Vitamin B_{12} injections versus oral supplements

How much money could be saved by switching from injections to pills?

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abstract

OBJECTIVE To estimate savings, using a third-party payer perspective, if all elderly patients currently receiving vitamin B_{12} (cobalamin) injections were switched to high-dose oral therapy.

DESIGN We modeled high-dose oral B_{12} supplement costs to include drugs, pharmacists' fees, and one-time conversion costs consisting of two physician visits and laboratory monitoring. The number of vitamin-injection visits avoided by switching to oral therapy was predicted using a multivariate model that considered covariates for overall patient illness.

SETTING Ontario family physicians' and internists' practices.

PARTICIPANTS Population-based administrative databases for Ontario were used to identify all people between 65 and 100 years who received parenteral vitamin B_{12} during 1995 and 1996.

MAIN OUTCOME MEASURES The cost of parenteral vitamin B_{12} for each patient, including drugs, injections, pharmacists' fees, and injection-associated physician visits, was measured directly from the databases.

RESULTS The annual cost of parenteral vitamin B_{12} therapy averaged $145.88 per person and totaled a maximum $25 million over 5 years. Converting all patients to high-dose oral B_{12} and treating them for 5 years would cost $7.4 million. Depending on how many vitamin-injection visits are avoided by switching to oral therapy, between $2.9 million and $17.6 million would be saved. Switching to oral B_{12} administration saved costs as long as 16.3% of injection-associated visits were avoided.

CONCLUSION Switching all patients from B_{12} injections to oral cobalamin therapy could result in substantial savings.

résumé

OBJECTIF Estimer les économies réalisées, du point de vue d'une tierce partie devant assumer les frais, si on changeait à une thérapie à forte dose par voie orale tous les patients âgés à qui on administre présentement des injections de vitamine B_{12} (cobalamine).

CONCEPTION Nous avons modélisé les coûts des suppléments vitaminiques à forte dose par voie orale pour inclure les médicaments, les honoraires du pharmacien et des coûts de conversion forfaitaires comportant deux visites d'un médecin et un monitoring en laboratoire. Le nombre de visites évitées pour recevoir l'injection par le fait de passer à la thérapie par voie orale a été prédit à l'aide d'un modèle multivariable qui tenait compte des covariables de l'état de santé global des patients.

CONTEXTE Des pratiques de médecins de famille et d'internistes en Ontario.

PARTICIPANTS On s'est servi des bases de données administratives fondées sur la population pour identifier toutes les personnes de 65 à 100 ans qui recevaient de la vitamine B_{12} par voie parentérale durant 1995 et 1996.

PRINCIPALES MESURES DES RÉSULTATS Le coût de la vitamine B_{12} par voie parentérale pour chaque patient, notamment le produit, les injections, les honoraires du pharmacien et les visites au médecin associées à l'injection a été mesuré directement à partir des bases de données.

RÉSULTATS Le coût annuel de la thérapie à la vitamine B12 par voie parentérale se situait en moyenne à 145,88 $ par personne et se chiffrait au total à un maximum de 25 millions $ sur cinq ans. La conversion à une thérapie à la vitamine B12 à forte dose par voie orale chez tous les patients et leur traitement pendant cinq ans coûteraient 7,4 millions $. Selon le nombre de visites pour injection de vitamine évitées par le changement à une thérapie par voie orale, des économies se situant entre 2,9 millions $ et 17,6 millions $ pourraient être réalisées. Le recours à une administration par voie orale de vitamine B12 réduisait les coûts en autant qu'une proportion de 16,3 % de visites associées à l'injection étaient évitées.

CONCLUSION Le passage des injections de B_{12} à une thérapie à la cobalamine par voie orale chez tous les patients pourrait se traduire par des économies substantielles.

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Cet article a fait l'objet d'une évaluation externe.

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In 1991, Frank A. Lederle identified high-dose oral vitamin B_{12} (cobalamin) treatment for pernicious anemia as "medicine's best kept secret."[1] Lederle noted that only 2 µg of cobalamin is required for daily metabolic functions. Because 2.0% of oral vitamin B_{12} is absorbed by small bowel mucosa independent of intrinsic factor or the terminal ileum, a daily 1000-µg dose of oral cobalamin provides more than enough vitamin to patients with pernicious anemia as well as patients whose B_{12} deficiency is caused by atrophic gastritis or decreased intake.

Clinical studies with extensive follow up have found that B_{12} levels in patients with pernicious anemia remain normal with high-dose oral therapy.[2-4] A recently published randomized trial found that oral B_{12} supplementation was superior to parenteral therapy for correcting serum B_{12}, methylmalonic acid, and homocysteine levels.[5] Published clinical studies have not found high-dose oral B_{12} to be unsuccessful in treating patients.[6]

Little is known in North America, however, about the effectiveness of oral B_{12} therapy. Several review articles regarding treatment of B_{12} deficiency have acknowledged oral B_{12} therapy[7,8] or have supported its use.[9-12] Three clinical studies favouring high-dose oral B_{12} therapy have also been published.[5,13,14] Regardless, oral therapy is seldom used in North America[15] despite being widely accepted elsewhere.[16] Informal discussion with family physicians, who treat nearly all B_{12} deficiency in Canada, revealed that few use high-dose oral instead of parenteral B_{12} for replacement therapy.

Oral B_{12} therapy is advantageous for patients because it avoids repeated physician visits and painful injections. It can also save money.[9,16,17] None of the articles retrieved from a MEDLINE search between 1966 and 1999 using the MeSH heading "vitamin B_{12}" and the text word "oral" explicitly compared the costs of parenteral and oral B_{12} supplementation. With this study, we sought to determine the costs and potential savings of switching all elderly Ontarians from parenteral B_{12} to high-dose oral therapy.

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METHODS

Patients and databases

All Ontarians between 65 and 100 years old who were prescribed parenteral vitamin B_{12} between July 1995 and June 1996 were identified in the Ontario Drug Benefit (ODB) database. The ODB database records the drug and the prescription date for each claim.

Resources used for parenteral and oral regimens

To measure resources used to administer parenteral B_{12} to these patients, we identified all physician claims for an intramuscular injection (fee codes G372 and G373) recorded in the Ontario Health Insurance Program (OHIP) database for the year following the B_{12} prescription. The Ontario Health Insurance Plan (and its database records) covers almost all physician services. To avoid including injections for other reasons (eg, allergy testing by clinical immunologists), only those performed by family physicians and internists (as identified by the Registered Physicians Database) were included. Because vaccinations are claimed using a separate code, intramuscular injections for patients prescribed B_{12} should almost exclusively represent B_{12} injections, although we are unable to determine whether injections were provided for other indications. Only visits claimed by the injecting physician for that patient on the day of the injection were counted.

We estimated the resources necessary to switch all patients from parenteral B_{12} to high-dose oral B_{12} regimens. We assumed that physicians would meet each patient to explain the advantages of oral therapy and provide instructions for its use. As has been recommended,[18] we also assumed that each patient would have follow-up monitoring where laboratory tests (including hemoglobin, white blood cell count, and a vitamin B_{12} measurement) would be performed. We assumed that physicians would bill an intermediate assessment (fee code A007) for both these visits and that all patients would switch to and stay on oral B_{12} therapy.

Costs of parenteral and oral regimens

We used a third-party payer perspective to calculate costs because of the data available to us, and this perspective is the least susceptible to error and uncertainty. Drug costs were abstracted from the ODB formulary. We identified the least expensive wholesale price for oral high-dose B_{12} preparations by contacting each manufacturer. Although high-dose B_{12} is not now covered by ODB, we assumed for this study

that the plan would pay for the medication. As per usual ODB practice, a pharmacist fee of 10% was added to the wholesale price of the vitamin. The pharmacist's dispensing fee (a maximum of $6.11) was not included as a cost because this is paid by patients. The OHIP fee schedule determined costs for injections, physician visits, and laboratory investigations.

To calculate the annual costs of parenteral B_{12} therapy, we determined, for each person, the total number of injections and injection visits and multiplied each by their unit costs. We assumed that one parenteral B_{12} prescription would last 1 year for each patient. Annual costs were multiplied to calculate 5-year costs. This estimate is conservative because it assumes that the total number of elderly persons receiving B_{12} injections will remain static, whereas the proportion of elderly in the population is growing.

For 5-year costs of high-dose oral B_{12} therapy, we assumed that conversion costs (ie, extra physician visits and investigations incurred by switching patients to oral therapy) were one-time costs only. Thereafter, all newly diagnosed patients with B_{12} deficiency would be started on oral B_{12} therapy and therefore avoid the conversion costs. Again we assumed that the total number of elderly receiving therapy for B_{12} deficiency remained static.

Other direct and indirect costs, including nursing time, syringes, needles, alcohol swabs, and patient travel, were not considered because they are not specifically paid for by the provincial plan. Because these costs are part of parenteral therapy alone, their exclusion ensures a consistent bias against oral therapy as the proposed alternative. Such consistent biasing of assumptions in favour of usual or conventional care, and against any new alternative under consideration, is recommended for economic evaluations by Sonnenberg et al.[19] All costs are expressed in Canadian dollars.

Cost savings

We calculated savings associated with switching to oral therapy under two scenarios. In the first scenario, costs were calculated assuming that *all* injection-associated visits would be avoided by switching to oral therapy.

In the second, more conservative, scenario, we calculated savings based on the number of physician visits avoided by switching to oral B_{12}. To do this, we predicted the annual number of physician visits required for each B_{12} patient as a function of five markers of illness. To derive a model that predicts the annual number of physician visits, we identified all elderly Ontarians *not* receiving B_{12} injections and their annual number of physician visits from the OHIP database. We chose covariates for the model that should correlate with overall patient illness. This included age and sex (from the Registered Persons Database), number of medications chronically used (from the ODB database), annual number of emergency room visits (from the OHIP database), and the annual number of hospitalizations (from the Hospital Discharge Abstract Database). This last database records all hospitalizations in Ontario.

We used Poisson regression[20] to model the annual number of physician visits as a function of these covariates (**Table 1**). Poisson regression is the most appropriate method for modeling count data for two reasons. Poisson regression, as opposed to ordinary least squares regression, constrains the predicted response to be nonnegative. Second, Poisson regression allows the variance of the predicted count to increase as the predicted count increases, an occurrence often seen with count data.

For each B_{12} patient, values for these covariates were determined from the databases and substituted into this model to predict the number of physician

Table 1. Poisson regression model predicting annual number of outpatient physician visits for the elderly: *The model was derived using all elderly Ontarians not taking B_{12} injections and was used to predict the annual number of outpatient physician visits expected based on age, sex, total number of medication groups, annual number of emergency room visits, and annual number of hospital admissions. The annual number of outpatient visits increased for parameters whose coefficient was positive. In the model, age-c represents the centred value for age and equaled age-74.3. Sex was 1 if a patient was male, and 0 otherwise. All coefficients in the model differed significantly from 1.0 (*$P < .0001$ *for all parameters). X indicates an interaction term. The deviance-based generalized R^2 for the model is 0.12.*

Log (annual number of visits)	= 1.3394 + 0.0294*age – c
	+ 0.0008*age – c^2
	+ 0.0502*sex
	+ 0.3697*total number of drug groups
	+ 0.0001*annual number of emergency room visits
	+ 0.0622*annual number of hospital admissions
	– 0.0029*age – c X sex
	– 0.0008*age – c^2 X sex

visits if patients were not receiving B_{12} therapy. We used the difference between the observed number of physician visits (including those for injections) and the expected number of physician visits as the maximum number of injection visits avoided by oral therapy. If this difference was less than zero, no visits would be avoided by switching to oral therapy. If this difference exceeded zero as well as the number of injection visits, all injection visits would be avoided by switching to oral therapy. If this difference exceeded zero but was less than the number of injection visits, we randomly selected those avoided by switching to oral therapy. Costs were then recalculated using only avoided visits.

Sensitivity analysis

The cost of parenteral B_{12} therapy is heavily influenced by the proportion of injection-associated physician visits that would be avoided by switching patients to oral therapy. We therefore conducted a sensitivity analysis by randomly selecting, for each patient, a varying proportion of injection visits that were avoided by switching the patient to oral therapy. This identified the proportion of injection visits that needed to be avoided for oral B_{12} therapy to save money.

Table 2. Cost of parenteral B_{12} therapy for 1 and 5 years: Annual costs were determined for 34 264 seniors in Ontario who received a parenteral B_{12} prescription between July 1, 1995, and June 30, 1996. Annual costs were used to determine 5-year costs.

THERAPY	MEAN ANNUAL NUMBER PER PERSON (SD)	TOTAL ANNUAL NUMBER	UNIT COST ($)	ANNUAL COST ($)	5-YEAR COST ($)
DRUGS (A)					
Cyanocobalamin	1	33 892	4.04*	136 923.68	684 618.40
Rubramin	1	372	9.63*	3582.36	17 911.80
TOTAL A				140 506.04	702 530.20
INJECTIONS (B)					
With visit	5.50 (6.17)	188 514	2.10	395 879.40	1 979 397.00
Sole reason for visit	1.44 (3.58)	49 437	4.90	242 241.30	1 211 206.50
TOTAL B				638 120.70	3 190 603.50
ALL INJECTION VISITS (C)					
High cost	0.27 (1.4)	9273	38.65-105.40	405 699.95	2 028 499.75
Low cost	4.88 (5.6)	167 328	7.50-28.80	3 814 245.75	19 071 228.75
TOTAL C				4 219 945.70	21 099 728.50
AVOIDABLE INJECTION VISITS (D)					
High cost	0.16 (1.1)	5354	38.65-105.40	233 339.25	1 166 696.25
Low cost	1.47 (3.2)	50 446	7.50-28.80	1 037 854.35	5 189 271.75
TOTAL D				1 271 193.60	6 355 968.00
TOTAL COST: All visits for B_{12} injection alone (A + B + C)				4 998 572.44	24 992 862.20
TOTAL COST: Only some visits for B_{12} injection alone (A + B + D)				2 049 820.34	10 249 101.70

Rubramin is the trade name for a cyanocobalamin preparation. Visits costing more than $30 were arbitrarily classified as "high cost." All costs are presented in Canadian dollars and were not adjusted for inflation.
** Includes 10% pharmacist's fee.*

RESULTS

Between July 1995 and June 1996, 34 462 seniors had a prescription for parenteral vitamin B_{12} filled. We excluded 198 (0.6%) patients because their age or sex was not recorded. The mean age of the remaining 34 264 patients was 78.5 years (standard deviation [SD] 7.4); 22 809 (66.6%) were women.

More than three quarters (26 227) of patients receiving parenteral B_{12} had one or more injections claimed in the year following the B_{12} prescription (total 237 951, mean 6.9, SD 7.0). For 176 601 (74.2%) of these injections, a visit was identified. On average, patients received injections every 41.8 days (SD 27.6).

Costs for parenteral B_{12} therapy

The annual and 5-year cost of parenteral B_{12} is summarized in **Table 2**. Physician visits were the most expensive component of parenteral B_{12} therapy (mean $123.16 [SD 141.11] per person yearly). If all injection-associated visits were avoided by switching to oral therapy, we estimate that parenteral B_{12} therapy costs almost $5 million yearly (mean $145.88 per person yearly) or $25 million over 5 years (**Table 2**). If injection visits were avoided only if the total number of physician visits (including injection and noninjection visits) exceeded the expected number of physician visits (**Table 1**), we estimate parenteral B_{12} therapy to cost $2.04 million yearly or $10.3 million over 5 years.

The annual and 5-year cost of high-dose oral B_{12} therapy is summarized in **Table 3**. We estimated the total cost of switching all 34 264 people to oral therapy and treating them for 5 years at $7.4 million. Therefore, if all injection visits were avoided, $17.6 million would be saved over 5 years by switching all seniors from parenteral to oral B_{12} therapy. If injection visits were avoided only when the total number of physician visits (including injection and noninjection visits) exceeded the expected

Table 3. Cost of oral vitamin B_{12} therapy for 1 and 5 years: Costs of converting 34 264 elderly patients to oral B_{12} therapy and treating them for 5 years were estimated. Conversion costs apply only to those who are actually switched to oral therapy and are therefore not repeated each year.

COST VARIABLES	ANNUAL NUMBER PER PERSON	TOTAL ANNUAL NUMBER	UNIT COST ($)	ANNUAL COST ($)	5-YEAR COST ($)
DRUG (A)					
Drug (1-g vitamin B12 tablets*)	365	12 506 360	0.084†	1 050 534.24	5 252 671.20
TOTAL A			1 050 534.24	5 252 671.20	
CONVERSION COSTS (B)					
Physician visits	2	68 528	16.25	1 113 580.00	1 113 580.00
Laboratory tests	1	34 264	2.07	70 926.48	70 926.48
• White blood cell count	1	34 264	2.07	70 926.48	70 926.48
• Vitamin B12 level	1	34 264	20.68	708 579.52	708 579.52
• Blood sample	1	34 264	4.65	159 327.60	159 327.60
TOTAL B				2 123 340.08	2 123 340.08
TOTAL COST (A + B)				3 173 874.32	7 376 011.28

All costs are in Canadian dollars and were not adjusted for inflation.
**Swiss Herbal Co.*
†Includes 10% pharmacist's fee.

number of physician visits, $2.9 million would be saved over 5 years by switching to oral therapy.

Sensitivity analysis

Because the physician visit is the most expensive component of parenteral B_{12} therapy (**Table 2**), this study is sensitive to injection-associated physician visits avoided when patients are switched to oral therapy. Our sensitivity analysis showed that switching all patients to oral therapy would decrease costs as long as 16.3% of injection visits were avoided when oral therapy was used (**Figure 1**).

DISCUSSION

The cost of administering parenteral vitamin B_{12} for 1 year is considerable, and the potential savings from switching all patients to oral cobalamin therapy are substantial. Cost savings from oral therapy result primarily from decreased number of physician visits associated with injections. Costs are saved as long as 16.3% of injection-associated visits are avoided by switching to high-dose oral B_{12}.

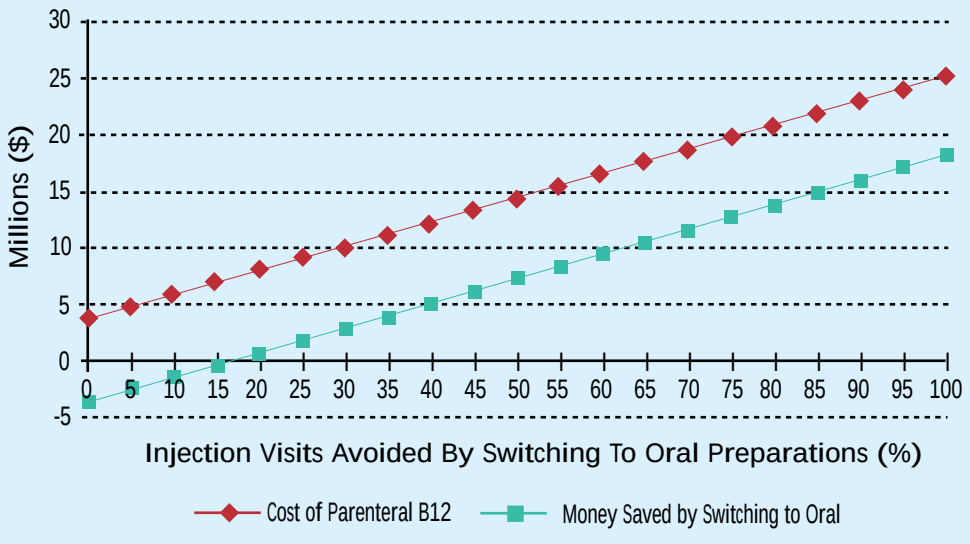
Compared with the Ontario annual health care budget of $18.5 billion, the savings associated with oral B_{12} therapy are small. Considering alternative uses of these funds, however, gives the savings a new meaning. For example, the institutional cost in Ontario for uncomplicated coronary artery bypass surgery in elderly patients is $16 500.[21] Switching all elderly Ontarians from parenteral to oral B_{12} therapy could therefore "purchase" between 175 and 1067 coronary artery bypass surgeries over 5 years.

We believe that our study underestimates savings from oral therapy. First, we excluded patients younger than 65 years. Second, if claims for B_{12} injections were not recorded because physicians did not submit a claim or because of coding errors, the cost of both the injection and the physician visit associated with the injection were not considered. This could explain why 23.5% of patients who received a prescription for an injectable B_{12} formulation had no injections claimed, and why 25.8% of injections had no visit claimed. It is also possible that some patients received B_{12} injections from home care nurses or family members, costs of which were not considered in the parenteral group.

Third, conversion costs were liberal. We believe that most physicians would discuss switching to oral therapy during a regularly scheduled appointment, thereby reducing some costs of conversion for physician visits (**Table 3**). Also, laboratory costs of monitoring patients were considered for only oral and not parenteral patients.

Finally, other direct and indirect costs of parenteral B_{12} administration, such as nursing and patient

Figure 1. Sensitivity analysis determining the effect on savings of varying the proportion of injection visits avoided by switching to oral B_{12} therapy: *As the proportion of injection-associated visits avoided by switching to oral B_{12} supplementation increases, the money saved by converting to oral therapy also increases.*



time, were not considered. Therefore, the strict third-party payer perspective used in this study probably underestimates the true savings associated with switching to oral therapy.

Oral B_{12} supplementation has other advantages. It avoids patient discomfort and inconvenience. Decreasing low-yield patient visits decreases the burden for many overworked family physicians. [22] Compared with parenteral therapy, oral B_{12} supplementation could be a rare example of a medical technology that is both better and cheaper than previous methods.[23]

Several factors should be considered when interpreting our results. First, some patients could be unwilling to switch to oral therapy, even given its obvious advantages. Second, patient noncompliance could cause complications and therefore increase the cost of oral therapy. We are unsure whether noncompliance with daily pills would exceed that of injections[24] or whether patients previously compliant with injections would not be so with oral therapy. While patients could occasionally miss their daily oral dose of vitamin B_{12} without consequences, this point highlights that physicians must consider patient compliance before switching from directly observed parenteral therapy to oral supplements.

Third, some physicians might monitor patients who have recently been switched to oral therapy more closely than we allowed for. It is possible, however, that such physicians also monitor patients closely while continuing parenteral therapy, costs not considered in our study. Fourth, frequent repeat visits by patients for B_{12} injections can facilitate patient-physician communication, permitting early detection and treatment of serious disease. Although switching to oral B_{12} therapy might decrease the frequency of which patients see their family physicians, we do not believe that this would prevent patients from visiting their family physicians as needed.

Fifth, the oral group did not consider costs resulting from patients currently taking oral B_{12} supplements having their vitamin paid by ODB. Because the number of these people is small and the cost of B_{12} pills is low, this would likely have a limited effect on our estimates. Sixth, our cost analysis applies to Ontario only. We suspect, however, that substituting parenteral B_{12} with high-dose therapy would save costs elsewhere.

Finally, and most worrisome, switching to oral therapy represents a form of "cost-shifting" to patients. Ontario Drug Benefit mandates that chronic medications are dispensed no more frequently than every 3 months. Because patients pay up to $6.11 each time they obtain a prescription, direct costs for patients are greater for oral B_{12} (four prescriptions annually) than parenteral therapy (one prescription annually). Other patient costs, however, such as travel and time, are avoided by switching to oral therapy.

Editor's key points

- High-dose oral vitamin B_{12} is rarely used to treat pernicious anemia in North America, despite its proven efficacy and acceptance in Europe.
- If family physicians switched to oral vitamin B_{12} treatment, substantial savings in financial costs, physician time, and patient inconvenience would result..

Points de repère du rédacteur

- L'administration de vitamine B_{12} à forte dose par voie orale est rarement utilisée pour le traitement de l'anémie pernicieuse en Amérique du Nord, en dépit de son efficacité éprouvée et de son acceptation en Europe.
- Si les médecins de famille optaient plutôt pour un traitement à la vitamine B_{12} par voie orale, il pourrait en résulter des économies substantielles en termes de coûts, de temps pour les médecins et d'inconvénients pour les patients.

CONCLUSION

We believe that switching patients from parenteral to high-dose oral B_{12} supplements is advantageous for both patients and the health care system. High-dose oral B_{12} formulations should be made readily available to physicians and their patients and active measures taken to promote this safe and cost-saving alternative to B_{12} injections.

Contributors

Dr van Walraven *acquired the data for this study and drafted the manuscript.* **Drs van Walraven**, **Austin**, *and* **Naylor** *contributed to the design, analysis, and interpretation of the data; critically revised the manuscript; and approved the final version of the article.*

Competing interests

None declared

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References

1. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret. *JAMA* 1991;265:94-5.
2. Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of vitamin B_{12} without intrinsic factor. *Acta Med Scand* 1968;184:247-58.
3. Waife SO, Jansen CJ, Crabtree RE, Grinnan EL, Fouts PJ. Oral vitamin B_{12} without intrinsic factor in the treatment of pernicious anemia. *Ann Intern Med* 1963;58:810-7.
4. Berlin R, Berlin H, Brante G, Pilbrant A. Vitamin B_{12} body stores during oral and parenteral treatment of pernicious anaemia. *Acta Med Scand* 1978;204:81-4.
5. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998;92:1191-8.
6. Lederle FA. Cyanocobalamin—a case for withdrawal. *J R Soc Med* 1993;86:308-9.
7. Stabler SP, Lindenbaum J, Allen RH. Vitamin B-12 deficiency in the elderly: current dilemmas. *Am J Clin Nutrition* 1997;66:741-9.
8. Pruthi RK, Tefferi A. Pernicious anemia revisited. *Mayo Clin Proc* 1994;69:144-50.
9. Watts DT. Vitamin B_{12} replacement therapy: how much is enough? *Wisc Med J* 1994;93:203-5.
10. Markle HV. Cobalamin. *Crit Rev Clin Lab Sci* 1996;33:247-356.
11. Delva MD. Vitamin B_{12} replacement. To B_{12} or not to B_{12}? *Can Fam Physician* 1997;43:917-22.
12. Elia M. Oral or parenteral therapy for B_{12} deficiency. *Lancet* 1998;352:1721-2.
13. Verhaeverbeke I, Mets T, Mulkens K, Vandewoude M. Normalization of low vitamin B_{12} serum levels in older people by oral treatment. *J Am Geriatr Soc* 1997;45:124-5.
14. Altay C, Cetin M. Oral treatment in selective vitamin B_{12} malabsorption. *J Pediatr Hematol Oncol* 1997;19:245-6.
15. Lederle FA. Oral cobalamin for pernicious anemia: back from the verge of extinction. *J Am Geriatr Soc* 1998;46:1125-7.
16. Berlin R. Vitamin B_{12} injections. *Br Med J Clin Res Ed* 1985;291:56.
17. Middleton J, Wells W. Vitamin B_{12} injections: considerable source of work for the district nurse. *Br Med J Clin Res Ed* 1985;290:1254-5.
18. Hathcock JN, Troendle GJ. Oral cobalamin for treatment of pernicious anemia? *JAMA* 1991;265:96-7.
19. Sonnenberg FA, Roberts MS, Tsevat J, Wong JB, Barry M, Kent DL. Toward a peer review process for medical decision analysis models. *Med Care* 1994;32(Suppl 7):JS52-JS64.
20. Cameron AC, Trivedi PK. *Regression analysis of count data*. Cambridge, Engl: Cambridge University Press; 1998.
21. Naglie G, Tansey C, Krahn MD, O'Rourke K, Detsky AS, Bolley H. Direct costs of coronary artery bypass grafting in patients aged 65 years or more and those under age 65. *Can Med Assoc J* 1999;160:805-11.
22. Borsellino M. Overwork, stress rural doctors' companion. *Med Post* 1997;32(33):2.
23. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J* 1992;146:473-81.
24. Savage D, Lindenbaum J. Relapses after interruption of cyanocobalamin therapy in patients with pernicious anemia. *Am J Med* 1983;74:765-72.

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