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Oral vitamin B_{12} versus intramuscular vitamin B_{12} for vitamin B_{12} deficiency: a systematic review of randomized controlled trials*

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Background. Vitamin B_{12} deficiency is common, increasing with age. Most people are treated in primary care with intramuscular vitamin B_{12}. Several studies have reported equal efficacy of oral administration of vitamin B_{12}.

Objectives. We set out to identify randomized controlled trial (RCT) evidence for the effectiveness of oral versus intramuscular vitamin B_{12} to treat vitamin B_{12} deficiency.

Methods. We conducted a systematic review searching databases for relevant RCTs. Outcomes included levels of serum vitamin B_{12}, total serum homocysteine and methylmalonic acid, haemoglobin and signs and symptoms of vitamin B_{12} deficiency.

Results. Two RCTs comparing oral with intramuscular administration of vitamin B_{12} met our inclusion criteria. The trials recruited a total of 108 participants and followed up 93 of these from 90 days to 4 months. In one of the studies, mean serum vitamin B_{12} levels were significantly higher in the oral (643 ± 328 pg/ml; $n = 18$) compared with the intramuscular group (306 ± 118 pg/ml; $n = 15$) at 2 months ($P < 0.001$) and 4 months (1005 ± 595 versus 325 ± 165 pg/ml; $P < 0.0005$) and both groups had neurological responses. In the other study, serum vitamin B_{12} levels increased significantly in those receiving oral vitamin B_{12} and intramuscular vitamin B_{12} ($P < 0.001$).

Conclusions. The evidence derived from these limited studies suggests that 2000 μg doses of oral vitamin B_{12} daily and 1000 μg doses initially daily and thereafter weekly and then monthly may be as effective as intramuscular administration in obtaining short-term haematological and neurological responses in vitamin B_{12}-deficient patients.

Keywords. Cobalamin, cyanocobalamin, hydroxocobalamin, pernicious anaemia, vitamin B_{12}.

Introduction

Vitamin B_{12} deficiency is common; prevalence estimates among the general population range from 1.5 to 15%.[1–4] Adequate treatment is essential as vitamin B_{12} is necessary for the development of red blood cells, normal growth and nervous system maintenance. Vitamin B_{12} deficiency causes anaemia, fatigue, mood disturbance and other neuropsychiatric and neurological complications. Vitamin B_{12} deficiency has also been linked with an increased risk of myocardial infarction and stroke.[5]

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Vitamin B_{12} is absorbed in the terminal ileum. This absorption is almost entirely dependent upon intrinsic factor (IF). The most common, non-dietary cause of vitamin B_{12} deficiency is autoimmune pernicious anaemia. Other common causes include gastrectomy, ileal resection, pancreatic insufficiency and malabsorption syndromes such as Crohn's disease and coeliac disease. Less common causes include use of drugs such as metformin and proton pump inhibitors, and rarely malabsorption due to gastrointestinal bacterial overgrowth and infestation.

Vitamin B_{12} was first isolated in its cyano-form in 1948,[6,7] and is now widely used for the treatment of vitamin B_{12} deficiency. Most B_{12}-deficient individuals are treated with intramuscular vitamin B_{12}. Intramuscular injections are a 'considerable source of work' for health care professionals,[8] and can be painful.[9] While serious adverse reactions are rare, injections can be dangerous in anticoagulated patients. There is little difference in the cost of oral versus intramuscular therapy when medication alone is considered. However, intramuscular administration often involves a trip to a health facility or a home visit by a health professional to administer the injection.[10]

Effective oral treatment could therefore save considerable health service resources by reducing contacts with health personnel.[11] Several case–control and case series studies have suggested equal efficacy of the oral route.[12–14] The mechanism for this oral route is most probably that free vitamin B_{12} can be absorbed both passively (without binding to IF) as well as actively (following binding to IF) in the terminal ileum. Passive diffusion accounts for 1–2% of total absorption and is unaffected in patients with pernicious anaemia or gastro-duodenal surgical resection.[15,16]

Vitamin B_{12} is rarely prescribed in the oral form in most countries, other than Canada and Sweden, where such replacement recently accounted for 73% of the total vitamin B_{12} prescribed.[17] Possible reasons for doctors not prescribing oral formulations include unawareness of this option or concerns regarding effectiveness due to unpredictable absorption.[10,18]

In view of international variations in practice and the considerable resource implications associated with the choice of route for replacement therapy, we conducted a systematic review of randomized controlled trials (RCTs) evaluating vitamin B_{12} replacement using oral vitamin B_{12}.

A more detailed review has been published in *The Cochrane Database of Systematic Reviews*.[19]

Methods

We considered published and unpublished RCTs providing evidence for the effectiveness of oral vitamin B_{12} to treat vitamin B_{12} deficiency in participants with low serum vitamin B_{12} levels. We used a cut-off point of 180 pmol/l (or 240 pg/ml) as threshold serum level for vitamin B_{12} deficiency. We considered studies comparing oral vitamin versus intramuscular vitamin B_{12}.

We excluded studies evaluating vitamin B_{12} in the prevention of cardio-vascular diseases because the dose of vitamin B_{12} used in these studies is generally much smaller compared with doses used to treat vitamin B_{12} deficiency and the vast majority of patients included in these studies are not vitamin B_{12} deficient. We also excluded studies of patients with primary folate deficiency (because the concomitant use of folate would confound the metabolic outcome measures), and studies of patients with end-stage renal disease or on haemodialysis (because renal disease would also confound the metabolic outcome measures). We planned to note whether included patients suffered from conditions associated with gut malabsorption.

Our main outcome measure was serum vitamin B_{12} levels. Additional outcome measures were serum homocysteine and methylmalonic acid levels, haemoglobin and mean corpuscular volume (MCV), clinical signs and symptoms of vitamin B_{12} deficiency, costs, adverse effects, acceptability to patients and quality of life.

We searched The Cochrane Library (issue 4, 2004; including *The Cochrane Database of Systematic Reviews* and the *Cochrane Central Register of Controlled Trials*); the Database of Reviews of Effectiveness; MEDLINE (1966 to November 2004); EMBASE (1980 to December 2004); Lilacs—www.bireme.br (January 1982 to December 2004). Our search strategy was based on the strategy described in the *Cochrane Reviewers' Handbook* (Optimal Search Strategy for RCTs). We used it in conjunction with the terms 'pernicious anaemia' and 'vitamin B_{12} deficiency' for searches of Medline Ovid Web, and adapted it slightly for other electronic databases. The search strategy is available as Supplementary Data on the journal's website www.fampra.oxfordjournals.org. The bibliographies of all relevant papers identified by this strategy were searched for additional studies. We contacted the authors of relevant studies, experts in the field and manufacturers of oral and intramuscular preparations of vitamin B_{12} to enquire about additional published or unpublished studies, ongoing trials and to obtain additional references.

All abstracts or titles identified by the electronic searches were independently scrutinized by two researchers. When uncertainty arose, or when there were differences between these reviewers, hard copies of papers were obtained and reviewed and decisions made by consensus. The group checked whether inclusion and exclusion criteria were met; disagreement was resolved by consensus.

We obtained a copy of all selected papers, and two researchers independently extracted data using piloted data extraction forms.

We used the scheme described in the Cochrane Collaboration Handbook for assessing methodological quality. This scheme uses the criteria specified by Schulz and by Jadad[20,21] and involves assessing studies for publication, selection, performance, attrition and detection bias. Based on these criteria a 3-point rating scale was used, with the following grading: A—all quality criteria met: low risk of bias (plausible bias is unlikely to alter the results seriously); B—one or more of the quality criteria only partly met: moderate risk of bias (plausible bias raises some doubt about the results) and C—one or more criteria not met: high risk of bias (plausible bias seriously weakens confidence in the results).

The methodological quality of the included studies was independently assessed by two researchers and disagreements brought back to the whole group for resolution by consensus.

Results

Final searches were performed in early 2005. After manually removing all duplicates, we pre-selected 797 abstracts. After scrutiny of these, we obtained the full paper for 42 studies. Two studies met the inclusion criteria. We identified another 15 studies through searching bibliographies of selected articles and other relevant studies, and obtained the full text for these additional studies. These were mainly from the 1950s and early 1960s. A total of 57 studies were thus selected for review of the full paper. Most publications were written in English (88%), but we found seven papers that we felt warranted closer scrutiny written in other languages (Italian, French, Danish and Czech).

Fifty-five studies were excluded. The most common reason for exclusion was a non-randomized trial design (58%) or the study did not meet intervention criteria (32%).

Two RCTs[22,23] fulfilled our inclusion criteria. Two groups of researchers independently extracted data from these reports using piloted data extraction forms. We did not extract data from non-randomized studies or studies that clearly did not meet the inclusion criteria. The whole group checked all the relevant studies in relation to inclusion and exclusion criteria. Characteristics of these studies are shown in the 'Table of Included Studies' (Table 1).

Description of included studies

Two studies compared oral administration of vitamin B_{12} versus intramuscular administration of vitamin B_{12}.[22,23] Participants in both studies had low serum vitamin B_{12} levels and both were set in outpatient hospital clinics. The first study was carried out in USA by Kuzminski and colleagues,[23] and the second in Turkey by Bolaman and colleagues.[22] Kuzminski and colleagues recruited 38 patients with a mean age of 72 years (for those randomized to oral treatment) and 71 years (for those randomized to intramuscular treatment) and followed 33 of them up for 4 months. Twenty-eight of these patients had conditions that may be associated with malabsorption from the gut (including seven with pernicious anaemia and three with ileal resection), although patients with inflammatory bowel disease and coeliac disease appear not to have been included. Bolaman and colleagues recruited 70 patients with a mean age of 60 years for the oral group and 64 years for the intramuscular group and followed 60 of them up for 90 days. Thirty-five of these patients had conditions affecting the ileum that may be associated with malabsorption from the gut. Again, however, patients with inflammatory bowel disease and coeliac disease appear not to have been included. The dose of oral vitamin B_{12} used by Kuzminski and colleagues was 2000 μg;[23] Bolaman and colleagues used 1000 μg.[22] The dose of intramuscular vitamin B_{12} was 1000 μg in both studies.[22,23]

Bolaman and colleagues[22] used the 'block randomization method' described by Altman.[22,24] We considered the block randomization a satisfactory method for removing bias from the allocation procedure if applied correctly. Kuzminski and colleagues[23] used a 'Statistical Analysis System' for randomization but did not provide further details and did not describe attempts to conceal the assignment of participants. Neither study reported a sample size calculation. Patients in both studies knew whether they were taking oral or intramuscular medication, since no placebo was used.

We considered the length of follow-up in these studies insufficient because of the long biological half-life of body stores of vitamin B_{12}. This is estimated to be more than 480 days.[25] Further details of the methodological quality of the included studies can be found in Table 2.

Effect of interventions

In the study by Kuzminski and colleagues,[23] mean serum vitamin B_{12} levels were significantly higher in the oral (643 ± 328 pg/ml; $n = 18$) compared with the intramuscular group (306 ± 118 pg/ml; $n = 15$) at 2 months ($P < 0.001$). The difference was even greater at 4 months (1005 ± 595 versus 325 ± 165 pg/ml; $P < 0.0005$). Serum methylmalonic acid concentrations decreased to <3 SD above the normal range in all participants except one in the oral and two in the intramuscular group. Mean concentrations of the metabolites were not significantly different between the oral and the intramuscular groups, except at 4 months, when the value was higher in the intramuscular group ($P < 0.05$). Elevated serum total homocysteine decreased to 3 SD above the normal range in most participants, but the decrease was over 4 months in the oral group and during the first month in the

TABLE 1 *Included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Bolaman (2003)[22]	Allocation: randomized Observation period: 90 days	Patients aged 16 years and over with megaloblastic anaemia due to cobalamin deficiency 70 patients enrolled, 10 excluded. Outcomes measured for 60 patients. 26 oral group. 34 intramuscular group. Mean age 60 (±15) for the oral group and 64 (±10) for the intramuscular group. 14 patients with atrophic gastritis, 7 with chronic antral gastritis, 7 with chronic pangastritis, 6 with alkaline reflux gastritis and 1 with erosive gastritis. Unknown in 15 patients. Inclusion criteria: -serum cobalamin level <160 pg/ml -megaloblastic anaemia -MCV >94 fL Exclusion criteria: -vomiting and/or diarrhoea -alcohol use >40 g/day -incapacity to give informed consent -history of malignancy -folate deficiency -inability to ingest oral medication -use of medication might interfere with folate metabolism -pregnant or possibly pregnant -breastfeeding	1000 μg cobalamin oral or intramuscular once daily for 10 days. After 10 days, once a week for 4 weeks and after that once a month for life	Primary outcomes: -serum cobalamin -haemoglobin -MCV -WBC -platelet count -mini-mental state examination -neurological assessment Additional outcomes: -tolerability -costs -side effects not reported	Not blinded	B[a]
Kuzminski (1998)[23]	Allocation: randomized Observation period: 4 months	Newly diagnosed cobalamin deficient patients 38 randomized. Outcomes measured for 33 patients Mean age 72 (±11) for the oral group and 71 (±15) for the intramuscular group. 17 patients with chronic atrophic gastritis, 7 with pernicious anaemia, 3 with ileal resection, 1 with gastric stapling. Inclusion criteria: -serum cobalamin level <160 pg/ml -elevation of serum methylmalonic acid (MMA), total homocysteine or both metabolites >3 SDs above the mean in normal controls Exclusion criteria: -location outside immediate geographical area -incapacity to give informed consent -refusal to participate -associated life-threatening illness -primary folate deficiency	1000 μg intramuscular cyanocobalamin on days 1, 3, 7, 10, 14, 21, 30, 60 and 90 2000 μg oral cyanocobalamin daily for 120 days	Primary outcomes: -serum cobalamin -methylmalonic acid -homocysteine -neurologic responses Additional outcomes: -side effects not reported	Not blinded	B

[a] B—moderate risk of bias (plausible bias raises some doubt about the results).

TABLE 2 *Methodological quality of included studies*

Study	Randomization	Alloc. Conceal.	Blinding	N. Randomized	Withdrawals	Intent_to_treat	Follow-up
Kuzminski (1998)[23]	Unclear	Unclear	No	38	5	No	4 months
Bolaman (2003)[22]	Block randomization method	Probably adequate	No	70	10	No	90 days

TABLE 3 *Details of effectiveness Kuzminski 1998*

	Pre-treatment (mean ± SD)		4 months after (mean ± SD)	
	Intramuscular	Oral	Intramuscular	Oral
Serum vitamin B_{12} (pg/ml)	95 ± 92	93 ± 46	325 ± 165	1,005 ± 595
Serum folate (ng/ml)	7.1 ± 6.1	6.1 ± 3.0	9.1 ± 11.9	9.4 ± 14.2
Serum methylmalonic acid (nmol/l)	3630 ± 7040	3850 ± 6930	265 ± 190	169 ± 90
Serum total homocysteine (μmol/l)	40.0 ± 26.2	37.2 ± 44.9	12.2 ± 4.1	10.6 ± 4.4
Hematocrit (%)	39.5 ± 2.9	37.6 ± 6.2	40.6 ± 4.4	40.5 ± 2.9
MCV (fL)	102 ± 11	100 ± 12	91 ± 7	90 ± 7

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intramuscular group. In two patients in each group the response was not optimal. Four of the eighteen participants randomized to receive oral vitamin B_{12} and 4 of the 15 randomized to receive intramuscular vitamin B_{12} had a neurological response with a marked improvement or clearing of paresthesias, ataxia or memory loss. Further details of outcomes are summarized in Table 3.

In the study by Bolaman and colleagues,[22] serum vitamin B_{12} levels increased in those receiving oral vitamin B_{12} (n = 26) and in those receiving intramuscular vitamin B_{12} (n = 34) for 90 days. The authors reported a statistically significant difference between day 0 and day 90 within both groups ($P < 0.001$) but did not analyse differences between both groups. Participants receiving oral and intramuscular vitamin B_{12} improved in terms of cognitive function, sensory neuropathy and vibration sense and differences between both groups were not statistically significant.

We did not perform a meta-analysis because of differences in inclusion criteria, dose of oral vitamin B_{12} and replacement regimen, and follow-up period and outcome measures.

Discussion

This review identified limited evidence from RCTs that oral vitamin B_{12} is an effective treatment for vitamin B_{12} deficiency in the short term. Evidence for long-term effectiveness was not identified. High doses of oral vitamin B_{12} (2000 μg) daily are as effective as the intramuscular administration[23] in obtaining short-term haematological and neurological responses in patients with vitamin B_{12} deficiency. High doses of oral vitamin B_{12} (1000 μg) initially daily and thereafter weekly and then monthly are also as effective as intramuscular vitamin B_{12}.[22]

This body of evidence has serious limitations as it includes only two open studies with relatively short follow-up periods (90 days and 4 months) and small number of participants (n = 38 and n = 70) with some attrition. In addition, there are methodological limitations to both studies. Kuzminski and colleagues[23] did not clearly describe the method of randomization. Intention to treat analysis was not performed or mentioned in either study. Meta-analysis was not appropriate.

Neither study was conducted in Primary Care where most vitamin B_{12}-deficient patients are treated. Another factor affecting applicability to primary care settings is that the studies used different treatment regimes and strict and numerous exclusion criteria.

A crucial aspect our study addresses is whether or not patients with conditions that might cause malabsorption may be safely treated with oral vitamin B_{12} in primary care. This was difficult to ascertain because in the trials numbers are small, follow-up short and trials did not include patients with common conditions that might interfere with absorption in

the terminal ileum such as Crohn's disease, coeliac disease or ulcerative colitis. Three patients with ileal resection and seven with pernicious anaemia were included in one of the studies. Despite these cautions, we did find evidence of a satisfactory short-term response to oral vitamin B_{12} replacement even in patients with some conditions, mainly affecting the upper gastrointestinal tract that may be associated with malabsorption.

In addition to the included RCTs, we also identified many non-randomized studies assessing the effectiveness of oral vitamin B_{12}. These studies, dated from the early 50s to recently, were mainly 'before and after studies' and all the included participants with vitamin B_{12} deficiency responded to oral vitamin B_{12} replacement therapy in clinical and/or laboratory terms. However, it is not clear in most of these studies how many included patients suffered from conditions that may cause malabsorption. There is considerable experience in Sweden in using oral vitamin B_{12} to treat vitamin B_{12} deficiency, where satisfactory clinical experience of treating over 145 700 patient years has been described.[17] Once again, it is not clear whether this experience included important numbers of patients that were suffering from malabsorptive conditions. Many patients with mild, dietary B_{12} deficiency may have been included in this body of evidence. However, given that there is RCT evidence for a satisfactory haematological, biochemical and clinical short-term response for oral B_{12} replacement in some patients with conditions associated with malabsorption, and evidence for satisfactory response in large numbers of vitamin B_{12}-deficient patients, oral vitamin B_{12} replacement is probably a safe option for most patients with low serum vitamin B_{12} levels. However, dietary enhancement may have the same effect in many of these patients. A further large, pragmatic trial in primary care is needed to determine whether oral vitamin B_{12} is effective in patients with major common cases of malabsorption in primary care settings. In the meantime, for patients newly diagnosed with vitamin B_{12} deficiency and who have an intact terminal ileum, an initial *intramuscular* dose of vitamin B_{12} followed by a trial of *oral* replacement may be considered. However, given the long half-life of body stores of vitamin B_{12}, this strategy might not be the most appropriate for identifying those who will not respond to oral replacement therapy. A reasonable alternative is to institute a trial of oral vitamin B_{12} from the time of diagnosis, with careful laboratory and clinical assessments of response. Those not responding should be started on intramuscular treatment.

This change in clinical practice might benefit many patients in terms of fewer visits to health carers and reduced discomfort associated with injections. Nursing time would be freed up for treating other patients. However, adherence and monitoring will remain an important consideration, regardless of the route of administration.

Summary

Vitamin B_{12} deficiency can cause anaemia and neurological complications. Vitamin B_{12} is rarely prescribed in the oral form in most countries. Two randomized controlled studies were included in this review. The trials recruited a total of 108 participants and followed up 93 of these from 90 days to 4 months. The evidence derived from these limited studies suggests that high oral doses of B_{12} (1000 and 2000 μg) could be as effective as intramuscular administration in achieving haematological and neurological responses.

Declaration

Authors' contributions: CCB. Formulation of study question, searching, protocol writing, data extraction, piloting form for data extraction, study quality assessment, interpretation of data, report writing. JV-A. Coordination, searching, protocol writing, data extraction, interpretation of data, report writing. RC-J. Protocol writing, data extraction, report writing, suitability of data for meta-analysis. AM. Advice about appropriate biochemical and clinical endpoint, design and piloting of data extraction form, critical appraisal of findings, report writing. KH. Statistical advice on study design, protocol writing, data extraction, study quality assessment, suitability of data for meta-analysis, interpretation of data and report writing. AP. Clinical appraisal of findings, report writing, expertise on care of older people with long-term medication. IM. Biochemical advice. Critical appraisal of findings. Review writing. AG. Haematological advice. Critical appraisal of findings. Review writing.

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Conflict of interest: we have not received any commercial sponsorship for this review.

Andrew McCaddon is a Scientific Consultant for, and shareholder of, COBALZ LIMITED—a private company developing 'glutathionylcobalamin' as an alternative orally available form of vitamin B_{12}.

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References

[1] Pennypacker LC, Allen RH, Kelly JP, Matthews LM, Grigsby J, Kaye K. High prevalence of cobalamin deficiency in elderly outpatients. *J Am Geriatr Soc* 1992; **40:** 1197–1204.

[2] van Walraven C, Naylor C. Use of vitamin B12 injections among elderly patients by primary care practitioners in Ontario. *Can Med Assoc J* 1999; **161:** 146–149.

[3] Rajan S, Wallace JI, Beresford SA, Brodkin KI, Allen RA, Stabler SP. Screening for cobalamin deficiency in geriatric outpatients: prevalence and influence of synthetic cobalamin intake. *J Am Geriatr Soc* 2002; **50:** 624–630.

[4] Figlin E, Chetrit A, Shahar A *et al*. High prevalences of vitamin B_{12}, folic acid deficiency in elderly subjects in Israel. *Br J Haematol* 2003; **123:** 696–701.

[5] Nygard O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med* 1997; **337:** 230–236.

[6] Rickes E, Brink N, Koniuszy F, Wood T, Folkers K. Crystalline vitamin B_{12}. *Science* 1948; **107:** 396.

[7] Smith E. Purification of anti-pernicious anaemia factor from liver. *Nature* 1948; **161:** 638.

[8] Middleton J, Wells W. Vitamin B12 injections: considerable source of work for the district nurse. *Br Med J (Clin Res Ed)* 1985; **290:** 1254–1255.

[9] Elia M. Oral or parenteral therapy for B12 deficiency. *Lancet* 1998; **352:** 1721–1722.

[10] Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret? *J Am Med Assoc* 1991; **265:** 94–95.

[11] van Walraven C, Austin P, Naylor CD. Vitamin B12 injections versus oral supplements. How much money could be saved by switching from injections to pills? *Can Fam Physician* 2001; **47:** 79–86.

[12] Spies T, Stone R, Lopez G, Milanes F, Toca R, Aramburu T. Vitamin B_{12} by mouth in pernicious and nutritional macrocytic anaemia and sprue. *Lancet* 1949; **2:** 454–456.

[13] Ross G, Mollin D, Cox E, Ungley C. Hematologic responses and concentration of vitamin B_{12} in serum and urine following oral administration of vitamin B_{12} without intrinsic factor. *Blood* 1954; **9:** 473–488.

[14] Ungley C. Absorption of vitamin B_{12} in pernicious anaemia. I. Oral administration without source of intrinsic factor. *Br Med J* 1950; **2:** 905–908.

[15] Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. *Acta Med Scand* 1968; **184:** 247–258.

[16] 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.

[17] Norberg B. *Oral High-dose Cyanocobalamin—A Contagious Concept*. Rondel. Available at http://www.rondellen.net, 2001 (accessed 03 March 2004).

[18] Lederle FA. Oral cobalamin for pernicious anemia: back from the verge of extinction. *J Am Geriatr Soc* 1998; **46:** 1125–1127.

[19] Vidal-Alaball J, Butler CC, Cannings-John R *et al*. Oral vitamin B12 versus parenteral vitamin B_{12} for vitamin B_{12} deficiency. *The Cochrane Database of Systematic Reviews* 2005; issue 3.

[20] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17:** 1–12.

[21] Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *J Am Med Assoc* 1995; **273:** 408–412.

[22] Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: a single-center, prospective, randomized, open-label study. *Clin Ther* 2003; **25:** 3124–3134.

[23] Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998; **92:** 1191–1198.

[24] Altman DG, Bland JM. Statistics notes: how to randomise. *BMJ* 1999; **319:** 703–704.

[25] Basu TK, Dickerson JWT. *Vitamins in Human Health and Disease*. Wallingford: CAB International; 1996.