Should vitamin B₁₂ tablets be included in more Canadian drug formularies? An economic model of the cost-saving potential from increased utilisation of oral versus intramuscular vitamin B₁₂ maintenance therapy for Alberta seniors

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ABSTRACT

Objective: The aim of this study was to estimate the cost-savings attainable if all patients aged ≥65 years in Alberta, Canada, currently on intramuscular therapy were switched to oral therapy, from the perspective of a provincial ministry of health.

Setting: Primary care setting in Alberta, Canada.

Participants: Seniors of age 65 years and older currently receiving intramuscular vitamin B₁₂ therapy.

Intervention: Oral vitamin B₁₂ therapy at 1000 μg/day versus intramuscular therapy at 1000 μg/month.

Primary and secondary outcome measures: Cost saving from oral therapy over intramuscular therapy, from the perspective of the Alberta Ministry of Health, including drug costs, dispensing fees, injection administration fees, additional laboratory monitoring and physician visit fees.

Results: Over 5 years, if all Albertans aged 65 years and older who currently receive intramuscular B₁₂ are switched to oral therapy, our model found that costs alone. Even if no additional physician visits are billed to oral therapy, our model found that

Conclusions: Oral B₁₂ therapy has been shown to be an effective therapeutic option for patients with vitamin B₁₂ deficiency, yet only three provinces and the Non-Insured Health Benefits program include oral tablets on their formulary rather than the parenteral preparation. To ensure judicious use of limited health resources, clinicians and formulary committees are encouraged to adopt oral B₁₂ therapy as a clinically and cost-effective first-line therapy for vitamin B₁₂ deficiency.

BACKGROUND

For over 20 years, oral vitamin B₁₂ has been referred to as ‘medicine’s best kept secret’.¹ Hesitation by clinicians to treat B₁₂ deficiency with oral preparations dates back to a 1959 report by the U.S.P. Anti-Anemia Preparations Advisory Board suggesting inadequate absorption of oral dosage forms.³ Despite evidence of the effectiveness of oral B₁₂ therapy,⁵⁻⁹ intramuscular administration remains the most commonly prescribed route in North America.¹⁰

Approximately 5% of Canadians are B₁₂ deficient,¹¹ with Framingham data suggesting that B₁₂ deficiency in community-dwelling adults aged 67 years and older may be as high as 12%.¹² Deficiency can occur as a result of gastric atrophy or previous gastric or intestinal surgery, use of antacids and other medications (metformin), inadequate animal product intake, and as a result of deficiency in intrinsic factor, which is required for the absorption of cobalamin from the gut.¹³ ¹⁴

Strengths and limitations of this study

- Minimal assumptions built into the model, as exact costs and the exact number of eligible residents comprising the population were available.
- Three randomised controlled trials and two prospective case series support our use of a cost-minimisation analysis approach.
- Comprehensive sensitivity analyses employed using Monte Carlo simulation to incorporate multiple variables.
- Study is from the perspective of the provincial ministry of health (the payer) and does not adopt a societal perspective since much of the additional information required for that is not available.
- Despite being set in one Canadian province, the use of intramuscular B₁₂ therapy is prevalent worldwide. Therefore, these results, while not directly generalisable to other jurisdictions, point to an economic argument for greater uptake of oral B₁₂ therapy which is likely consistent across other jurisdictions.
While the absorbability of oral $B_{12}$ has been questioned, a number of studies have reported successful results with oral therapy including treatment in patients with pernicious anaemia or bowel resection. Since 1% of orally ingested $B_{12}$ is absorbed via passive diffusion independent of the presence of intrinsic factor, daily oral doses of 1000 $\mu$g or more are considered sufficient to meet daily requirements even in patients with insufficient intrinsic factor.

While oral tablets often cost more to acquire than $B_{12}$ injection solution, the costs associated with administering the injections in the form of health professionals’ time and resources can be significant. A 2001 cost study estimated that between $C22.9 and $C17.6 million could be saved over 5 years in the province of Ontario if elderly patients on intramuscular $B_{12}$ were switched to oral therapy. In addition, a British study estimated that 2000 nursing hours are required to provide 1 year of injections to 492 patients in their homes. Across Canada, only Nova Scotia, Northwest Territories, Yukon and the Non-Insured Health Benefits program for First Nations and Inuit consider oral $B_{12}$ tablets to be a benefit in their provincial drug formularies, while all provinces and territories cover the injectable product.

The objective of this study was to estimate the cost savings of treatment using daily oral vitamin $B_{12}$ supplementation at a dosage of 1000 $\mu$g daily versus monthly 1000 $\mu$g/mL intramuscular injections in Alberta seniors over the age of 65 years who are currently using $B_{12}$ injection solution. Such a study is warranted in order to update the 2001 study in Ontario to reflect current costs, and to renew discussion about the best allocation of limited healthcare resources and whether oral $B_{12}$ should be covered by all Canadian provincial formularies.

**METHODS**

**Study type**

A cost-minimisation analysis (CMA) was performed wherein alternatives compared are considered to be equivalent in terms of factors that are relevant to the decision such as efficacy and tolerability, so the lowest cost alternative is selected. While a major assumption, three randomised trials (including a total of 66 participants on oral therapy and 75 patients on intramuscular therapy) and three prospective case series of 151 patients switching from intramuscular to oral therapy have concluded that the oral route is as clinically effective as the intramuscular route. Across all case series, no patients switched from intramuscular to oral therapy required a switch back to intramuscular replacement as a result of therapeutic failure. Costs were modelled over a period of 5 years, and the perspective of the Alberta Ministry of Health was adopted for this study.

**Setting/patients**

The study population consists of individuals aged 65 years or older with an Alberta Health Care number receiving intramuscular $B_{12}$ therapy. The number of Alberta seniors dispensed injectable $B_{12}$ over a 1-year period (January–December 2012) was determined from prescription dispensing records collected by IMS Brogan.

**Primary outcome**

Cost savings achievable by the province of Alberta if patients aged ≥65 years and currently receiving intramuscular $B_{12}$ therapy are switched to oral therapy. Cost savings are estimated in Canadian currency.

**Cost determination**

All costs are reported in Canadian dollars.

**Cost of $B_{12}$ tablets**

The suggested retail price of Swiss Naturals, Jamieson and Nature’s Bounty brands of 1000 $\mu$g $B_{12}$ tablets were obtained from the manufacturers and averaged to obtain the cost per tablet. In Alberta, the maximum professional fee allowed for dispensing products with an acquisition cost of ≤$C74.99 is $C11.93 (consists of $C10.22 professional fee and $C1.71 inventory allowance).

**Quantity of $B_{12}$ tablets and professional fees**

It was assumed that patients would receive a 3-month supply with each fill, therefore, amassing four professional fees annually and 365 tablets. Albertans aged 65 years and older are automatically enrolled into a ‘Coverage for Seniors’ programme, where the patient copay is 30% of the cost to a maximum of $C25. Since this study assumes the perspective of the provincial Ministry of Health, the payer is assumed to cover 70% of the total drug cost. Despite being a non-prescription product, sales tax was not applied since such tablets would be dispensed through the pharmacy as a tax-free product similar to a prescription drug.

**Cost of $B_{12}$ injection**

Parenteral $B_{12}$ in Alberta is available in 10 mL multidose vials at a concentration of 1000 $\mu$g/mL. The cost per millilitre for the two products currently available in Alberta (DIN 00521515 and DIN 01987003) was determined from the Alberta Health Drug Benefit List. In Alberta, the total charge allowable for injectable drugs other than insulin is 5/3 of the product’s acquisition cost. Therefore, with an acquisition cost of $C4.50 per vial of parenteral $B_{12}$, the total charge allowed—including the drug and professional fee—cannot exceed $C7.50 or $C0.75 per dose.

**Quantity of $B_{12}$ injection**

At the usual dosage of 1000 $\mu$g/month, one vial contains a 10-month supply of drug. Therefore, 1.2 vials would be required for a 1-year supply.

**Cost of additional laboratory monitoring**

Costs for the laboratory analyses were obtained from Alberta Health Services, laboratory technicians’ time to draw and analyse the blood samples were estimated by...
consulting with practicing laboratory technicians, and laboratory technician wages were obtained from a Government of Alberta occupational survey with a 20% fringe benefit applied.

Quantity of additional laboratory monitoring
To ensure adequate response to therapy, we assumed that patients to be switched from intramuscular to oral B12 would receive a baseline complete blood count and serum B12 prior to the switch, repeated once after the switch to confirm effectiveness. It was assumed that this additional monitoring would occur only upon switch from intramuscular to oral therapy, with long-term monitoring occurring at the same rate as if the patient had remained on intramuscular injections, therefore representing no additional cost of oral therapy over intramuscular therapy following the initial switch.

Cost of injection administration
Currently, physicians, nurses and pharmacists are authorised to administer B12 by intramuscular injection in Alberta. Fees for physician office administration of injections and pharmacist administration of injections are provided in Table 1.

Quantity of injection administrations
The proportion of patients on intramuscular B12 therapy receiving their monthly injections from their physician’s office or their pharmacy is unknown. For the purpose of the study, based on the experience of the authors including a practicing pharmacist and family physician, it was assumed that 25% of all B12 injections are administered in a community pharmacy with the remainder administered in a medical clinic.

Cost of additional physician visits
The current cost of $C35.91 for a standard family physician consultation visit in Alberta was utilised in the model.

Quantity of additional physician visits
Based on available administrative data, we were unable to determine the number of additional physician visits received by and billed for patients on intramuscular versus oral B12 supplementation apart from simply the administration of the injection in the medical clinic. For the base case scenario, we assumed that 10% of injections administered in a physician’s office also included a billed physician consultation which would not have occurred if the patient were not on intramuscular B12 and have explored other scenarios in sensitivity analyses as described below.

Model assumptions
A number of assumptions were made with the model in addition to those previously described. It was assumed that patients on oral B12 therapy were able to self-administer the medication, and if assistance was required, it was assumed that they already required this assistance for other medications rather than solely for B12 tablets. Since B12 tablets can be taken concurrently with other medications, it was not assumed that additional assistance would be needed if oral B12 were added to their medication regimen. The cost of supplies to administer the intramuscular injection (needle, syringe, alcohol swab, gloves, bandage and sharps disposal) were excluded from the model as these are relatively inexpensive and were not felt to significantly contribute to the overall cost of the injectable product.

Discounting
Consistent with CADTH guidelines for the economic evaluation of health technologies, a discount rate of 5% for outcomes occurring after 1 year was applied to the reference case, with sensitivity analyses performed around this value as described below.

Sensitivity analyses
Multway sensitivity analysis was performed in the form of 10 000 Monte Carlo simulation iterations, adjusting

| Table 1 Expected values and distribution parameters for the deterministic model and probabilistic sensitivity analyses |
|---|---|---|
| Parameter | Expected value±SE | Distribution |
| Study population | 28 252±10% | γ |
| Cost per B12 tablet | $C0.16±0.008 | γ |
| Professional fee for dispensing tablets | $C11.93 | − |
| Cost per B12 injectable dose | $C0.75 | − |
| Cost for CBC and serum B12 analyses | $C6.50 | − |
| Laboratory technician time for blood sample draw and analyses (hours) | 0.75 (range 0.25–1) | Triangular |
| Laboratory technician wage and benefits | $C44.60 (range $C35.82–$C51.41) | Triangular |
| Fee for administration of intramuscular injection in a physician’s office | $C10.30 | − |
| Cost for physician consultation visit | $C35.91 | − |
| Fee for administration of intramuscular injection in a pharmacy | $C20.00 | − |

Normal distribution sample values probabilistically from a normal curve with specified mean (expected value) and SD. Triangular distribution sample values probabilistically within the range specified, with increasing probability as values near the expected value.

*Indicates parameter only included in year 1 of the model.

CBC, complete blood count.
for a number of variables. Model inputs and the probabilistic distributions used in the sensitivity analyses are presented in table 1. The base case scenario was calculated using the expected value for each variable and assumed a 10% rate of additional physician consultations for patients on intramuscular versus oral therapy.

Sensitivity analysis was also performed for different proportions of additional physician office visits including a billed consultation. While the base scenario assumed a 10% rate of office consultations during injection visits, the analyses were repeated for rates of 0% and 25%. Discounting rates of 0% and 3% were also tested in sensitivity analysis.

**RESULTS**

Estimated 5-year cost savings associated with switching all Alberta seniors currently receiving injectable B12 to oral therapy is $13 975 883. Base scenario and sensitivity analysis results are presented in table 2. Our model found that even if no additional physician visits were billed for among patients receiving intramuscular therapy, over $8 million could be saved from reduced administration costs alone.

Owing to the additional laboratory monitoring performed in the year of the change from intramuscular to oral therapy, the model found the switch to be moderately cost effective in the first year, with larger savings realised in years 2–5. 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.

**DISCUSSION**

Over 5 years, the province of Alberta can be expected to free nearly $14 million in healthcare costs if all seniors over the age of 65 years currently receiving intramuscular B12 are switched to oral tablets. Despite evidence confirming that sufficient B12 is absorbed by passive diffusion at a dose of 1000 μg daily to be effective even in patients lacking intrinsic factor or with gastrointestinal disease,14 the intramuscular route continues to be commonly prescribed. With high health professional workloads and increasingly restricted healthcare budgets, a switch from intramuscular to oral therapy will not only free health professional resources to see patients at greater need, but can also result in cost savings for reinvestment into other needed services.

The option of oral supplementation is well received by patients. A Canadian study by Kwong et al8 found that 73% of patients receiving B12 injections were willing to try oral B12, and of those who tried the oral therapy, 71% wished to permanently remain on oral therapy. Travel inconveniences were the most common reason for preferring the oral route. The authors concluded that oral therapy would decrease physician burden, increase patient control over therapy and avoid patient discomfort and inconvenience. While willingness-to-pay for re-

<table>
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<th>Proportion in-office injections including a fee for a physician visit (%)</th>
<th>Discounting rate for years 2–5 (%)</th>
<th>Mean cost saving for payer</th>
<th>Mean cost saving per patient</th>
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injections would be administered in conjunction with a regular visit rather than as the sole reason for a visit by a nurse. However, if additional home care visits are indeed being performed for B12 injections, then the savings of switching to oral B12 would obviously be greater. Importantly, the model also assumed that all patients making the switch to oral therapy saw clinical benefit and did not require a switch back to intramuscular therapy, therefore representing maximum saving potential. This assumption is consistent with previously published randomised controlled trials and case series reporting treatment success across all patients studied.\textsuperscript{3-9} Additionally, we assumed in the base scenario that additional laboratory monitoring is only required for the first year following the switch to oral therapy, with monitoring as usual for the remaining years. Considering that adherence to self-administered oral therapy may be lower than a healthcare professional-administered injection, even if an additional set of laboratory tests were performed each year for the 5-year term of the model, the estimated cost savings would still amount to $C12 million.

Direct comparison between our model and the results of the 2001 cost-saving paper cannot be performed due to differing model assumptions and available data. Overall, both models report significant cost-saving potential of the switch from the perspective of a government payer over 5 years. However, due to higher current professional fees for injection administration, our model found overall cost savings even if no additional physician visits occurred for patients receiving B12 injections, whereas the previous study found a break-even point when 16.3\% of additional physician visits were avoided.

The use of CMA is controversial as it assumes equal efficacy and tolerability between the two options being compared; however, we feel this assumption is justifiable based on published data comparing the oral and intramuscular routes.\textsuperscript{3-9} However, the total number of patients studied in the randomised trials (total n=141 across 3 studies) and case series (n=151) remains relatively small and doses employed across each study differed. Further research on a larger population, comparing standard-dose intramuscular therapy with standard-dose oral therapy is therefore recommended and is currently being planned. Additionally, payers considering adding oral B12 tablets to their formularies should consider allowing for the coverage of intramuscular therapy in the event of documented treatment failure on oral supplementation, until large-scale studies confirming equivalence are conducted, or allowing for short-term intramuscular therapy for patients with neurological symptoms followed by oral maintenance therapy. Indeed, a planned randomised controlled trial of 320 patients of age ≥65 in Spain will be directly comparing oral with intramuscular B12 and is expected to examine the non-inferiority of oral therapy over 1 year (clinicaltrials.gov NCT01476007).

Overall, our model estimates that $C8–24 million in cost savings can be realised over 5 years if all Alberta seniors currently receiving intramuscular vitamin B\textsubscript{12} are switched to oral therapy. Within closed systems like universal healthcare, this is unlikely to represent true cost savings, but rather room for reallocation of resources to other health system needs. With an ageing population and increasing rates of chronic disease, switching of patients from intramuscular to oral vitamin B\textsubscript{12} replacement appears to be not only clinically efficacious but also an effective use of limited healthcare resources.

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