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# Comparative effectiveness of vitamin D supplementation via buccal spray versus oral supplements on serum 25-hydroxyvitamin D concentrations in humans: a systematic review protocol.

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Lippincott, Williams & Wilkins

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1 **This is the submitted version of this paper. The final draft post referring will be archived as**  
2 **soon as available.**

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5 **Comparative effectiveness of vitamin D supplementation via buccal spray versus oral**  
6 **supplements on serum 25-hydroxyvitamin D concentrations in humans: a protocol for a**  
7 **systematic review**

8  
9 **Introduction**

10 Vitamin D with parathyroid hormone (PTH) regulates intestinal absorption of calcium, maintaining  
11 adequate concentrations for bone mineralization.<sup>1,2</sup> Vitamin D deficiency has been associated with  
12 the pathogenesis of several diseases including cardiovascular disease, some cancers and  
13 autoimmune diseases.<sup>3-5</sup> Many experts report of a major global pandemic of vitamin D deficiency and  
14 insufficiency, affecting one billion people worldwide.<sup>6-8</sup> Vitamin D deficiency is linked with bone  
15 metabolism disorders and reduced bone mineral density.<sup>2</sup> In view of the high prevalence of vitamin D  
16 deficiency and the risk to musculoskeletal health, professional societies and government bodies  
17 worldwide have in the past decade issued dietary reference intakes (DRI) for vitamin D. The DRI for  
18 the general population over one year of age is 10 micrograms (mcg) a day in UK, equivalent to 400  
19 international units (IU), and 15 mcg (600 IU) in USA and the rest of Europe.<sup>9-11</sup>

20  
21 Vitamin D exists in two forms; vitamin D3 (cholecalciferol) is a fat soluble vitamin that is mainly  
22 derived from 7-dehydrocholesterol upon exposure of the skin to UV-B radiation<sup>1</sup> and vitamin D2  
23 (ergocalciferol) which is found in only a few foods including fatty fish, egg yolk and fortified foods.<sup>1,2</sup>  
24 The liver and kidney convert vitamin D2 and D3 into the biologically active form of vitamin D, calcitriol  
25 (1,25 dihydroxyvitamin D [1,25-OHD]). The widely accepted measure of vitamin D nutrient status is  
26 via measurement of serum 25-hydroxyvitamin D (25-OHD) concentration<sup>12,13</sup> because it has longer  
27 half-life (2-3 weeks versus 4 hours) than the active form (1,25-OHD).<sup>1</sup> In the adult population, serum  
28 25-OHD concentration <12 ng/ml is considered deficient, 12-20 ng/ml insufficient and >20 ng/ml  
29 sufficient based on rickets prevention<sup>10,14</sup> however there is considerable international debate on the  
30 definition and optimal serum levels of vitamin D.<sup>1,3,15</sup>

31  
32 Several factors influence vitamin D status in the human body: sun exposure, skin pigmentation, oral  
33 intake of the vitamin, its absorption from the intestine and its distribution in the body, as vitamin D is  
34 predominantly sequestered in adipose tissue.<sup>1,16,17</sup> Vitamin D deficiency often occurs in people who  
35 are not exposed to sufficient sunlight, and in individuals with intestinal malabsorption disorders (e.g.  
36 inflammatory bowel disease or short bowel syndrome) the prevalence may be as high as 78%.<sup>9,18</sup>  
37 Conventional vitamin D replacement is an oral dietary supplement, such as a tablet, but in patients  
38 with malabsorption, up to 2-3 times the usual amount of oral vitamin D may be required to achieve  
39 sufficiency.<sup>15,19</sup> Additionally, the response to supplementation in malabsorptive disorders can be  
40 unpredictable.<sup>18,20,21</sup>

41  
42 Vitamin D absorption occurs through a combination of passive diffusion and active transport  
43 mechanisms involving membrane carriers and cholesterol transporters.<sup>22,23</sup> Vitamin D is lipid soluble  
44 and can be absorbed with long-chain triglycerides in the small intestine.<sup>24,25</sup> Ingested vitamin D is  
45 incorporated into chylomicrons which are released into the systemic circulation via the lymphatic  
46 system and then activated in the liver.<sup>26,27</sup> Absorption studies indicate that individuals with  
47 malabsorption are 30-70% less likely to absorb oral vitamin D.<sup>21,28</sup> The gastrointestinal tract is  
48 aqueous in nature; there is some evidence that vitamin D delivered in an oil-based formulation has  
49 improved solubility and ability to be incorporated into chylomicrons.<sup>29,30</sup> A systematic review that  
50 evaluated the impact of different vehicles (powders, lipids, ethanol) on the absorption of vitamin D  
51 supplements reported that absorption was greatest in the oil-based vehicle.<sup>31</sup> When the response to  
52 escalating doses of oral vitamin D supplements fails, intramuscular (IM) vitamin D is an alternative.  
53 However IM injections are associated with high inter-individual variability in absorption<sup>32</sup> and slower  
54 onset of repletion<sup>33</sup>. Additionally, an IM injection can be a painful procedure,<sup>20</sup> and also requires a  
55 visit to a healthcare facility at one to three month intervals, adding to the administrative burden. There  
56 is interest in the potential of vitamin D supplementation in people with malabsorption via the buccal  
57 and sublingual mucosa of the oral cavity which is able to circumvent the gastrointestinal tract.<sup>34,35</sup>

58  
59 The membranes of the oral cavity consist of the buccal membrane (inner cheek and gumline), palatal  
60 (roof of the mouth) and sublingual region (under the tongue)<sup>36</sup> however the buccal and sublingual  
61 routes have a higher membrane permeability.<sup>37</sup> Vitamin D is lipophilic (fat soluble) and sprays  
62 typically contain a solubilizing agent, such as oil in a micro-emulsified preparation and excipients  
63 including emulsifiers and permeation enhancers. This facilitates absorption across the oral  
64 membrane and into the systemic circulation, thus bypassing the gastrointestinal tract.<sup>36-38</sup> Buccal  
65 spray delivery may result in a more effective route of administration and could reduce the burden  
66 associated with the IM route.<sup>37</sup> To date, only one case study of sublingual vitamin D is identified in  
67 the literature, and corrected a vitamin D deficiency in an adult with Crohn's disease and end-  
68 ileostomy.<sup>39</sup> However, a few studies have investigated buccal vitamin D spray, in comparison to  
69 capsules or placebo and in all no safety concerns have been identified.<sup>40-42</sup>

70  
71 In 2015, the first clinical trial of buccal spray vitamin D in humans was published. In an Indian study,  
72 Satia et al.<sup>42</sup> performed a two-way cross-over of buccal spray vitamin D versus equivalent dose gel  
73 capsule in a study lasting 30 days per treatment arm with a 30-day washout in between. A daily  
74 regimen of 3000 international units (IU) buccal spray significantly increased mean serum 25-  
75 OHD concentration as compared to the soft gelatin capsule, by 1.9 times in both healthy subjects  
76 (percentage change from baseline, 43% vs. 22%,  $p < 0.0001$ ) and 2.6 times in those with intestinal  
77 malabsorption (118% vs. 36%,  $p < 0.005$ ). In 2016, Todd et al.<sup>40</sup> investigated a daily dose of 3000 IU  
78 buccal spray versus capsules in healthy participants (n22) in a randomized, two-way cross-over study  
79 conducted in wintertime lasting four weeks with a 10 week washout between treatments. In contrast,  
80 both spray and capsule were equally effective in raising serum 25-OHD concentrations (percentage

81 change from baseline 44% and 51%, respectively,  $p = 0.313$ ).<sup>40</sup> The discrepancies between these  
 82 study results may in part result from differences in baseline vitamin D levels. In the former study by  
 83 Satia et al.,<sup>42</sup> there was considerable intra-subject variability in baseline vitamin D levels between  
 84 healthy subjects and those with malabsorption. It is known that 25(OH)D concentration has a  
 85 significant inverse correlation with baseline 25(OH)D concentrations, with those that are deficient  
 86 responding more rapidly to supplementation than those that are replete.<sup>43,44</sup> In 2017, Todd et al.<sup>41</sup>  
 87 used 3000 IU buccal vitamin D spray per day over a study period of 12 weeks and corrected vitamin  
 88 D deficiency in athletes (n42) versus placebo spray ( $p = 0.006$ ) however the spray was used as a  
 89 secondary endpoint. No other directly relevant reviews on buccal spray vitamin D are available in the  
 90 literature and it is not clear whether other studies have investigated buccal spray to treat a low vitamin  
 91 D level.

92  
 93 The primary objective of this review is to determine if there is enough evidence to conclude whether  
 94 vitamin D supplementation via buccal spray is comparable in effectiveness to oral supplements, taken  
 95 via the oral-gastric route. The secondary objective is to identify any adverse effects, as reported by  
 96 the researcher. Safety is important to consider as treatments can be effective but are not useful if  
 97 they have undesirable side effects. Effectiveness will be determined through evaluation of  
 98 quantitative experimental studies using buccal spray vitamin D versus an oral comparator or placebo  
 99 on measured serum 25-hydroxyvitamin D (25-OHD) levels. This will provide information on how the  
 100 buccal spray compares in efficacy to another type of vitamin D supplement, or a placebo. It is  
 101 anticipated that this information may help to inform clinical practice. We will consider experimental  
 102 studies: randomized controlled trials (RCTs) and controlled studies (quasi-experimental studies) in  
 103 both in adults and in children with no restriction imposed on health status (i.e. healthy subjects or  
 104 patient groups).

105  
 106 To our knowledge, this is the first review to have been conducted on the effectiveness of buccal spray  
 107 vitamin D on serum 25-OHD levels. A search of the *JBI Database of Systematic Reviews and*  
 108 *Implementation Reports* and *JBI Registered Systematic Reviews*, Cochrane Systematic Review  
 109 Database, MEDLINE (Ovid), DARE, PROSPERO, EPISTEMONIKOS, and ACCESSSS on 12/06/18  
 110 reveals no systematic or review paper on buccal spray vitamin D.

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 112 **Review Question**

113 What is the effectiveness of vitamin D supplementation via buccal spray compared to oral  
 114 supplements on serum 25-hydroxyvitamin D concentrations in humans?

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 116 **Keywords**

117 Buccal spray; Comparative effectiveness; 25-hydroxyvitamin D; Supplements; Vitamin D

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 119 **Inclusion and Exclusion Criteria**

120 A summary of the inclusion criteria can be found in Appendix I: Inclusion and exclusion criteria

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#### Population

This review will consider both children and adults with no restriction on age, gender, ethnicity or health status. In vitro or studies in animals are excluded. The purpose of the study is to evaluate the effectiveness of vitamin D supplementation via spray in humans. Findings from both the adult and pediatric population are relevant as they will provide important information regarding the effectiveness of buccal spray vitamin D delivery on serum vitamin D levels. In addition, no restriction is placed on the health status of the study population. A preliminary search reveals studies in both healthy and malabsorption populations, with and without vitamin D deficiency. One study has combined both healthy and malabsorption populations together for comparison. In such an under-researched area, restricting the review to only select populations would exclude potentially relevant studies which address the research question. It may also highlight studies in which population groups were compared, which may facilitate sub-group analysis.

#### Intervention(s)

This review will consider studies that evaluate vitamin D supplementation of oral or buccal vitamin D spray (either vitamin D2 or vitamin D3) administered to the buccal mucosa. A preliminary scope of the literature reveals that the majority of studies use buccal vitamin D3 spray. Although most authorities advise that vitamin D3 is more effective than vitamin D2,<sup>12,14</sup> restricting the review to vitamin D3 may potentially exclude relevant studies. In some studies, the term 'oral spray' is used and in two studies, oral spray was administered to the buccal mucosa which is the area of interest. Studies which supplemented individuals with oral spray vitamin D not specifically to the buccal membrane but to the mouth will be excluded as the absorption of spray may be reduced on the surface of the tongue due to saliva<sup>36</sup>. This review will also exclude studies using sublingual vitamin D supplementation, via spray or liquid, as there may be differences in the membrane permeability which may not be comparable to the buccal route.<sup>36</sup> Furthermore, no studies have been identified in preliminary scoping.

#### Comparator(s)

We will consider for inclusion studies that compared the intervention to orally ingested vitamin D; vitamin D3 (cholecalciferol), vitamin D2 (ergocalciferol), at any dose, formulation, duration, or placebo. Comparing the intervention with all existing alternative interventions may help to identify its effectiveness against supplements which are conventionally prescribed. A sub-group analysis based on these different forms (i.e. vitamin D2 or vitamin D3) and formulations (i.e. tablet, capsule, liquid) will be considered. We will allow concomitant comparators (i.e. intervention and comparator vs. intervention). Additionally, inclusion of a comparator that is a placebo may also provide additional information of the spray's efficacy which will be useful to evaluate.

#### Outcomes

160 The primary outcome is selected to represent effects of buccal spray vitamin D versus comparator on  
161 serum vitamin D levels as measured by 25-hydroxyvitamin D or 25-OHD at baseline and at follow-up  
162 (pre-and post). Studies must report 25-OHD at baseline and at follow-up or the change in 25-OHD  
163 level from baseline to the end of the study and the significance between intervention and comparator.

164  
165 We will include studies which report 25-OHD as nmol/L or ng/ml. For consistency, throughout the  
166 study, vitamin D will be reported as IU (1 IU = 0.025 µg) and serum 25-OHD will be reported as ng/mL  
167 (1ng/mL = 2.5 nmol/L).<sup>9</sup> No restriction will be placed on the methodology used to measure serum 25-  
168 OHD. Many laboratory methods are used to measure 25-OHD (e.g. liquid chromatography-tandem  
169 mass spectrometry, chemiluminescence immunoassay and enzyme linked immunosorbent assay).  
170 These differing techniques result in notable intra- and inter-assay variability.<sup>14</sup> Internationally, there  
171 are efforts to standardize the measurement of vitamin D via the Vitamin D Standardization Program  
172 (VDSP) however entering into this program is voluntarily and there is presently no obligation to abide  
173 with these standards.<sup>45</sup>

174  
175 We will consider including studies of buccal spray vitamin D in which serum 25-OHD was measured  
176 as a secondary endpoint (surrogate outcome). The review question is to evaluate the effectiveness of  
177 buccal spray on serum 25-OHD levels and exclusion of studies using the spray in such an under-  
178 researched area could exclude potentially relevant studies.

179  
180 The secondary outcome will be any reports of adverse effects, as reported by the researcher. Studies  
181 will not be excluded if they do not acknowledge adverse effects. In the event of non-disclosure of  
182 safety or adverse effects, researchers will be contacted to provide this information.

183

#### 184 **Study Types**

185 This review will include experimental study designs: randomized controlled trials (RCTs), and quasi-  
186 experimental studies (non-randomized studies). RCTs are arguably the best study type to inform of  
187 clinical effectiveness.<sup>46</sup>

188

#### 189 **Study Setting**

190 No restriction will be placed on the context of study designs, both hospital inpatients, outpatients and  
191 free dwelling individuals will be considered.

192

#### 193 **Methods**

194 This systematic review will be conducted in accordance with the Joanna Briggs Institute methodology  
195 for systematic reviews of effectiveness evidence. Available from:

196 Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of  
197 effectiveness. In: Aromataris E, Munn Z (Editors). *Joanna Briggs Institute Reviewer's Manual*. The  
198 Joanna Briggs Institute, 2017. Available from <https://reviewersmanual.joannabriggs.org/>

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200 **Search Strategy**

201 The search strategy aims to find both published and unpublished studies in any setting and in both  
 202 adults and children. Gray literature can make important contributions to a systematic review and can  
 203 help to reduce the risk of publication bias i.e. from null or negative results.<sup>47</sup> This will illustrate the full  
 204 available research evidence and may identify gaps in the research base.<sup>48</sup>

205 A three-step search strategy will be utilized in this review. The initial search strategy and terms will be  
 206 chosen in discussion with a medical librarian and information specialist with expertise in systematic  
 207 review methodology. An initial limited search of MEDLINE and CINAHL will be undertaken followed  
 208 by an analysis of the text words contained in the title and abstract, and of the index terms used to  
 209 describe the article. A second search using all identified keywords and index terms will then be  
 210 undertaken across all included databases. Thirdly, forward and backward citation searching will be  
 211 conducted using the reference lists and citations of all identified reports and articles to search for  
 212 additional studies. The initial keywords and search terms will include:

213  
 214 (oral OR buccal) AND (spray) AND (vitamin D OR cholecalciferol OR ergocalciferol OR 25-  
 215 hydroxyvitamin D).

216  
 217 Due to resource limitations of translation, the search will be restricted to studies written in the English  
 218 language. To our knowledge, the first quantitative study to report on buccal spray vitamin D  
 219 supplementation was in 2015. Studies published between 2008 to the present will be included.  
 220 Extending the inclusion date to 10 years is more likely to reflect current buccal spray formulations.  
 221 Studies will be excluded if they are published before 2008. If relevant, the reviewers intend to contact  
 222 authors of primary studies for further information. The search will be limited to humans.

223 A full search strategy for MEDLINE (Ovid) and CINAHL is detailed in Appendix II: Search strategy.

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225 **Information Sources**

226 A total of six databases will be searched: MEDLINE (Ovid), 2008-Present dataset, Epub Ahead of  
 227 Print; EMBASE (Ovid), 2008-Present, Epub Ahead of Print; PubMed, CINAHL, AMED and The  
 228 Cochrane Library.

229

230 The search for unpublished studies (gray literature) will include: a search of the Cochrane Handbook  
 231 of gray literature databases, ProQuest Dissertation Publishing (PQDP) and search engines will be  
 232 used with keywords relating to the research question.

233

234 Trial registers to be searched include: The Cochrane Central Register of Controlled Trials  
 235 (CENTRAL), U.S. National Library of Medicine (ClinicalTrials.gov) database; World Health  
 236 Organization International Clinical Trials Registry Platform (ICTRP); All Trials (alltrials.net) and  
 237 Restoring Invisible and Abandoned Trials (RIAT).

238

239 **Study Selection**

240 Following the search, all identified citations will be collated and uploaded into Endnote X8 citation  
241 management system and duplicates removed.<sup>49</sup> Titles and abstracts will then be screened by two  
242 independent reviewers for assessment against the pre-defined (a priori) inclusion criteria for the  
243 review. Studies that meet the inclusion criteria will be retrieved in full and their details imported into  
244 JBI SUMARI. Included studies will undergo a process of critical appraisal. The results of the search  
245 will be reported in full in the final report and presented in a PRISMA flow diagram.<sup>50</sup> Full text studies  
246 that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an  
247 appendix in the final systematic review report. Any disagreements that arise between the reviewers  
248 will be resolved through discussion, or with a third reviewer.

249

### 250 **Assessment of Methodological Quality**

251 Papers selected for retrieval will be assessed by two independent reviewers for methodological  
252 validity prior to inclusion in the review using the standardized critical appraisal instruments from the  
253 Joanna Briggs Institute.<sup>51</sup> All studies, regardless of their methodological quality, will undergo data  
254 extraction and synthesis (where possible). Any disagreements that arise will be resolved through  
255 discussion, or with a third reviewer.

256

### 257 **Data Extraction**

258 The data extracted will include specific details about the interventions, populations, study methods  
259 and outcomes of significance to the review question. Authors of papers will be contacted to request  
260 missing or additional data where required. Two attempts will be made to contact the corresponding  
261 authors for missing information.

262

### 263 **Data Synthesis**

264 Data will be initially analysed through a narrative synthesis method. During analysis, if a subset of  
265 data appears comparable, it may be possible to perform a meta-analysis. To be eligible for meta-  
266 analysis, a trial must report the mean change in 25-OHD levels from baseline for each trial group and  
267 the corresponding standard deviation or standard error. Where possible, quantitative data will be  
268 pooled in a statistical meta-analysis using the JBI Meta-Analysis of Statistics Assessment and Review  
269 Instrument (JBI-MASARI). All results will be subject to double data entry. Effect sizes will be  
270 expressed as either odds ratios (for categorical data) and weighted mean differences (for continuous  
271 data) and their 95% confidence intervals (CIs) will be calculated for analysis. Relative risks and 95%  
272 CIs will be calculated for dichotomous data. Analysis of continuous data will be undertaken using the  
273 mean and standard deviation values to derive weighted mean differences (WMDs) and their 95% CIs.  
274 Heterogeneity will be assessed statistically using the standard Chi-squared and I squared tests and  
275 also explored using subgroup analyses, i.e. buccal spray and comparator. If this indicates a high  
276 level of heterogeneity among the trials included in an analysis, a random effects meta-analysis will be  
277 performed for the overall summary. The choice of model (random or fixed effects) and method for  
278 meta-analysis will be based on the guidance by Tufanaru et al.<sup>52</sup> Sensitivity analysis will be  
279 performed to test decisions regarding subgroup analysis. If 10 or more studies are included in a



280 meta-analysis, a funnel plot will be presented, with the aims of assessing for signs of asymmetry with  
 281 respect to publication bias. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord  
 282 test) will be performed where appropriate. Where statistical pooling is not possible, the findings will  
 283 be presented in narrative format including tables and figures to aid in data presentation where  
 284 appropriate.

285

286 **Assessing Confidence**

287 The study findings will be reported in narrative form and a 'summary of findings' table will be created  
 288 using GRADEPro GDT software. The GRADE approach for grading the quality of evidence will be  
 289 followed. The 'Summary of Findings' table will present the following information where appropriate:  
 290 the risk of bias assessments for each aspect of methodological quality (randomization; blinding;  
 291 measurement; statistical analysis) for each individual study and the overall risk of bias of the entire set  
 292 of included studies.

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294 **Conflicts of Interest**

295 The authors declare no conflict of interest.

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**Appendix I: Inclusion and exclusion criteria (PICO)**

<b>PICO</b>	<b>Inclusion</b>	<b>Exclusion</b>
<b>Population</b>	<p>Humans:</p> <ul style="list-style-type: none"> <li>- Adults and children</li> <li>- Healthy or disease state</li> </ul> <p>We will allow concomitant populations (i.e. healthy and disease status)</p>	No restrictions
<b>Intervention</b>	<p>Buccal or oral vitamin D spray:</p> <ul style="list-style-type: none"> <li>- vitamin D2 or vitamin D3 applied to the buccal mucosa</li> </ul>	<p>Sublingual vitamin D</p> <p>Oral vitamin D spray applied to mouth not buccal mucosa</p>
<b>Comparator</b>	<p>Vitamin D in either form:</p> <ul style="list-style-type: none"> <li>- vitamin D3 (cholecalciferol), or</li> <li>- vitamin D2 (ergocalciferol) at any dose, duration, and formulation (i.e. tablet, capsule, liquid) or placebo</li> </ul> <p>We will allow concomitant comparators (i.e. intervention and comparator vs. intervention)</p>	No comparator
<b>Outcome</b>	Total serum 25-hydroxyvitamin D (25-OHD) levels (pre- and post)	Total serum 25-hydroxyvitamin D (25-OHD) levels not reported

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**Appendix II: Search strategy**

**MEDLINE (Ovid)**

**Search #**

**Searches**

administration, buccal  
oral sprays.sh.  
#1 OR #2  
buccal.ti,ab,kw.  
oral\*.ti,ab,kw.  
#4 OR #5  
spray\*.ti,ab,kw.  
#6 AND #7  
#3 OR #8  
vitamin D/  
vitamin D\*.ti,ab,kw.  
c?olecalciferol\*.ti,ab,kw.  
ergocalciferol\*.ti,ab,kw.  
25-hydroxyvitamin D\*.ti,ab,kw.  
#10 OR #11 OR #12 OR #13 OR #14  
#9 AND #15  
Publication Year: 2008-Current

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**CINAHL Plus with Full-Text**

**Search #**

**Searches**

(MH "Administration, Buccal")  
 TI buccal  
 AB buccal  
 TI oral  
 AB oral  
 #2 OR #3 OR #4 OR #5  
 TI spray  
 AB spray  
 #7 OR #8  
 #6 AND #9  
 #1 OR #10  
 (MH "Vitamin D+")  
 TI vitamin D\*  
 AB vitamin D\*  
 (MH "Cholecalciferol")  
 TI cholecalciferol\*  
 AB cholecalciferol\*  
 (MH "Ergocalciferols")  
 TI ergocalciferol\*  
 AB ergocalciferol\*  
 TI "25-hydroxyvitamin D"  
 AB "25-hydroxyvitamin D"  
 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR  
 #20 OR #21 OR #22  
 #11 AND #23  
 Publication Date: 2008-2018



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