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# Testing Vitamin B12 Levels in Neuropathy, Alopecia, Dizziness, and Fatigue: A Rapid Review

Health Quality Ontario

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*Evidence Development and Standards Branch at Health Quality Ontario*

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## Rapid Review Methodology

Rapid reviews are completed in very short time frames. Clinical questions are developed by the Evidence Development and Standards branch at Health Quality Ontario, in consultation with experts, end users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials and guidelines. Other publication types are not included. Systematic reviews are evaluated using a rating scale developed for this purpose. If a systematic review has evaluated the included primary studies using the GRADE Working Group criteria (http://www.gradeworkinggroup.org/index.htm), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies in the systematic review are retrieved and the GRADE criteria are applied to a maximum of 2 outcomes. All rapid reviews are developed and finalized in consultation with experts.

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Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy-makers.

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series*, which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

## About Health Quality Ontario Publications

To conduct its rapid reviews, Evidence Development and Standards and its research partners review the available scientific literature, making every effort to consider all relevant national and international research; collaborate with partners across relevant government branches; consult with expert advisory panels, clinical and other external experts, and developers of health technologies; and solicit any necessary supplemental information.

In addition, Evidence Development and Standards collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

## Disclaimer

This rapid review is the work of the Division of Evidence Development and Standards branch at Health Quality Ontario, and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a rapid review, it may not reflect all the available scientific research and is not intended as an exhaustive analysis. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its rapid reviews. In addition, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current as of the date of the literature search specified in the Research Methods section. Health Quality Ontario makes no representation that the literature search captured every publication that was or could be applicable to the subject matter of the report. This rapid review may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

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# Background

Overuse, underuse, and misuse of interventions are important concerns in health care and lead to individuals receiving unnecessary or inappropriate care. In April 2012, under the guidance of the Ontario Health Technology Advisory Committee's Appropriateness Working Group, Health Quality Ontario (HQO) launched its Appropriateness Initiative. The objective of this initiative is to develop a systematic framework for the ongoing identification, prioritization, and assessment of health interventions in Ontario for which there is possible misuse, overuse, or underuse.

For more information on HQO's Appropriateness Initiative, visit our website at www.hqontario.ca.

## Objective of Analysis

The objective of this analysis is to identify the clinical utility of testing vitamin B12 levels in cases of neuropathy, alopecia, dizziness, and fatigue.

## Clinical Need and Target Population

Vitamin B12 (cobalamin) is a water-soluble, essential vitamin. A deficiency in vitamin B12 can lead to a specific set of neurological disorders (subacute combined degeneration of the spinal cord, cognitive impairment) and one hematological disorder (megaloblastic anemia) disorders. Though it is unclear what the prevalence of vitamin B12 deficiency is in the general population, United States estimates indicate it to be between 2% and 6%. (1)

Based on a summary of studies, Kaferle and Strzoda (2) estimated that vitamin B12 deficiency was the cause of macrocytosis in 6% to 28% of the cases. However, not all cases of vitamin B12 deficiency are associated with macrocytosis or anemia, there may be other causes. The purpose of this rapid review is to determine if neuropathy, alopecia, dizziness or fatigue are associated with B12 deficiency. The 1988 studies by Carmel (3) and by Lindenbaum et al (4) noted that about 15% of patients can have low vitamin B12 levels without laboratory findings consistent with anemia or macrocytosis. This is referred to as subclinical B12 deficiency.

### Ontario Context

In fiscal year 2010/2011, more than 2.9 million serum vitamin B12 laboratory tests were billed to the province at a cost of approximately $40 million (Cdn). The number of vitamin B12 tests performed, particularly in the community setting, has increased since fiscal year 2005/2006 (Figure 1). In 2007, the serum vitamin B12 test was added to the laboratory requisition form that physicians use to request lab tests, and the number of tests increased by nearly 1 million between 2007 and 2008. The test was removed from the laboratory requisition form in November 2012. The volumes will be tracked by HQO in future years to see if there is a decrease in the volume of B12 tests.

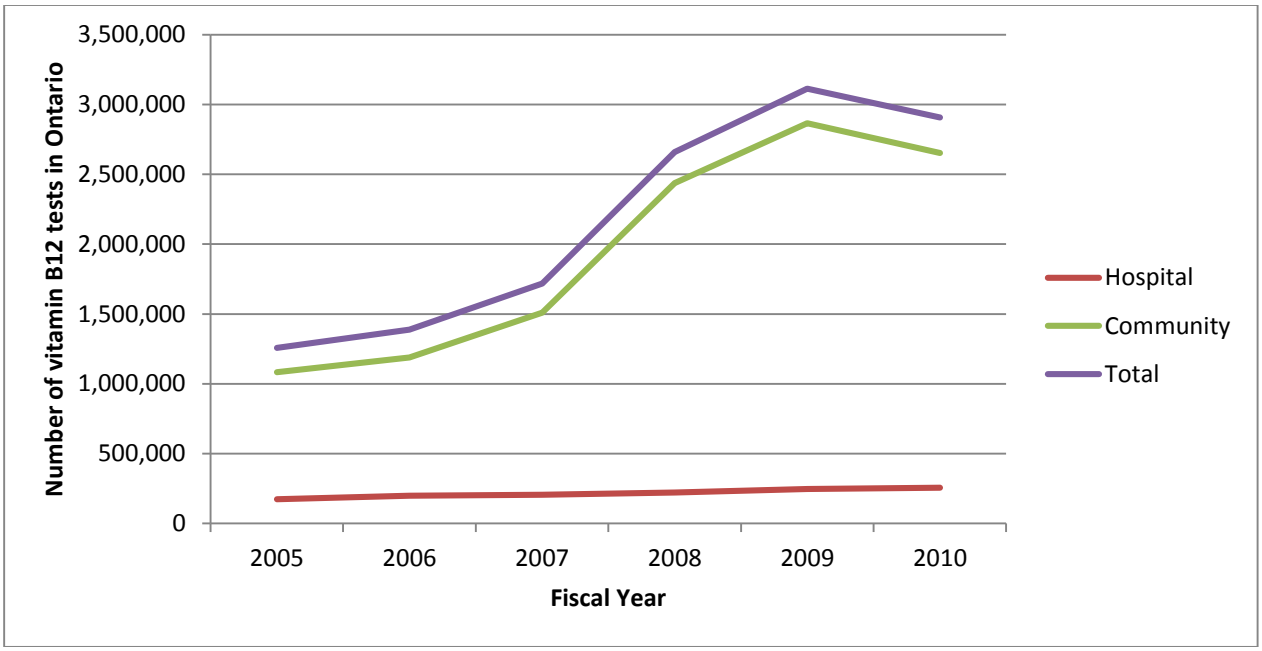


**Figure 1. Number of vitamin B12 tests in Ontario from FY 2005/2006 to 2010/2011**

# Diagnostic Accuracy of Serum Vitamin B12 Testing

In 2011, Willis et al (5) published a systematic review and meta-analysis of the diagnostic accuracy of tests for assessing vitamin B12. They searched the literature published from 1990 to 2009 and identified 54 studies for inclusion. They reported that no consistent reference standard was used to measure the accuracy of the serum vitamin B12 test, making it difficult to establish its accuracy, and that sensitivity and specificity varied across the studies. Sensitivity ranged from 13% to 75%, and specificity from 45% to 100%. Willis et al (5) attributed the wide ranges of sensitivity and specificity to the inconsistent use of a reference standard.

Hvas and Nexo (6) also published an article on the diagnostic accuracy for serum vitamin B12 testing. Although their review was not systematic, they described the strengths and weaknesses of each of the serum tests used to assess vitamin B12. Table 1 lists a summary of the tests based on their review. (6)

The National Health and Nutrition Examination Survey measures the health status of Americans. Part of the survey includes assessments of vitamin B12 biomarkers including cobalamin, methymalonic acid (MMA), and total homocysteine (Hcy). They established that, because of the challenges in sensitivity and specificity of tests, 2 tests (preferably cobalamin and MMA) should be performed when assessing vitamin B12 levels. They recommended MMA over total Hcy because Hcy also increases in the absence of other vitamins (folate and B6). (7;8)

**Table 1. Summary of Laboratory Tests to Assess Serum Vitamin B12 Deficiency**

| Laboratory Test | Rationale for Test | Advantages | Disadvantages |
|---|---|---|---|
| Cobalamin | Decreases in vitamin B12 deficiency | Readily accessible test<br>$10–$15 per test in Ontario<br>Most commonly used test with the most literature about abnormal cutoffs | Sensitivity and specificity is unclear |
| MMA[a] | Increases with vitamin B12 deficiency | High sensitivity | Questionable specificity<br>$105 per test in Ontario |
| Hcy[a] | Increases with vitamin B12 deficiency | High sensitivity | Low specificity influenced by lifestyle factors (smoking, alcohol consumption, coffee consumption)<br>~$65 per test in Ontario |
| Holotranscobalamin[a] | Decreases with vitamin B12 deficiency<br>Newer test, clinical utility unclear | High sensitivity | Specificity unclear |

Abbreviations: Hcy, total homocysteine; MMA, methymalonic acid;
[a]These laboratory tests are uninsured in community laboratories in Ontario.
Source: Hvas and Nexo. (6)

# Rapid Review

## Research Question

What is the clinical utility of serum vitamin B12 testing in cases of neuropathy, alopecia, dizziness, or fatigue?

## Research Methods

### Literature Search

A literature search was performed on June 17, 2013, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), and EBM Reviews for studies published from January 1, 2003, to June 17, 2013. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

### Inclusion Criteria

- English language full-text publications
- published between January 1, 2003, and June 17, 2013
- systematic reviews, meta-analyses, guidelines, randomized controlled trials, observational studies
- studies assessing the clinical utility of testing serum vitamin B12 levels in patients with suspected neuropathy, alopecia, dizziness, or fatigue

### Exclusion Criteria

- case reports, editorials, non-systematic reviews
- studies assessing the effectiveness of B12 supplementation in patients with confirmed neuropathy, alopecia, dizziness, or fatigue

### Outcomes of Interest

- Serum vitamin B12 measurements

## Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (9) The overall quality was determined to be very low, low, moderate, or high using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting

for all residual confounding factors. (9) For more detailed information, please refer to the latest series of GRADE articles. (9)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

| | |
|---|---|
| **High** | High confidence in the effect estimate—the true effect lies close to the estimate of the effect |
| **Moderate** | Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different |
| **Low** | Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect |
| **Very Low** | Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect |

# Results of Rapid Review

The database search yielded 1,970 citations published between January 1, 2003, and June 17, 2013 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

Four studies (1 systematic review and 3 observational studies) met the inclusion criteria. The reference lists of the included studies and health technology assessment websites were hand searched to identify other relevant studies, and the 5 studies from the systematic review were also included for a total of 9 included citations. No studies on the clinical utility of serum vitamin B12 testing in cases of suspected dizziness or fatigue were found. Table 2 lists the number of studies found for each condition reviewed in this analysis.

**Table 2. Studies Identified for the Analysis**

| Condition | Number of studies | Study design |
|---|---|---|
| Neuropathy | 8 | 1 systematic review (included 4 case series and 1 narrative review)<br>2 observational studies |
| Alopecia | 1 | 1 observational study |
| Dizziness | 0 | N/A |
| Fatigue | 0 | N/A |

Abbreviations: N/A, not applicable

## Neuropathy

On behalf of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine and the American Academy of Physical Medicine and Rehabilitation, England et al (10) recommended that "screening laboratory tests may be considered for all patients with [distal symmetric polyneuropathy]," and that tests with the highest yield of abnormality are blood glucose, serum B12 (with MMA) and serum protein immunofixation electrophoresis. The recommendation, classified as Level C (defined as "possibly effective, ineffective or harmful for the given condition in the specified population") was based on evidence from the 5 studies summarized in Table 3. The studies found that between 1% and 5% of the patients with peripheral neuropathy have serum B12 levels indicating B12 deficiency. (11-15) As noted previously, the prevalence of B12 deficiency in the general population is estimated to be between 2% and 6%. (1)

**Table 3. Summary of Studies That Contributed to the Recommendations by England et al (10)**

| Author, Year | Study Design | Participants with Neuropathy due to B12 Deficiency, n (%) | Results/Conclusion/Comment |
|---|---|---|---|
| Saperstein et al, 2003 (11) | Prospective case series | 27 (8%) had neuropathy due to B12 deficiency; only 15 (5%) of these had elevated serum B12 levels, whereas the remaining 12 had normal B12 levels but abnormal MMA levels | Reviewed diagnostic work-up in 324 patients with peripheral neuropathy. |
| Johannsen et al, 2001 (12) | Prospective case series | 3 (2%) due to nutrition deficiency—not specifically B12 | Reviewed diagnostic work-up in 147 patients with chronic polyneuropathy. The cause of neuropathy was identified in 75% of patients, with the majority of diagnoses relating to diabetes or alcohol abuse. |
| Lubec et al, 1999 (13) | Retrospective case series | 7 (4%) | Reviewed diagnostic work-up in 171 patients with peripheral neuropathy. They were able to define the cause of the neuropathy in 124 patients (73%). |
| Barohn, 1998 (14) | Narrative, non-systematic review | N/A | Summarizes testing that should be done in assessing neuropathy. Not a systematic review. |
| Fagius, 1983 (15) | Retrospective case series | 1 (1%) | Reviewed diagnostic work-up in 91 patients with cryptogenic polyneuropathy. The cause of neuropathy was definite or probable in 8 patients (9%). Fagius concluded "The findings suggest that only a limited investigation is justified in most cases of chronic polyneuropathy without obvious cause." |

Abbreviations: MMA, methymalonic acid; N/A, not applicable.

In addition to the 5 studies identified by England et al (10), 2 cross-sectional studies (16;17) on the clinical utility of vitamin B12 testing in patients with neuropathy were also found.

Hin et al ((16;17) assessed the association of B12 levels with cognitive impairment, depression, and neuropathy in 1,000 community dwelling people aged 75 years or older. Among the participants, 13% had low vitamin B12 levels. They concluded that "although symptoms of neuropathy were common in this age group, they were unrelated to low vitamin B12 concentrations" and that "there was no significant association of neuropathy with any of the laboratory measurements."

In 2012, Leishear et al (17) reported the results of a study of the relationship between B12 levels and peripheral nerve function in 2,287 older adults (aged 72–83 years). They found that 7.0% of the participants had B12 deficiency and 10.1% had subnormal B12 levels. No significant differences in peripheral neuropathy symptoms were found between participants with low B12 levels (includes B12 deficiency and subnormal B12 levels) and those with normal B12 levels.

The GRADE quality of evidence is very low.

## Alopecia

Only 1 study on the association between vitamin B12 levels and alopecia was identified. (18) In 2013, Ertugrul et al (18) published a prospective study with contemporaneous controls comparing vitamin B12 levels in 75 patients with alopecia to 54 controls without alopecia. They did not find a significant difference in serum vitamin B12 levels between the patients and the controls ($P = 0.735$).

The GRADE quality of evidence is very low.

## Dizziness

No studies were identified on the clinical utility of serum vitamin B12 levels and dizziness.

## Fatigue

No studies were identified on the clinical utility of serum vitamin B12 levels and fatigue.

# Conclusions

- There is very low quality evidence that there is no association between vitamin B12 levels and neuropathy.
- There is very low quality evidence that there is no association between low vitamin B12 levels and alopecia.
- There were no studies identified on the clinical utility of serum vitamin B12 testing in cases with dizziness or fatigue.

# Acknowledgements

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## Clinical Expert Advisory Panel for Appropriate Utilization of Vitamin B-12 Testing for Neurocognitive-Based Indications

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|---|---|---|
| **Chair** | | |
| Dr. Joel Ray | St. Michael's Hospital/University of Toronto | Scientist/ Assistant Professor, Department of Medicine |
| **Family Medicine** | | |
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| **Geriatric Medicine** | | |
| Dr. Angeles Garcia | Queen's University | Professor, Department of Medicine |
| **Neurology** | | |
| Dr. Stephen H. Pasternak | University of Western Ontario | Director, Cognitive Neurology & Alzheimer's Disease Research |
| Elizabeth Finger | University of Western Ontario | Assistant Professor, Clinical Neurological Sciences |
| **Medial Biochemistry & Medical Genetics** | | |
| Dr. David E. C. Cole | University of Toronto | Professor, Laboratory Medicine & Pathobiology |
| **Health Care System Representation** | | |
| Laurie Sweeting | Ministry of Health & Long Term Care | Senior Program Consultant |

# Appendices

## Appendix 1: Literature Search Strategy

**Search date:** June 17, 2013
**Databases searched:** Ovid MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, CDSR, ACP Journal Club, DARE, CCTR, CLCMR, CLHTA, CLEED, CINAHL
**Limits:** 2003-current; English
**Filters**: none
**Database:** EBM Reviews - Cochrane Database of Systematic Reviews 2005 to April 2013, EBM Reviews - ACP Journal Club 1991 to May 2013, EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2013, EBM Reviews - Cochrane Central Register of Controlled Trials May 2013, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment 2nd Quarter 2013, EBM Reviews - NHS Economic Evaluation Database 2nd Quarter 2013, Embase 1980 to 2013 Week 24, Ovid MEDLINE(R) 1946 to June Week 1 2013, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations June 14, 2013

| # | Searches | Results |
|---|---|---|
| 1 | exp Vitamin B 12 Deficiency/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 9533 |
| 2 | exp Vitamin B 12/df use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 20 |
| 3 | Transcobalamins/df use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 114 |
| 4 | exp Cyanocobalamin Deficiency/ use emez | 6360 |
| 5 | ((b12 or b 12 or cyanocobalamin or cobalamin* or transcobalamin* or cobamide? or hydroxocobalamin or hydroxo-cobalamin or hydroxycobalamin) adj3 (deficien* or inadequa* or insufficien* or low blood level* or low serum level* or low plasma level* or suboptimal or sub-optimal or subnormal or sub-normal)).ti,ab. | 9357 |
| 6 | (an?emia* adj2 (addison* or pernicious* or megaloblastic)).ti,ab. | 11238 |
| 7 | or/1-6 | 26073 |
| 8 | exp Vitamin B 12/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 18786 |
| 9 | Transcobalamins/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 964 |
| 10 | Transcobalamin/ use emez | 614 |
| 11 | Cyanocobalamin/ use emez | 28781 |
| 12 | (b12 or b 12 or cyanocobalamin or cobalamin* or transcobalamin* or cobamide? or hydroxocobalamin or hydroxo-cobalamin or hydroxycobalamin).ti,ab. | 50994 |
| 13 | or/8-12 | 68160 |
| 14 | exp Peripheral Nervous System Diseases/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 123067 |
| 15 | exp neuropathy/ use emez | 342430 |
| 16 | (neuropath* or neuritis or nerve disease* or nerve disorder* or pns disease* or (nervous system adj (disorder* or disease*)) or axonopath* or nerve dystroph* or neurodystroph*).ti,ab. | 230709 |
| 17 | exp Dizziness/ | 41789 |
| 18 | (dizz?ness or orthostatis or light?headedness).ti,ab. | 31421 |
| 19 | exp Alopecia/ | 44083 |
| 20 | (alopecia* or baldness or pseudopelade* or atrichosis or hairlessness or mucinosis follicular*).ti,ab. | 29106 |
| 21 | exp Fatigue/ | 137276 |
| 22 | exp Fatigue Syndrome, Chronic/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed | 4569 |
| 23 | (fatigue* or infectious mononucleosis like syndrome* or (myalgic adj encephalomyelitis) or royal free disease* or tiredness).ti,ab. | 140163 |
| 24 | or/14-23 | 875465 |
| 25 | (7 or 13) and 24 | 4433 |
| 26 | limit 25 to yr="2003 -Current" [Limit not valid in DARE; records were retained] | 2532 |
| 27 | limit 26 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained] | 2282 |
| 28 | remove duplicates from 27 | 1905 |

**CINAHL**

| # | Query | Results |
|---|---|---|
| S1 | (MH "Vitamin B12 Deficiency+") | 639 |
| S2 | ((b12 or b 12 or cyanocobalamin or cobalamin* or transcobalamin* or cobamide? or hydroxocobalamin or hydroxo-cobalamin or hydroxycobalamin) N3 (deficien* or inadequa* or insufficien* or low blood level* or low serum level* or low plasma level* or suboptimal or sub-optimal or subnormal or sub-normal)) | 864 |
| S3 | (an?emia* N2 (addison* or pernicious* or megaloblastic)) | 283 |
| S4 | S1 OR S2 OR S3 | 1,067 |
| S5 | (MH "Vitamin B12") | 2,064 |
| S6 | (b12 or b 12 or cyanocobalamin or cobalamin* or transcobalamin* or cobamide? or hydroxocobalamin or hydroxo-cobalamin or hydroxycobalamin) | 3,651 |
| S7 | S5 OR S6 | 3,651 |
| S8 | S4 OR S7 | 3,789 |
| S9 | (MH "Peripheral Nervous System Diseases+") | 23,684 |
| S10 | (neuropath* or neuritis or nerve disease* or nerve disorder* or pns disease* or (nervous system N1 (disorder* or disease*)) or axonopath* or nerve dystroph* or neurodystroph*) | 23,522 |
| S11 | (MH "Dizziness") | 1,239 |
| S12 | (dizz?ness or orthostatis or light?headedness) | 2,844 |
| S13 | (MH "Alopecia") | 1,170 |
| S14 | (alopecia* or baldness or pseudopelade* or atrichosis or hairlessness or mucinosis follicular*) | 1,622 |
| S15 | (MH "Fatigue+") | 11,272 |
| S16 | (fatigue* or infectious mononucleosis like syndrome* or (myalgic N1 encephalomyelitis) or royal free disease* or tiredness) | 20,277 |
| S17 | S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 | 61,065 |
| S18 | S8 AND S17 | 205 |
| S19 | S8 AND S17<br>Limiters - Published Date from: 20030101-20131231; English Language | 179 |

# Appendix 2: GRADE Tables

**Table A1: GRADE Evidence Profile for the Clinical Utility of Serum Vitamin B12 Testing in Neuropathy and Alopecia**

| No. of Studies (Design) | Risk of Bias | Inconsistency | Indirectness | Imprecision | Publication Bias | Upgrade Considerations | Quality |
|---|---|---|---|---|---|---|---|
| **Clinical utility of serum vitamin B12 testing in patients with neuropathy** | | | | | | | |
| 6 (observational)[a] | Serious limitations (− 1)[b] | No serious limitations | No serious limitations | No serious limitations | Undetected | None | ⊕ Very Low |
| **Clinical utility of serum vitamin B12 testing in patients with alopecia** | | | | | | | |
| 1 (observational) | No serious limitations | Serious limitations (−1)[c] | No serious limitations | No serious limitations | Undetected | Not sufficient to upgrade, but worth noting that this is a negative study | ⊕ Very Low |

[a] Because the studies were extracted from the systematic review by England et al (10), the systematic review itself is not listed. Also, the narrative review by Barohn (14) is not included because it is not a primary study nor a systematic review.

[b] No control groups.

[c] As there was only 1 observational study, consistency could not be assessed.

**Table 5: Risk of Bias Among Observational Trials for Clinical Utility of Serum Vitamin B12 Testing in Neuropathy and Alopecia**

| Author, Year | Appropriate Eligibility Criteria | Appropriate Measurement of Exposure | Appropriate Measurement of Outcome | Adequate Control for Confounding | Complete Follow-Up |
|---|---|---|---|---|---|
| Ertugrul et al, 2013 (18) (alopecia) | No limitations | No limitations | No limitations | No limitations | No limitations |
| Leishear et al, 2012 (17) (neuropathy) | No limitations | No limitations | No limitations | Limitations[a] | No limitations |
| Hin et al, 2006 (16) (neuropathy) | No limitations | No limitations | No limitations | Limitations[a] | No limitations |
| Saperstein et al, 2003 (11) (neuropathy) | No limitations | No limitations | No limitations | Limitations[a] | No limitations |
| Johannsen et al, 2001 (12) (neuropathy) | No limitations | No limitations | No limitations | Limitations[a] | No limitations |
| Lubec et al, 1999 (13) (neuropathy) | No limitations | No limitations | No limitations | Limitations[a] | No limitations |
| Fagius, 1983 (15) (neuropathy) | No limitations | No limitations | No limitations | Limitations[a] | No limitations |

[a] No control group.

# References


(1) McLean E, DeBenoist B, Allen LH. Review of the magnitude of folate and vitamin B12 deficiencies worldwide. Food Nutr Bull. 2008;29(2):S38-51.

(2) Kaferle J, Strzoda CE. Evaluation of macrocytosis. Am Fam Physician. 2009;79(3):203-8.

(3) Carmel R. Pernicious anemia. The expected findings of very low serum cobalamin levels, anemia, and macrocytosis are often lacking. Arch Intern Med. 1988;148(3):1712-4.

(4) Lindenbaum J, Healton EB, Savage DG, Brust JCM, Garrett TJ, Podell ER, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med. 1988;318:1720-8.

(5) Willis CD, Elshaug AG, Milverton JL, Watt AM, Metz MP, Hiller JE. Diagnostic performance of serum cobalamin tests: a systematic review and meta-analysis. Pathology. 2011;43(5):472-81.

(6) Hvas AM, Nexo E. Health technology assessment: A "must" for laboratory medicine? Scandinavian Journal of Clinical and Laboratory Investigation. 2003;63(5):317-8.

(7) Bailey RL, Carmel R, Green R, Pfeiffer CM, Cogswell ME, Osterloh JD, et al. Monitoring of vitamin B-12 nutritional status in the United States by using plasma methylmalonic acid and serum vitamin B-12. Am J Clin Nutr. 2011;94(2):552-61.

(8) Yetley EA, Pfeiffer CM, Phinney KW, Bailey RL, Blackmore S, Bock JL, et al. Biomarkers of vitamin B-12 status in NHANES: a roundtable summary. Am J Clin Nutr. 2011;94(1):313S-21S.

(9) Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.

(10) England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ, Cohen JA, et al. Practice parameter: the evaluation of distal symmetric polyneuropathy: the role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2009;72(2):185-92.

(11) Saperstein DS, Wolfe GI, Gronseth GS, Nations SP, Herbelin LL, Bryan WW, et al. Challenges in the identification of cobalamin-deficiency polyneuropathy. Arch Neurol. 2003;60(9):1296-301.

(12) Johannsen L, Smith T, Havsager AM, Madsen C, Kieldsen MJ, Dalsgaard NJ, et al. Evaluation of patients with symptoms suggestive of chronic polyneuropathy. J Clin Neuromuscul Dis. 2001;3(1):47-52.

(13) Lubec D, Mullbacher W, Finsterer J, Mamoli B. Diagnostic work-up in peripheral neuropathy: an analysis of 171 cases. Postgrad Med J. 1999;75(4):723-7.

(14) Barohn RJ. Approach to peripheral neuropathy and myopathy. Semin Neurol. 1998;18(1):7-18.

(15) Fagius J. Chronic cryptogenic polyneuropathy. The search for a cause. Acta Neurol Scand. 1983;67(2):173-80.

(16) Hin H, Clarke R, Sherliker P, Atoyebi W, Emmens K, Birks J, et al. Clinical relevance of low serum vitamin B12 concentrations in older people: The Banbury B12 study. Age Ageing. 2006;35(4):416-22.

(17) Leishear K, Ferrucci L, Lauretani F, Boudreau RM, Studenski SA, Rosano C, et al. Vitamin B12 and homocysteine levels and 6-year change in peripheral nerve function and neurological signs. J Gerontol A Biol Sci Med Sci. 2012;67(5):537-43.

(18) Ertugrul DT, Karadag AS, Takci Z, Bilgili.S.G., Ozkol HU, Tutal E, et al. Serum holotranscobalamine, vitamin B12, folic acid and homocysteine levels in alopecia areata patients. Cutan Ocul Toxicol. 2013;32(1):1-3.

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