## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Should Vitamin B12 Tablets be Included in More Canadian Drug Formularies? An Economic Model of the Cost-Saving Potential from Increased Utilization of Oral Versus Intramuscular Vitamin B12 Maintenance Therapy for Alberta Seniors |
| **AUTHORS** | Houle, Sherilyn; Kolber, Michael; Chuck, Anderson |

## VERSION 1 - REVIEW

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| **REVIEWER** | Emmanuel ANDRES<br>University Hospital of Strasbourg, Strasbourg, France |
| **REVIEW RETURNED** | 13-Dec-2013 |

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| **GENERAL COMMENTS** | - original study<br>- well designed study<br>- well structured paper |

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| **REVIEWER** | Jörn Schneede<br>Jörn Schneede, MD, PhD<br>Head of the Dpt. of Clinical Pharmacology<br>Institute of Pharmacology and Clinical Neuroscience<br>Umeå University |
| **REVIEW RETURNED** | 30-Dec-2013 |

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| **GENERAL COMMENTS** | I very much welcome the authors' initiative to provide a pharmacoeconomic evaluation of oral versus intramuscular vitamin B12 treatment. However, the comparison should be fair. The total body retention of 1 mg i.m. injected B12 is - depending of the type of B12-preparation - 20-35%, which should be sufficient for 2-3 months of B12-requirements. The majority of recommendations for i.m. B12-supplementation indicate dosing intervals of 1-3 months. Thus, in the probabilistic sensitivity analysis should have included 2 and 3 months of dosing intervals for i.m. injections. Reducing the number of injections from 12 to 6 or even 4 times per year most certainly would have had large impact on the cost-estimations in the model over 5 years. Further, the possible risk and costs of a relapse of B12-deficiency in the oral treatment group should have been included in the model and discussed. A single additional laboratory monitoring during the 5-year period does not seem to be sufficient. The compliance rates of long-term medication therapies may be as low as 40% to 50% [1] and orally treated patients might have to be monitored at least once or twice per year. The costs of yearly or twice yearly laboratory monitoring should have been included in the sensitivity analysis. On the other hand, the risks of i. m. B12-therapy might also have been considered in the model. Anaphylactic reactions, even though rare, are mostly observed in connection with |

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| | i.m. administration of B12. More importantly, the risks of local reactions on the injection site should have been included in the model. About 1/3 of the elderly is expected to either be treated with oral anticoagulant or antiplatelet drugs [2] increasing the risk of haematomas in connection with frequent B12-injection. This is a major argument for oral B12-treatment of the elderly and this aspect should have been included in the model in some way.<br><br>1. Jin, Jing, Grant Edward Sklar, Vernon Min Sen Oh, and Shu Chuen Li. “Factors Affecting Therapeutic Compliance: A Review from the Patient’s Perspective.” Therapeutics and Clinical Risk Management 4, no. 1 (February 2008): 269–286.<br><br>2. Labuz-Roszak, Beata, Krystyna Pierzchala, Michal Skrzypek, Marta Swiech, and Agnieszka Machowska-Majchrzak. “Oral Anticoagulant and Antiplatelet Drugs Used in Prevention of Cardiovascular Events in Elderly People in Poland.” BMC Cardiovascular Disorders 12 (2012): 98. doi:10.1186/1471-2261-12-98.<br><br>The authors should have supplied some figures depicting the results from the Monte Carlo simulations and to give an impression of the uncertainty of the probabilistic sensitivity analyses. In addition, the authors might present a picture over the development of costs during year 1, 2, 3, 4 and five of oral treatment. Further, a decision tree with the different assumptions and cost-determinants and (possibly) risks/complications of the two treatment options should be given. An earlier published similar cost-minimization analysis could serve as a source of inspiration for figures:Touchette, D R, and D H Rhoney. “Cost-minimization Analysis of Phenytoin and Fosphenytoin in the Emergency Department.” Pharmacotherapy 20, no. 8 (August 2000): 908–916.<br><br>Five years is a rather long time horizon in an elderly population with increased risk of dementia. The risk of poor compliance and relapse of B12-deficiency should have been included in the sensitivity analysis. The need of repeated laboratory monitoring preferably by functional markers of B12-deficiency such as methylmalonic acid and/or total homocysteine to assure adequate compliance should have been included in the model.<br><br>On the other hand, the risks of frequent B12-injections in a population of elderly people with prevalent co-medication with anticoagulant and antiplatelet drugs should have been considered, too.<br><br>Finally, and most importantly, the sensitivity analysis should have included scenarios where only 6 or 4 B12 injections per year are given.<br><br>The authors should have made a clearer distinction between early remission therapy of B12-deficiency, especially if neurological symptoms are present, where B12-injection still are preferred and B12- maintenance therapy in the stable phase of the disease.<br><br>It should be mentioned in the title, already, that the paper deals with B12 maintenance therapy and that the analyses relate to the Canadian health care system, only. |

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| | Last but not least, the authors should state explicitly that all calculations are made using Canadian dollars as currency.<br><br>I have high-lighted parts of the text in the attached PDF-file where I supply additional comments to the manuscript, which I hope the authors will find helpful.<br><br>The authors refer to a popular statement of Lederle from 1991 that oral cobalamin treatment of pernicious anemia (PA) was "medicine's best kept secret". In fact, the first effective treatment was oral as early as in 1926 (ingestion of large amount of raw liver) and of the literature on oral treatment of vitamin B12 deficiency actually is huge. I do not think that the wording "secret" is adequate and the authors might consider omitting this "populistic" phrase. Parenteral supplementation has been the mainstay of treatment of most forms of vitamin B12 deficiency in the majority of countries world-wide [1]. This therapeutic tradition is most likely a result of the 1959 US Pharmacopeia Anti-Anemia Preparations Advisory Board recommendation, where trend-setting experts advised against the use of oral therapy for pernicious anemia because of its unpredictable efficacy [2]. This recommendation still appears to be influential. The authors could mention these aspects and should also cite the largest study on the feasibility of long-term (64 patients, follow-up time up to 72 months) oral treatment with cobalamin in PA patients published so far [3]. This study had great impact on Swedish therapeutic traditions and to date >80% of B12-prescriptions in Sweden are oral preparations.<br><br>1. Stabler, Sally P. “Vitamin B12 Deficiency.” New England Journal of Medicine 368, no. 2 (2013): 149–160. doi:10.1056/NEJMcp1113996.<br><br>2. BETHELL, F H, W B CASTLE, C L CONLEY, and I M LONDON. “Present Status of Treatment of Pernicious Anemia.” Journal of the American Medical Association 171 (December 12, 1959): 2092–2094.<br><br>3. Berlin, H, R Berlin, and G Brante. “Oral Treatment of Pernicious Anemia with High Doses of Vitamin B12 Without Intrinsic Factor.” Acta Medica Scandinavica 184, no. 4 (October 1968): 247–258. http://www.ncbi.nlm.nih.gov/pubmed/5751528. |

- The reviewer also provided a marked PDF copy with comments. Please contact the editorial office for full information.

**VERSION 1 – AUTHOR RESPONSE**

As a model, it is highly unlikely that all clinical scenarios can be included with sufficient accuracy. We feel our model has captured the most common costs and those most likely to significantly impact the model, without introducing risk regarding the validity of the model assumptions. Readers of economic models should therefore be cognizant that they serve as an estimate of potential cost avoidance, and cannot be assumed to capture all potential outcomes of therapy or individual responses.

| Comment / Revision Request | Response / Action Taken |
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| The total body retention of 1 mg i.m. injected B12 is - depending of the type of B12-preparation - 20-35%, which should be sufficient for 2-3 months of B12-requirements. The majority of recommendations for i.m. B12-supplementation indicate dosing intervals of 1-3 months. Thus, in the probabilistic sensitivity analysis should have included 2 and 3 months of dosing intervals for i.m. injections. | Canadian product monographs for parenteral B12 consistently indicate monthly dosing, and from our experience this is the frequency that the vast majority of patients are dosed at in practice. While a longer interval may be possible, we believe this assumption only applies to a very small number of individuals in our population. Given this low proportion in practice, we believe it is therefore unlikely to make a significant difference on the overall result if factored into a sensitivity analysis in a way that reflects the frequency of occurrence in practice. The majority of studies in the literature comparing oral to IM therapy also utilized a monthly frequency. |
| The possible risk and costs of a relapse of B12-deficiency in the oral treatment group should have been included in the model and discussed. | As stated in the limitations paragraph of the discussion section:<br><br>"The model also assumed that all patients making the switch to oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore representing maximum saving potential. This assumption is consistent with previously published randomized controlled trials and case series reporting treatment success across all patients studied [2-8]."<br><br>While we agree that relapse may occur, given that no patients in the RCTs or case series referenced required a switch back to IM therapy following the switch to oral and our experience using oral B12 in practice, we believe the frequency at which this occurs is very low and unlikely to have a significant effect on the overall findings of cost-savings. Without any information in the literature suggesting the frequency at which this may occur (since, as mentioned, no cases were reported in any of the trials referenced) this would have to be assumed without any supporting evidence and is therefore at high risk of being a flawed estimate. |
| A single additional laboratory monitoring during the 5-year period does not seem to be sufficient. The compliance rates of long-term | This is a valid point, as oral self-medication can indeed not be directly monitored for non-compliance as closely as a health professional-administered |

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| medication therapies may be as low as 40% to 50% and orally treated patients might have to be monitored at least once or twice per year. The costs of yearly or twice yearly laboratory monitoring should have been included in the sensitivity analysis. | monthly injection. A statement to this effect as well as the result of the base scenario assuming once-yearly additional monitoring was added to the paragraph in the Discussion section addressing model assumptions. Upon consultation with practicing family physicians, typical maintenance monitoring in Canada is every 1-2 years. |
| The risks of i.m. B12-therapy might also have been considered in the model. Anaphylactic reactions, even though rare, are mostly observed in connection with i.m. administration of B12. More importantly, the risks of local reactions on the injection site should have been included in the model. About 1/3 of the elderly is expected to either be treated with oral anticoagulant or antiplatelet drugs increasing the risk of haematomas in connection with frequent B12-injection. This is a major argument for oral B12-treatment of the elderly and this aspect should have been included in the model in some way. | We have decided not to include anaphylactic reactions in the model for the following reasons:<br>• As you mentioned, the rate of anaphylaxis is very rare and, therefore, unlikely to significantly affect the model outcomes (a MedLine search identified only 6 reported cases)<br>• Since this model looks at the cost effectiveness of switching patients already on IM B12 to oral therapy, it is assumed that they are on maintenance therapy and therefore have not experienced anaphylactic reactions<br><br>While we agree that hematoma is a possibility in patients receiving concurrent IM injections and anticoagulant/antiplatelet drugs and an additional supporting argument for greater use of oral therapy, such local reactions rarely result in hospitalization, a physician visit, or any other intervention. As our model focuses strictly on costs, we therefore do not feel it is applicable to our model given its rarity and its unlikely requirement for medical attention. We have, however, added a statement to the discussion where patient preferences are discussed to highlight this additional benefit of oral therapy. |
| The authors should have supplied some figures depicting the results from the Monte Carlo simulations and to give an impression of the uncertainty of the probabilistic sensitivity analyses. In addition, the authors might present a picture over the development of costs during year 1, 2, 3, 4 and five of oral treatment. Further, a decision tree with the different assumptions and cost-determinants and (possibly) risks/complications of the two treatment options should be given. | As our model compares the switch from one route of administration to another, both with very infrequent adverse effects resulting in medical costs, a decision tree of complications is unlikely to influence the overall study findings.<br><br>As with Figure 3 of the referenced paper, we found the utility of a diagram of the Monte Carlo simulation results to be minimal in terms of aiding the reader with interpreting the results of our model. As our model is built in 1-year increments, all iterations of the model resulted in cost-savings from oral $B_{12}$; |

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| Ref: Pharmacotherapy 2000;20(8):908–916. | therefore, a figure similar to Figure 2 of the referenced paper cannot be provided.<br><br>The final sentence of the Methods section addresses cost-savings per year for the first two years (below), with the estimates for years 3-5 only differing due to discounting. Therefore, we believe readers are able to see that while oral therapy is cost-saving across all 5 years, more savings are seen in years 2-5 since additional laboratory monitoring is completed only in year 1 according to our base scenario.<br><br>For the base scenario, cost savings in year 1 were estimated at $48.34 (SD $8.58) per patient, increasing to $126.55 (SD $2.04) in year 2. Over 5 years, average cost-savings per patient was estimated at $494.69. |
| Five years is a rather long time horizon in an elderly population with increased risk of dementia. The risk of poor compliance and relapse of B12-deficiency should have been included in the sensitivity analysis. | This time horizon was selected as it is consistent with the previous Canadian study of cost-minimization from oral B12 therapy published in 2001, and our study is intended to be an update to that paper.<br><br>Regarding risk of non-compliance due to dementia, this was not included in the model for the following reasons:<br><br>• Our model excludes residents of care facilities or nursing homes, where patients with significant dementia are likely to reside<br>• It is stated in the Methods that “if assistance [with medication administration] was required, it was assumed that they already required this assistance for other medications rather than solely for $B_{12}$ tablets.” It is exceedingly rare that seniors with dementia are only on $B_{12}$ therapy, so given Canada’s universal healthcare system, the use of home care for assistance with medication management is very common. Therefore, we believe this risk is relatively low<br>• As mentioned above, since this is assumed to be a relatively rare occurrence and actual data on the rate of this is unknown, we are unable to determine a frequency/proportion to include in the model. |

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| The need of repeated laboratory monitoring preferably by functional markers of B12-deficiency such as methylmalonic acid and/or total homocysteine to assure adequate compliance should have been included in the model. | We were unable to obtain cost estimates for these levels from our provincial laboratory service. Furthermore, current recommendations suggest the measurement of MMA and/or homocysteine primarily in the diagnosis of cobalamin deficiency for patients in the low-normal range rather than as part of ongoing monitoring. Additionally, from our experience, the rate at which either of these tests are ordered for monitoring purposes appears very low in Alberta. |
| The authors should have made a clearer distinction between early remission therapy of B12-deficiency, especially if neurological symptoms are present, where B12-injection still are preferred and B12- maintenance therapy in the stable phase of the disease. | As the model is based on a population already receiving IM therapy and making the switch from IM to oral therapy, we feel that most patients in this population with neurological symptoms have already received IM doses. Furthermore, two of the referenced RCTs of oral therapy included patients with neurological symptoms and found the response did not differ between oral and IM therapy. While it is true that some clinicians may choose to start with IM first and then switch to oral in this population, the evidence suggests this approach is not necessary.<br><br>A statement addressing the possibility for government payers to consider funding short-term IM therapy in patients with neurological symptoms followed by oral maintenance therapy was added to the discussion section. |
| It should be mentioned in the title, already, that the paper deals with B12 maintenance therapy and that the analyses relate to the Canadian health care system, only. | Title has been changed to:<br><br>Should Vitamin $B_{12}$ Tablets be Included in More Canadian Drug Formularies? An Economic Model of the Cost-Saving Potential of Oral Versus Intramuscular Vitamin $B_{12}$ Maintenance Therapy for Alberta Seniors |
| The authors should state explicitly that all calculations are made using Canadian dollars as currency. | This statement was added in the “Cost Determination” subsection of the Methods. |
| The authors refer to a popular statement of Lederle from 1991 that oral cobalamin treatment of pernicious anemia (PA) was "medicine's best kept secret". In fact, the first effective treatment was oral as early as in | Given that in North America, 76% of physicians report prescribing IM therapy[1] and only 3 of 13 provincial/territorial governments cover the oral product on drug formularies, we believe this statement is still valid from an implementation |

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| 1926 (ingestion of large amount of raw liver) and the literature on oral treatment of vitamin B12 deficiency actually is huge. I do not think that the wording "secret" is adequate and the authors might consider omitting this "populistic" phrase. | perspective. We agree that sufficient evidence exists on the merits of oral therapy, but clearly this message has not made its way to clinical practice.<br><br>1. Graham ID, Jette N, Tetroe J, Robinson N, Milne S, Mitchell SL. Oral cobalamin remains medicine's best kept secret. Archives of Gerontology and Geriatrics 2007;**44**(1):49–59. |
| Parenteral supplementation has been the mainstay of treatment of most forms of vitamin B12 deficiency in the majority of countries world-wide. This therapeutic tradition is most likely a result of the 1959 US Pharmacopeia Anti-Anemia Preparations Advisory Board recommendation, where trend-setting experts advised against the use of oral therapy for pernicious anemia because of its unpredictable efficacy. This recommendation still appears to be influential. The authors could mention these aspects and should also cite the largest study on the feasibility of long-term (64 patients, follow-up time up to 72 months) oral treatment with cobalamin in PA patients published so far. This study had great impact on Swedish therapeutic traditions and to date >80% of B12-prescriptions in Sweden are oral preparations | As we are unable to access the 1959 JAMA paper on the US Pharmacopeia recommendation through our library to verify the exact recommendation and rationale provided, we are unable to add this to the paper.<br><br>The study by Berlin *et al.* has been added to the paper as reference #8, with mention of it in the Introduction, Methods, and Discussion sections of the paper. |

**VERSION 2 – REVIEW**

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| **REVIEWER** | Jörn Schneede<br>Head of the unit of Clinical Pharmacology<br>Department of Pharmacology and Clinical Neuroscience |
| **REVIEW RETURNED** | 17-Feb-2014 |

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| **GENERAL COMMENTS** | The title appears rather long and entangled and could/should be shortened and phrased more neatly.<br><br>Overall, I am satisfied with the authors reply. However, I have still some proposals for changes that the authors might wish to consider. Further I attach one JAMA-publication from 1959, which the authors were unable to retrieve, but is most likely still influential for the current practice of parenteral B12-therapy in most countries of the world. |

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| | As a model, it is highly unlikely that all clinical scenarios can be included with sufficient accuracy. We feel our model has captured the<br>most common costs and those most likely to significantly impact the model, without introducing risk regarding the validity of the model assumptions. Readers of economic models should therefore be cognizant that they serve as an estimate of potential cost avoidance, and cannot be assumed to capture all potential outcomes of therapy or individual responses.<br>**Comment / Revision Request Response / Action Taken**<br>The total body retention of 1 mg i.m. injected B12 is - depending of the type of B12-preparation - 20-35%, which should be sufficient for 2-3 months of B12-requirements. The majority of recommendations for i.m. B12-supplementation indicate dosing intervals of 1-3 months. Thus, in the probabilistic sensitivity analysis should have included 2 and 3 months of dosing intervals for i.m. injections.<br>Canadian product monographs for parenteral B12 consistently indicate monthly dosing, and from our experience this is the frequency that the vast majority of patients are dosed at in practice. While a longer interval may be possible, we believe this assumption only applies to a very small number of individuals in our population. Given this low proportion in practice, we believe it is therefore unlikely to make a significant difference on the overall result if factored into a sensitivity analysis in a way that reflects the frequency of occurrence in practice. The majority of studies in the literature comparing oral to IM therapy also utilized a monthly frequency.<br>The possible risk and costs of a relapse of B12-deficiency in the oral treatment group should have been included in the model and discussed.<br>As stated in the limitations paragraph of the discussion section: "The model also assumed that all patients making the switch to oral therapy saw clinical benefit and did not require a switch back to IM therapy, therefore representing maximum saving potential. This assumption is consistent with previously published randomized controlled trials and case series reporting treatment success across all patients studied [2-8]." While we agree that relapse may occur, given that no patients in the RCTs or case series referenced required a switch back to IM therapy following the switch to oral and our experience using oral |

**VERSION 2 – AUTHOR RESPONSE**

In response to your current recommendation, we have added a sentence to the introduction referencing the JAMA publication from 1959 as the starting point of resistance to treating B12 deficiency with oral preparations, and added the paper to our reference list as item #2.