence

Mandy Wan, Guy's and St Thomas' NHS Foundation Trust, Evelina London Children's Hospital, Pharmacy Department, London, UK.
Email: mandy.wan@gstt.nhs.uk

Aim: To evaluate the type (licensed vs unlicensed) and cost of preparations used to fulfil vitamin D prescriptions in England over time, and to compare measured vitamin D content of selected vitamin D preparations against labelled claim.

Methods: Retrospective analysis of vitamin D prescription data in primary care in England (2008-2018). Laboratory analysis of 13 selected vitamin D preparations.

Results: Alongside a rise in the number of oral licensed colecalciferol preparations from 0 to 27 between 2012 and 2018, the proportion of vitamin D prescriptions in which licensed vitamin D preparations were supplied increased from 11.8 to 54.2%. However, the use of unlicensed food supplements (dose strength 400-50 000 IU) remained high, accounting for 39.7% of vitamin D prescriptions in 2018. The two licensed preparations showed mean (\pm SD) vitamin D content of $90.9 \pm 0.7\%$ and $90.5 \pm 3.9\%$ of the labelled claimed amount, meeting the *British Pharmacopeia* specification for licensed medicines (90-125% of labelled claim). The 11 food supplements showed vitamin D content ranging from $41.2 \pm 10.6\%$ to $165.3 \pm 17.8\%$ of the labelled claim, with eight of the preparations failing to comply with the food supplement specification (80-150% of labelled claim).

Conclusions: Despite the increasing availability of quality assured licensed preparations, food supplements continued to be used interchangeably with licensed preparations to fulfil vitamin D prescriptions. Food supplements, manufactured under less stringent quality standards, showed wide variations between measured and declared vitamin D content, which could lead to the risk of under- and over-dosing.

KEYWORDS

drug utilisation, pharmacy, quality use of medicines

1 | INTRODUCTION

Vitamin D has attracted considerable interest in recent years, not least because of increased awareness of the global prevalence of vitamin D

deficiency.¹ Since 2016, the advice from the UK government is that individuals should consider taking daily vitamin D supplement of 400 international units (IU) during the winter months (from October to March), and all year round for anyone who spends limited time

[Correction added on 3 September 2020, after first online publication: the middle initial of the fifth author has been inserted in this current version.]

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. British Journal of Clinical Pharmacology published by John Wiley & Sons Ltd on behalf of British Pharmacological Society

outdoors.² Vitamin D has also received wide media coverage arising from research linking vitamin D deficiency to an increased risk of myriad adverse health problems including diabetes, autoimmune conditions, cancers and infections, among others.³ This heightened interest has, in turn, been accompanied by a significant rise in healthcare and consumer spending on vitamin D preparations. In England, medical prescriptions for vitamin D monotherapy preparations in primary care increased by more than 8000% between 2008 and 2013, with the latest annual spending reported at £38 million.^{4,5} Likewise, consumer demand for vitamin D supplements has soared; 2018 retail data from the United Kingdom (UK) reported that vitamin D was the most popular vitamin monotherapy in this multimillion-pound industry.⁶ These figures are indicative of a growing trend and reflect widespread interest, although not substantiated by robust clinical trial data, in the role of vitamin D in health.³

Vitamin D is produced by cutaneous synthesis, with very small amounts obtained from the diet unless foods are fortified with vitamin D.^{7,8} Individuals who want to improve their dietary intake of vitamin D can do so through supplements. Vitamin D preparations with the intended purpose of supplementing dietary sources would generally fall within the legal definition of food supplements and are regulated under the provisions of general food law.^{9,10} However, vitamin D is also used clinically to treat or prevent vitamin D deficiency, and products making a medicinal claim would be subjected to the legislation governing medicinal products.^{11–13} These legal distinctions have consequently led to the availability of two types of vitamin D preparations which are regulated by two different quality standards. Notably, the regulatory requirements for manufacturing, quality control and labelling which apply to medicinal products are far more stringent than those relating to food supplements. While medicinal products are subjected to premarket licensing assessment and hence are referred to as licensed medicinal products, food supplements are outside of the licensing process (referred to as unlicensed preparations) and are readily available to the general public without medical supervision through retail outlets including supermarkets, pharmacies, health food stores and online retailers.

Deciding whether a product is a medicinal product or a food supplement is dependent on a number of factors and the amount of an ingredient is not the only criterion.¹¹ In practice, the classification is sometimes ambiguous in that two apparently similar preparations are classified differently, but to the consumer can appear to be virtually indistinguishable. The extent to which these situations arise with vitamin D preparations is not known and is further complicated by concerns about product quality, with reports of poor quality food-grade vitamin D preparations on sale in New Zealand, the United States and India.^{14–16} Questions over safety and legal issues associated with the use of food supplements to fulfil medical prescriptions of vitamin D in England has also been highlighted.⁵ However, neither the quality of food-grade vitamin D preparations, nor the trends in supply of these preparations, have been investigated in England to date. Therefore, the aims of this work were to evaluate the type and costs of preparations used to fulfil vitamin D

What is already known about this subject

- The supply of unlicensed vitamin D preparations (e.g. food supplements) against medical vitamin D prescriptions was common practice in England in 2014.
- Little is known about the quality difference between licensed and unlicensed vitamin D preparations marketed in England.

What this study adds

- The supply of licensed vitamin D preparations against prescriptions has increased over time.
- While the number of licensed vitamin D preparations has increased, 40% of all vitamin D prescriptions dispensed in 2018 were still of unlicensed preparations.
- Vitamin D content of unlicensed vitamin D preparations varies widely from labelled claim.

prescriptions in primary care in England over time, and to compare the measured vitamin D content of selected vitamin D preparations marketed in England against their labelled values.

2 | METHODS

2.1 | Licence status of vitamin D preparations

The National Health Service (NHS) Dictionary of Medicines and Devices (dm+d) via the NHS Technology Reference Data Update Distribution (TRUD) platform was used to identify all vitamin D preparations in use across primary care in England^{16,17}; both ergocalciferol (vitamin D₂) and colecalciferol (vitamin D₃) preparations were included. Combination preparations (eg, multivitamins, colecalciferol and calcium) were excluded in this study. For each preparation, we extracted data on its availability, dose strength, dosage form and type of vitamin D preparation, categorised as either licensed prescription-only medicines, licensed pharmacy medicines, licensed general sale list medicines, food supplements, “specials”, “imports” or “undetermined” (the legal definitions of these categories are provided in Supporting Information Method S1).

2.2 | Prescription data

All vitamin D prescriptions dispensed in primary care in England between 2008 and 2018 were extracted from Prescription Cost Analysis (PCA), a publicly available national dataset of prescription

reimbursement data.⁴ The PCA dataset complies with all aspects of the Code of Practice for Official Statistics and prescription processing activity has been internally audited to 99% accuracy. For each vitamin D presentation listed (further details on data processing of PCA dataset are provided in Supporting Information Method S2), we extracted data on the number of prescription items, unit quantity (ie, tablets or millilitres), net ingredient cost (NIC) and NIC per unit quantity (ie, cost per tablet).^{4,17,18} The NIC is the basic cost of the preparation at list price, excluding value added tax. Due to commercial confidentiality, contract prices are not released outside of the NHS.

2.3 | Vitamin D content analysis

As ergocalciferol prescriptions accounted for less than 1% of the annual total vitamin D prescriptions since 2015, only colecalciferol preparations were included in the laboratory analysis. Eleven colecalciferol food supplements, covering a range of dose strengths and different dosage forms, were purchased from five different UK pharmacies, health food stores and online retailers; this represents approximately 6% of the vitamin D food supplements listed in the NHS dm+d. The preparations were selected based on a convenience sample reflecting food supplements that were available for retail purchase and used by the general public. We also included two licensed preparations that are routinely used in the NHS: one UK licensed preparation and one imported licensed preparation from Germany. The UK and Germany operate to the same manufacturing quality standards with regard to licensed medicinal products. All preparations were stored at controlled room temperature in cardboard boxes and protected from light following purchase. All products were within their expiry date at the time of analysis.

A reverse-phase high-performance liquid chromatography (RP-HPLC) assay was developed to quantify colecalciferol content. All analytical work was carried out at King's College London (A. Patel and S. Jones). The assay was verified as fit for purpose against the criteria specified in the International Conference of Harmonisation (ICH) harmonised tripartite guideline on validation of analytical procedures.¹⁹ Details of the analytical development of the RP-HPLC method are provided in Supporting Information Method S3. Chromatographic separation was achieved on a C18 Synergi Hydro-RP column (250 × 4.6 mm, 4 μm, Phenomenex, USA) using an injection volume of 25 μL. The mobile phase comprised acetonitrile and methanol (55:45, %v/v), which was delivered at a flow rate of 1.5 mL/min with the column temperature held at room temperature. The ultraviolet detection was assessed at a wavelength of 265 nm. Data acquisition and processing were performed using ChromNAV software (Jasco, Tokyo, Japan).

Three individual samples from the 13 colecalciferol preparations were subject to extraction and HPLC analysis. Each of the three samples was injected twice in the HPLC and an average of the six results was reported. Details of the methods used to extract colecalciferol

from the preparations are provided in Supporting Information Method S3. The liquid preparations were vortexed for 2 minutes and the solid preparations were sonicated for 45 minutes to ensure the extraction solutions were homogeneous. To account for losses during extraction, ergocalciferol was used an internal standard to improve the accuracy in the quantification of colecalciferol.

2.4 | Data analysis

The characteristics of vitamin D preparations used across primary care in England were summarised using descriptive statistics. For prescription trend analysis, vitamin D prescriptions dispensed each year were calculated and presented as percentage of total prescription items and total NIC by type of vitamin D preparation. Using 2018 data, the NIC reported for each unlicensed preparation (food supplements, "specials", or "imports") was compared with the estimated NIC that would have been spent had licensed preparations been supplied instead. To do this, all vitamin D licensed preparations were categorised into mutually exclusive categories based on dosage form (eg. tablets, capsules, solution) and dose strength. A weighted NIC per unit quantity (ie. £ per tablet or £ per millilitre) was calculated for each category based on the NIC per unit quantity and the relative number of items with which each preparation was supplied within that category. The NIC per unit quantity for each of the unlicensed preparations was then substituted with the weighted NIC per unit quantity of the licensed equivalent with respect to dosage form and dose strength for calculating the estimated NIC value. In cases where there were no direct licensed equivalent substitutes, therapeutically equivalent substitutes (eg. 2000 IU tablet substituted for 2200 IU tablet) as reviewed and agreed by a clinician and a pharmacist were employed. In the analysis of prescription data, ergocalciferol and colecalciferol were also considered therapeutically equivalent.

For RP-HPLC analyses, peak areas were used for quantification of colecalciferol concentrations. The mean percentage difference from labelled content and standard deviation (SD) were calculated for all 13 preparations. An acceptable criterion of 90-125% of the stated amount was set in line with the *British Pharmacopoeia*, the official UK pharmaceutical standards for medicinal products.²⁰ We also compared our results against the food supplement standard, which has a wider acceptance range of 80-150% of the stated label amount.²¹ The relationship between preparation dose strength and the magnitude of percentage difference between measured and labelled contents was assessed with Spearman's correlation coefficient.

Data analysis was conducted using Stata 15 (Stata Corp, College Station, Texas, USA).

2.5 | Ethical approval

As the study used routinely collected data that was nonidentifiable and publicly available, ethics approval was not required.

3 | RESULTS

3.1 | Characteristics of vitamin D preparations

As of 9 September 2019, there was a total of 328 oral vitamin D preparations listed as available in the NHS dm+d; 35 (10.7%) were categorised as licensed prescription only medicines, 186 (56.7%) as food supplements, 102 (31.1%) as "specials" and 5 (1.5%) as "imports". A total of nine injectable formulations were also listed with three preparations each under the three categories of "licensed", "specials" and "imports".

The oral licensed medicinal preparations were available in a range of dose strengths (Table 1); tablets and capsules were available from 400 IU to 50 000 IU, and liquid preparations from 2 400 IU/mL to 50 000 IU/mL.

Food supplements, presented as tablets or capsules, spanned the same range of dose strengths (400 IU to 50 000 IU) as the licensed medicinal preparations (Table 1), but the liquid formulations were available in a narrower range from 400 IU/mL to 10 000 IU/mL. Oral preparations categorised as "specials" covered the broadest range of dose strengths of all the preparations from 20 IU/mL to 600 000 IU/mL.

3.2 | Trends in vitamin D prescriptions

During the study period, the number of different preparations used to fulfil vitamin D prescriptions increased from 42 to 268; the increase was attributed to an increase in the use of both colecalciferol food supplements and licensed oral medicinal-grade colecalciferol preparations (0 to 27) (Figure 1A).

TABLE 1 Dose strengths of oral vitamin D preparations listed as available in the NHS dm+d (as of 9 September 2019)

Dose strengths	Licensed preparations, n = 35	Food supplements, n = 186
Tablets/capsules (IU/dose unit)		
400	1	20
401-1000	11	56
1001-3000	0	18
3001-10 000	3	29
10 001-50 000	9	37
Liquid (IU/mL)		
400	0	1
401-1000	0	2
1001-3000	6	18
3001-10 000	0	2
10 001-50 000	5	0
Liquid (IU/drop or IU/spray)		
<400	0	1
400	0	1
401-1000	0	1

Between 2008 and 2018, the percentage increase in vitamin D prescriptions was 29 842%, (23 543 to 7 049 322) in primary care in England. Ergocalciferol prescriptions accounted for 96.8% of the total vitamin D prescriptions in 2008, decreasing to 5.6% by 2012 and 0.2% in 2018 (Figure 1B). Colecalciferol prescriptions showed a reciprocal trend to ergocalciferol.

Analysis by the type of preparation showed that the supply of licensed colecalciferol preparations increased from 8.7% in 2012 to 54.1% in 2018 (Figure 1B). The proportion of prescriptions using colecalciferol food supplements was 61.3% in 2012, and the proportion remained high at 39.7% in 2018. The overall use of "specials" preparations decreased over time and has remained at less than 0.6% since 2015.

3.3 | Vitamin D preparation quality

The two licensed medicinal-grade preparations had mean (\pm SD) percentage vitamin D contents compared to the label claims of $90.91 \pm 0.68\%$ and $90.53 \pm 3.93\%$, respectively, which correspond to the quality standard of medicinal products (90-125%). The vitamin D content of food-grade preparations varied from $41.2 \pm 10.6\%$ to $165.3 \pm 17.8\%$ of the labelled value (Figure 2). A total of eight of the

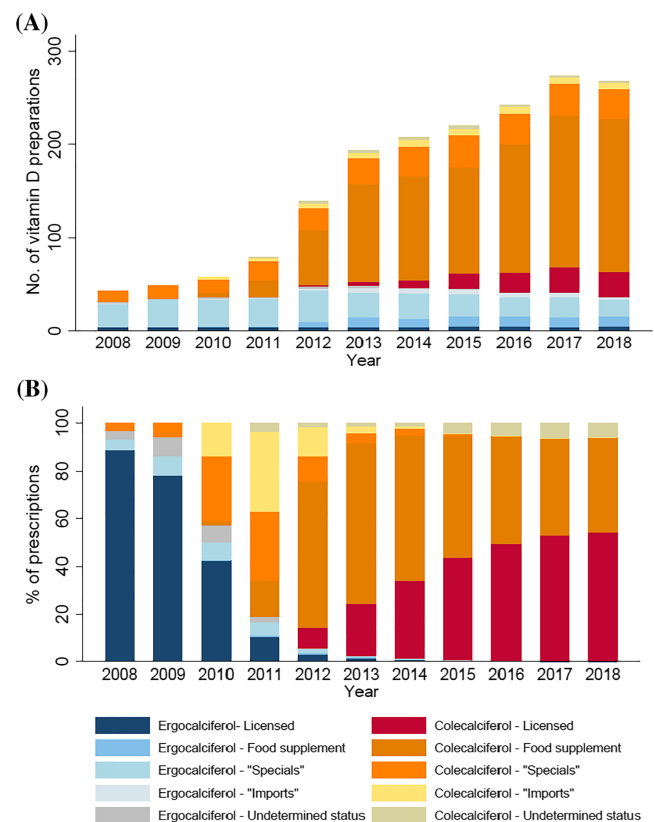


FIGURE 1 (A) Number of vitamin D preparations used to fulfil vitamin D prescriptions in primary care in England between 2008 and 2018 by type of vitamin D preparation. (B) Percentage of vitamin D prescriptions dispensed in primary care in England between 2008 and 2018 by type of vitamin D preparation

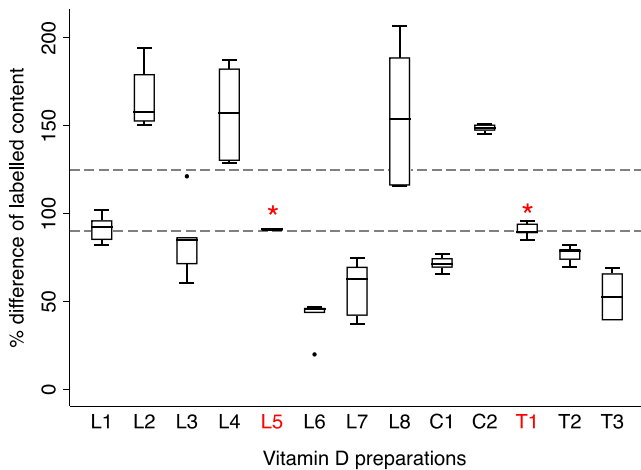


FIGURE 2 Percentage difference between measured colexicalferol content and labelled value for various colexicalferol preparations on the UK market. Red * represents licensed medicinal products; L, liquid preparation; C, soft gelatine capsule; T, tablet. Grey dotted lines represent the acceptable criterion of 90-125% as required of licensed medicines

11 food-grade preparations tested failed to comply with the food supplement standard of 80-150% of the labelled claim. There was no association between the dose strength of the preparation and the magnitude of percentage difference from labelled values ($P > 0.5$). Vitamin D food supplements presented as solutions in dropper bottles ($n = 3$) showed high intersample variability, with SDs of 42, 28.1 and 17.3.

3.4 | Cost comparison between licensed and unlicensed vitamin D preparations

In 2018, the total cost of vitamin D prescriptions was £38.4 million (Figure 3). Of that, £18.6 million was for tablets/capsules containing

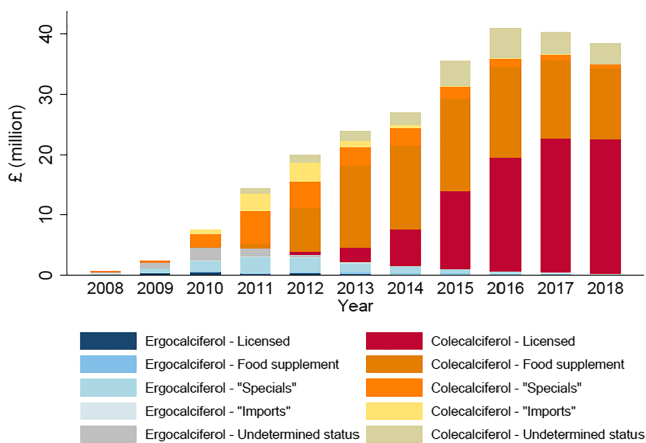


FIGURE 3 Net ingredient costs of vitamin D prescriptions dispensed in primary care in England between 2008 and 2018 by type of vitamin D preparation

≤800 IU of vitamin D, £15.9 million for tablets/capsules containing >800 IU of vitamin D, £3.7 million for oral solution and £0.1 million for injections.

A licensed equivalent preparation was identified for all 236 unlicensed preparations (food supplements, “specials”, and “imports”). The median cost difference between annual spending on an unlicensed preparation and the estimated cost that would have been spent for its licensed equivalent was a saving of £347, with wide variations in cost from a saving of £6980 to an additional cost of £313 (interquartile range).

If all unlicensed preparations as supplied in 2018 were replaced with licensed vitamin D preparations, the annual cost would have totalled £43.5 million, an increase of 13.4% higher than current cost. The increase in estimated cost was largely attributed to two food supplements that together accounted for 9% of the total vitamin D prescriptions in 2018 and whose unit costs were considerably lower even compared to other food supplements of the same strength (priced at £0.01 vs median cost of £0.1 per 1,000 IU tablet and £0.13 vs median cost of £0.28 per 20 000 IU capsule, respectively).

4 | DISCUSSION

Using national prescribing data, this study showed that patients presenting with a vitamin D prescription in 2018 were almost as likely to be supplied with a food supplement as a licensed medicinal product despite the availability of licensed preparations of equivalent strength. This suggests that food supplements and licensed preparations, both available in a wide range of dose strengths from 400 to 50 000 IU, were being used interchangeably. However, food supplements vary in vitamin D content by up to 60% compared to their labelled claim, with a potential risk of under- or over-dosing the patient. Existing regulations for vitamin D preparations need to be revised to minimise risk and support consumers in making informed decisions on the use of vitamin D preparations.

An earlier review highlighted safety and legal concerns associated with a high proportion of vitamin D prescriptions in primary care in England being supplied with food-grade vitamin D preparations.⁵ Arguably, in 2013, when there were only six licensed oral vitamin D preparations on the market, it may have been too soon to draw firm conclusions about the appropriateness of such a practice, but the current study, 5 years on, provides evidence that the initial concerns were valid. Not only has the present study shown that food supplements continue to be used in 39.7% of vitamin D prescriptions in primary care in England despite the availability of licensed preparations of equivalent strength, but these food supplements may be of sub-standard quality and are not necessarily lower in cost compared to licensed preparations.

The substantial difference between measured and declared vitamin D content in food supplements shown in our study is in keeping with published data from other countries.^{14-16,22,23} Compared with variations reported by LeBlanc et al for preparations marketed in the United States (9-140%) and Garg et al (8-201%) for

New Zealand, our results showed a narrower range of variability.^{14,15} This difference could be a reflection of the differences in legislative requirements between countries, but as eight of the 11 food supplements tested in the present study failed to comply with national food quality standards, this seems unlikely.²¹ Rather, the variability in vitamin D content in food supplements probably arises from differences in manufacturing and quality control practices between manufacturers, which in turn may reflect the general lack of regulatory oversight of food supplement manufacturers in these countries.¹⁰ Notably, our result showing variations in measured vitamin D contents outside of the acceptable range of the declared values suggests that food supplement manufacturers are likely to be operating with variable and less stringent control in handling product deviations, as well as pointing to challenges faced by the regulator in enforcing quality standards in this industry.^{10,24} The general perception that all food supplements are regarded as low risk may also be a contributing factor.

Our findings have implications in clinical practice. From a public health perspective, data generated from dietary intake assessments, which in turn may be used to provide the evidence base for developing public health policy on preventing vitamin D deficiency, could potentially be misleading if estimations of dietary intake rely entirely on label information for vitamin D food supplements. For individuals, our findings would suggest that some may receive up to 60% more or less vitamin D than intended. The clinical significance of this magnitude of variation for low-strength preparations may be of little clinical concern given vitamin D has a wide therapeutic window, although it is possible that high-risk individuals may not receive sufficient vitamin D to correct the risk of their vitamin D deficiency. For high-strength preparations, there is a risk of inducing vitamin D toxicity, with an associated risk of hypercalciuria and renal damage, particularly in at-risk populations. The rise in the number of reports of vitamin D toxicity, which have been attributed to errantly manufactured food-grade preparations, especially in individuals receiving high doses of vitamin D over a long period of time without medical supervision, should be of concern to both clinicians and consumers.^{25,26} Moreover, the mismatch between intended and actual dose received could mislead clinicians in suspecting other diagnoses and carrying out unnecessary investigations.

The findings also call for clinicians to question the continued use of food supplements to fulfil their vitamin D prescriptions. In England, the use of unlicensed preparations is legally permitted when there is no suitable licensed alternatives.²⁷ Therefore if generic prescriptions are being written by clinicians then it is difficult to understand why almost half of the time unlicensed food supplements are being supplied. The *British National Formulary*,²⁸ a reference book that contains highly authoritative information on medicines prescribing in the UK, lists both medicinal and food-grade vitamin D preparations, which may inadvertently be misinterpreted by clinicians to mean that the preparations can be used interchangeably. However, without evidence that a particular brand is superior to another and along with 81% of primary care prescriptions in England prescribed generically,²⁹

it is unlikely that clinicians are deliberately choosing food-grade preparations. An alternative explanation is that clinicians are not aware that food supplements are being used by pharmacists to fulfil their generic vitamin D prescriptions. It is possible that pharmacists are intentionally opting to use food supplements as a means to reduce NHS spending; after all, if only licensed preparations were used, this study predicted that the cost of vitamin D prescriptions in 2018 would have been 13.4% higher (£5 million) compared to the current cost.

The regulatory landscape for vitamin D preparations in England does not appear to help clinicians, pharmacists, patients or consumers to distinguish the differences in vitamin D product quality and intended use. There appears to be a regulatory anomaly for vitamin D preparations in that whilst all licensed vitamin D medicinal preparations of dose strength from 400 IU to 50 000 IU are classified by the drug regulator as products requiring medical prescription, ie, as described in law as “likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision”, equivalent strengths food supplements are readily available on the market for general sale.³⁰ Interestingly, there is no distinction between medicinal and food-grade vitamin D preparations in terms of their vitamin D content in England, which contrasts with countries such as Canada and Australia where all preparations containing more than 1000 IU of vitamin D are regulated as licensed medicinal products.^{12,13} Similarly, countries including Belgium, Norway and others have set statutory maximum limits for the amount of vitamin D permitted in food supplements.^{31,32} It is also of interest to note that food supplements, manufactured under less stringent quality standards in England, may have much lower or higher vitamin D contents than equivalent strengths of medicinal preparations due to having a wider tolerance range around the declared value on the label.

Our data show that vitamin D food supplements on general sale are available in a wide range of dose strengths of up to 50 000 IU. Considering the recommended nutrient intake (RNI) in England for most people is only 400 IU of vitamin D per day, and even after taking into account the higher doses recommended by some organisations (up to 2000 IU per day) and the recommended tolerable upper intake level of 4000 IU/day,^{2,33,34} the availability of these high-strength food supplements would detract from the public health message. Indeed, these high-strength food supplements are not intended for daily administration, but preparations labelled as 50 000 IU weekly, equating to 18 times above the RNI, are freely available for purchase by consumers and can be easily misused, eg, taken daily, without medical supervision. Such preparations expose consumers to unnecessary risks without evidence of benefit.²

From a clinical perspective, it would therefore seem sensible to regulate high-strength vitamin D preparations as medicinal products on the UK market. This would ensure that all prescriptions for the clinical treatment of vitamin D deficiency would be supplied with licensed medicinal-grade preparations, but at the same time not unnecessarily restrictive to ensure consumers have appropriate access

to preparations at recommended supplement doses to improve their dietary intake of vitamin D. In light of the UK government's recent recommendation to limit vitamin D prescribing to therapeutic treatment of vitamin D deficiency only, the £18.6 million saved in costs (based on 2018 figures for vitamin D tablets or capsules preparations containing ≤ 800 IU alone) would outweigh the additional estimated cost associated with using only licensed vitamin D preparations to fulfil vitamin D prescriptions.^{4,35} This would allow clinicians, pharmacists and patients to be assured that the dose of vitamin D being received by patients requiring treatment for vitamin D deficiency is as intended.

The problem with regulatory oversight of food supplements has been raised for many years, but the supply of food supplements against medical prescriptions when licensed equivalents are available, as shown in this study, further demonstrates the need for improved oversight of vitamin D preparations. Moreover, the prescribing trend for vitamin D preparations may reflect similar prescribing patterns of other supplements, and the implication of these on the clinical management of patients would deserve similar attention.

4.1 | Strengths and limitations of the study

We used the complete prescription reimbursement data set for all vitamin D prescriptions dispensed in primary care in England, not just a sample. Moreover, as our data set was based on prescription reimbursement and thus data interpretation was not affected by generic prescribing, we were able to provide a comprehensive analysis of the different vitamin D preparations used, providing real-world evidence of practice. We note that our analysis was based on data in England, but we expect similar prescription patterns across the UK given the similarities in primary care practice for prescribing and dispensing prescriptions.

We evaluated the vitamin D content of only a small sample of vitamin D preparations which may not be representative of all the preparations marketed in England and further comprehensive analysis is warranted. Nevertheless, the results we obtained were consistent with published literature. Our RP-HPLC method was verified as fit for purpose against the ICH standards in terms of accuracy, precision and linearity, and was used rather than the method stated in the *British Pharmacopeia* due to its ability to assess the vitamin D content in both food- and medicinal-grade preparations. We did not investigate the reasons for the variability in vitamin D contents using stability indicating methods because we were unsure of the grade of vitamin D originally employed in the food-grade preparations. We also did not investigate batch-to-batch variability in colexiferol content of the different preparations, and the number of samples per preparation tested was less than that recommended by the *British Pharmacopeia*. However, our study conclusion would remain valid in the case of minimum variability while the presence of batch-to-batch/sample-to-sample

variability would further highlight the problem of substandard quality with these food supplement preparations.

5 | CONCLUSIONS

The study showed that whilst food- and medicinal-grade vitamin D preparations were being used interchangeably to fulfil primary care vitamin D prescriptions, food-grade preparations, which are manufactured under less stringent quality standards, seldom contained the expected amount of vitamin D. The work provided evidence that the number and variety of licensed medicinal-grade vitamin D preparations was sufficient to enable the supply of only licensed medicinal-grade preparations against all vitamin D prescriptions. Clinicians and pharmacists must therefore change practice to use licensed vitamin D preparations whenever possible. We call on regulatory bodies to safeguard public health and ensure that only medicinal-grade vitamin D preparations are used to treat vitamin D deficiency.

ACKNOWLEDGEMENTS

M.W. is a doctoral student supported by a Clinical Doctoral Research Fellowship grant (ICA-CDRF-2016-02-057) from the UK National Institute for Health Research (NIHR). R.S. holds a Career Development Fellowship with the NIHR. Part of the work took place in the Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

CONTRIBUTORS

M.W., R.S. and J.P. were involved in the conception of the study. A.P., under the supervision of S.J., carried out the laboratory analysis. M.W. had full access to the prescription data set and performed the data extraction and analysis. M.W., A.P., J.P., G.R., S.J. and R.S. contributed to the interpretation of data. M.W. drafted the manuscript, which all authors contributed to and revised critically before approval of the final manuscript. M.W. is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DATA AVAILABILITY STATEMENT

The NHS Dictionary of Medicines and Devices and the NHS Prescription Cost Analysis dataset are publicly available via NHS Digital

at <https://isd.digital.nhs.uk/trud3/user/guest/group/0/home> and <https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis>, respectively. Openprescribing.net is also a free, openly accessible tool available at <https://OpenPrescribing.net>.

ORCID

Mandy Wan  <https://orcid.org/0000-0001-8802-0425>

REFERENCES

- Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? *J Steroid Biochem Mol Biol*. 2014;144PA:138-145.
- Scientific Advisory Committee on Nutrition. SACN vitamin D and health report. 2016.
- Theodoratou E, Zoulaki I, Zgaga L, Ioannidis JPA. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ*. 2014;348:g2035. <https://www.bmj.com/content/348/bmj.g2035>
- NHS Digital. Prescription Cost Analysis. <https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis> (accessed 14 Dec 2019)
- Davies JS, Poole CD, Feldschreiber P. The medico-legal aspects of prescribing vitamin D. *Br J Clin Pharmacol*. 2014;78(6):1257-1263.
- Mintel Press. D outshines C to become the UK's favourite vitamin. <https://www.mintel.com/press-centre/social-and-lifestyle/d-outshines-c-to-become-the-uks-favourite-single-vitamin-supplement>. Accessed December 14, 2019.
- Shroff R, Knott C, Rees L. The virtues of vitamin D – but how much is too much? *Pediatr Nephrol*. 2010;25(9):1607-1620.
- Holick MF. Vitamin D deficiency. *New Engl J Med*. 2007;357(3):266-281.
- Food Standards Agency. Food supplements. <https://www.food.gov.uk/business-guidance/food-supplements>. Accessed December 14, 2019.
- Dwyer JT, Coates PM, Smith MJ. Dietary supplements: regulatory challenges and research resources. *Nutrients*. 2018;10:41. <https://www.mdpi.com/2072-6643/10/1/41>
- Medicines and Healthcare products Regulatory Agency. A guide to what is a medicinal product. 2016. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/759581/012_GN8_-_final_2018_combined_doc_Oct.pdf. Accessed December 14, 2019.
- Government of Canada HC. Prescription Drug List. 2014. <https://hpr-rps.hres.ca/pdl.php?lang=en#a1>. Accessed December 14, 2019.
- The Therapeutic Goods Administration. Poisons Standard December 2019. <https://www.legislation.gov.au/Details/F2019L01471>. Accessed December 14, 2019.
- LeBlanc ES, Perrin N, Johnson JD, Ballatore A, Hillier T. Over-the-counter and compounded vitamin D: Is potency what we expect? *JAMA Intern Med*. 2013;173:585-586.
- Garg S, Sabri D, Kanji J, et al. Evaluation of vitamin D medicines and dietary supplements and the physicochemical analysis of selected formulations. *J Nutr Health Aging*. 2013;17:158-161.
- Khadgawat R, Ramot R, Chacko KM, Marwaha RK. Disparity in cholecalciferol content of commercial preparations available in India. *Indian J Endocrinol Metab*. 2013;17:1100-1103.
- NHS Digital. Technology Reference data Update Distribution: Dictionary of medicines and devices (dm+d). <https://isd.digital.nhs.uk/trud3/user/guest/group/0/pack/6>. Accessed December 14, 2019.
- OpenPrescribing.net, EBM DataLab, University of Oxford, 2020. <https://openprescribing.net/>. Accessed December 14, 2019.
- International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use. Quality guidelines. <https://www.ich.org/page/quality-guidelines>. Accessed December 14, 2019.
- Medicines and Healthcare products Regulatory Agency. *British Pharmacopoeia*, 2019. London: Stationery Office; 2019.
- European Commission. Guidance document for competent authorities for the control of compliance with EU legislation with regard to the setting of tolerances for nutrient values declared on a label. 2012. https://ec.europa.eu/food/sites/food/files/safety/docs/labelling_nutrition-vitamins_minerals-guidance_tolerances_1212_en.pdf. Accessed December 14, 2019.
- Nimalaratne C, Sun C, Wu J, Curtis JM, Schieber A. Quantification of selected fat soluble vitamins and carotenoids in infant formula and dietary supplements using fast liquid chromatography coupled with tandem mass spectrometry. *Food Res Int*. 2014;66:69-77.
- Verkaik-Kloosterman J, Seves SM, Ocké MC. Vitamin D concentrations in fortified foods and dietary supplements intended for infants: implications for vitamin D intake. *Food Chem*. 2017;221:629-635.
- Starr R. Too little, too late: ineffective regulation of dietary supplements in the United States. *Am J Public Health*. 2015;105(3):478-485.
- Taylor P, Davies J. A review of the growing risk of vitamin D toxicity from inappropriate practice. *Br J Clin Pharmacol*. 2018;64:1121-1127.
- Shea RL, Berg JD. Self-administration of vitamin D supplements in the general public may be associated with high 25-hydroxyvitamin D concentrations. *Ann Clin Biochem*. 2017;54(3):355-361.
- Medicines and Healthcare products Regulatory Agency. The supply of unlicensed medicinal products ('specials'), MHRA Guidance Note 14. 2014. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdf. Accessed December 14, 2019.
- Joint Formulary Committee. *British National Formulary (online)*. London: BMJ Group and Pharmaceutical Press <https://bnf.nice.org.uk/>. Accessed December 14, 2019.
- Medicines optimisation - generic prescribing|NHSBSA. <https://www.nhsbsa.nhs.uk/epact2/dashboards-and-specifications/medicines-optimisation-generic-prescribing>. Accessed December 14, 2019.
- European Parliament, Council of the European Union. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. 2001. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. Accessed December 14, 2019.
- The Norwegian Food Safety Authority. Notification regarding regulation relating to amendment of regulation on food supplements. 2016. <https://ec.europa.eu/growth/tools-databases/tris/en/search/?trisation=search.detail&year=2016&num=9040>. Accessed December 14, 2019.
- Federal Public Service for Health, Food Chain Safety and Environment. Royal Decree amending the Royal Decree of 3 March 1992 concerning the placing on the market of nutrients and foodstuffs to which nutrients have been added. 2016. <https://ec.europa.eu/growth/tools-databases/tris/en/search/?trisation=search.detail&year=2016&num=615>. Accessed December 14, 2019.
- Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930.
- Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): National Academies Press (US); 2011.

35. NHS England. Conditions for which over the counter items should not routinely be prescribed in primary care: Guidance for CCGs. 2018. <https://www.england.nhs.uk/wp-content/uploads/2018/03/otc-guidance-for-ccgs.pdf>. Accessed December 14, 2019.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Wan M, Patel A, Patel JP, Rait G, Jones SA, Shroff R. Quality and use of unlicensed vitamin D preparations in primary care in England: Retrospective review of national prescription data and laboratory analysis. *Br J Clin Pharmacol.* 2020;1–9. <https://doi.org/10.1111/bcp.14521>