

Influence of Treatment Parameters on Symptom Relief in Individuals with Vitamin B12 Deficiency

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Authors' contributions

This work was carried out in collaboration between all authors. Authors PAK and JAG designed the study and with author MMJH interpreted the results, conducted literature searches and wrote the manuscript. Author JAG was responsible for data analysis. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Ever-growing numbers of displeased vitamin B12 deficiency patients are joining online support groups seeking help. The current study attempted to assess, quantitatively, several of the concerns of these patients.

Methods: A survey was developed, advertised and administered to 204 vitamin B12 deficiency patients through the online research website *Mendus.org*. The survey assessed the impact, on symptoms, of discrete, historical, epochs of B12 treatment characterized by a) type of B12 used, b) administration route, c) dosage, d) frequency and e) additional supplements. The final sample consisted of data from 192 individuals.

Findings: B12 injections were associated with greater mean symptom improvement than oral supplements. However, the combination of injections and additional oral cobalamin resulted in the greatest improvement. There were no differences observed for the form of cobalamin used. Compared to daily (DLY) or weekly (WKLY) injections, monthly (MNTH) or every two to three

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month (MNTH+) injections were associated with less symptom improvement. While additional oral B12 improved the effectiveness of daily, weekly and monthly injections, it was insufficient to 'rescue' the ineffectiveness of MNTH+ injections. Lastly, folate intake, but not iron, was associated with greater symptom improvement.

Conclusions: Patient' symptom reports suggest that oral supplements are not as effective as B12 injections. This is in contrast to previous work that relied primarily on biomarker change as a proxy for effectiveness, suggesting more research is necessary. The frequency of injections perceived as most effective by patients was far in excess of that often prescribed, suggesting under-treatment may be occurring. Taken together, further investigation with more definitive tests and the inclusion of patient reports is necessary.

Keywords: Vitamin B12 deficiency; pernicious anemia; treatment; injection; oral; cobalamin.

1. INTRODUCTION

Vitamin B12 (cobalamin) deficiency is a common, though frequently missed, problem in adults. The World Health Organization (WHO) acknowledges that vitamin B12 deficiency could affect millions of people throughout the world [1]. Untreated vitamin B12 deficiency can lead to anemia, gastrointestinal disturbance and permanent neurological damage among other symptoms [2]. Serum cobalamin and other markers can be successfully normalized via low-cost oral or parenteral supplementation [3], depending on cause. Given the serious nature of untreated (or under-treated) B12 deficiency, alongside the relatively low cost of management, there would seem to be little justification for inadequate treatment by any modern medical system. Despite these facts an ever-growing community of B12 deficient patients feel they are not being adequately treated [4]. Furthermore, many physicians have echoed similar concerns [5-7].

In a study of 889 vitamin B12 deficient patients from the United Kingdom (UK) an astounding 64% were less than satisfied with their treatment [4]. Among the concerns of these patients was the increasing trend toward prescribing oral B12, over injections. Despite several small trials that have reported comparable effectiveness between the two administration routes [3,8-10], both professionals [5-7,11] and patient groups [12,13] argue that oral cobalamin may not work as well as injections for many individuals. Furthermore, the existing trials [3,8-10] largely failed to consider symptom improvement in their assessments, relying solely on B12 biomarkers such as the inaccurate serum B12 test [14,15]. Indeed, cases exist where neurological symptoms improved despite 'normal' B12 levels [16]. Finally, insufficient numbers of patients with B12 mal-absorption issues (e.g. pernicious anaemia (PA)) were included in the trials [3,8-10]

making it risky to recommend oral cobalamin to all B12 deficient patients.

A second major concern expressed repeatedly in support groups is the frequency with which injections are given when they are prescribed. Post after post involves patient deterioration after being changed to so-called 'maintenance' dosages, or, needing to persuade medical practitioners that they need B12 injections at all. In the UK and Ireland, maintenance doses of one injection every 2-3 months are recommended [17]. Yet the very report providing those recommendations duly notes that studies investigating the clinical benefit of injection frequency are 'absent' [17]. Furthermore, several leading B12 specialists seem to encourage maintenance injections at least monthly [5-7,11] (Dr. Robert Allen, written communication, August 2016).

To begin to address these concerns an extensive questionnaire was developed via the online research platform Mendus.org. The questionnaire was designed to provide quantifiable, historical data concerning: a) the presence and severity of common B12 deficiency symptoms, b) usage patterns of B12 including cobalamin type, administration route, dosage and frequency and c) the impact of these variables on symptom severity. Linear mixed modeling was used to assess symptom improvement in relation to oral versus injected cobalamin and frequency of injection. The impact of folate and iron on symptom improvement was also assessed.

2. METHODS

2.1 Design

The current study was a questionnaire, administered online via the citizen science website Mendus.org to vitamin B12 patients, with

a quasi-longitudinal design assessing historical use of vitamin B12. Participation was completely voluntary and anonymous. Informed consent to the sharing of their anonymous data, including publication if applicable, was provided upon registration (when the anonymous data tracking IDs were administered). The current study met both of the criteria commonly used for determining exemption from IRB review, namely, anonymity of the data and minimal risk [18].

2.2 Questionnaire

An extensive, quantitative, questionnaire was developed using eSurv (<http://esurv.org>) to probe participants' history of vitamin B12 treatment. Participants were asked to indicate the presence or absence of a list of 21 common vitamin B12 deficiency symptoms (Fig. 1), followed by a severity rating for each symptom (prior to treatment). The symptom rating scale ranged from 0-10 with written anchors at 0 (symptom not present), 5 (symptom of moderate strength) and 10 (symptom incredibly severe). Next they were asked to report their history of B12 usage in discrete epochs, defined as any unique combination of B12 form (e.g. cyanocobalamin), dosage (e.g. 1000 ug), administration route (e.g. injections) and frequency (e.g. weekly). Symptoms were rated using the same scale after each epoch was entered.

In order to clarify what was meant by discrete epochs of B12 use, participants were given the following fictitious example prior to beginning the questionnaire. They were asked to clarify and

make notes about their own epochs prior to starting.

When she discovered she had pernicious anaemia Louise first tried an oral methylcobalamin supplement for 6 months. Her symptoms did not improve and her doctor decided to try intramuscular injections of cyanocobalamin. She was first given a loading dose (one 1000 mcg shot 5 times per week for 2 weeks). Soon she was reduced to one shot per week for one month. Finally, she was put on a maintenance dosage (one injection per month). In this example Louise would report 4 discreet periods of B12 use in our survey.

- 1) Her 6 month oral methylcobalamin period
- 2) The cyanocobalamin loading dosage period (5x/week)
- 3) The intermediate cyanocobalamin dosage period (1x/week)
- 4) Her maintenance cyanocobalamin dosage period (1x/month)

For each epoch of B12 use reported participants were able to enter: date range, form of B12 (e.g. hydroxocobalamin), administration route (e.g. oral), dosage (e.g. 200 ug), frequency (e.g. daily), up to 3 types of (additional) supplementary B12 and whether they were taking iron and/or folate. The questionnaire allowed up to 10 discrete epochs of B12 use to be entered by a single individual. The maximum number of epochs reported was 8 with a mean of 2.2. The survey can be found at the following link: https://eSurv.org?u=B12_Survey1

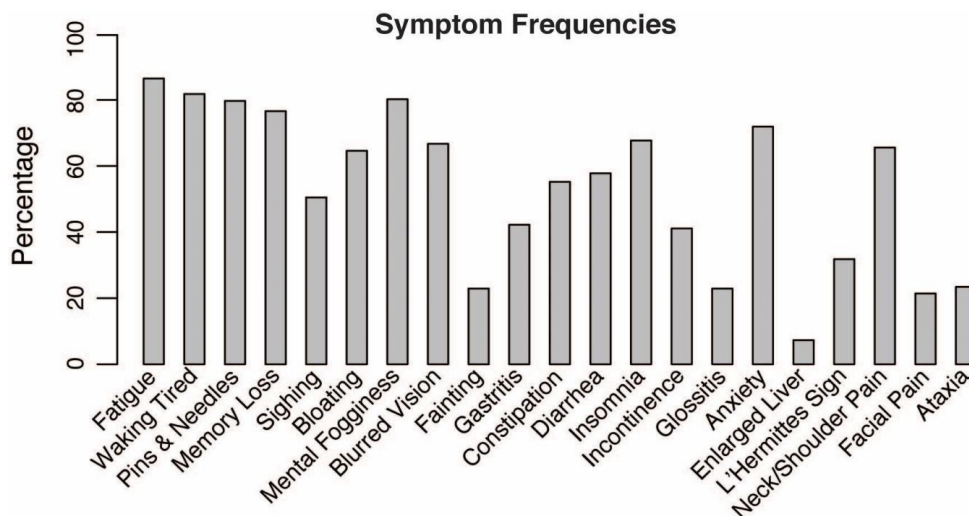


Fig. 1. Frequency, in the current sample, of 21 common symptoms of vitamin B12 deficiency

2.3 Population

The survey was advertised on numerous online pernicious anaemia and vitamin B12 deficiency support groups. Participation was anonymous, requiring only an ID from Mendus.org. Participation was not restricted to individuals officially diagnosed with vitamin B12 deficiency, however, a question was included to allow the exclusion of self-diagnosed individuals from the analysis if necessary. Data were submitted by 204 individuals. Several cases were excluded due to insufficient detail or duplicate entries. The final sample consisted of 413 discrete epochs provided by 192 individuals. A majority of the sample reported official diagnoses of B12 deficiency or pernicious anaemia (PA) (n=164, 87%) with n=114 reporting PA (59%). Twenty individuals were self diagnosed and 13 did not provide an answer. The sample was primarily female (91.7% or n=176).

2.4 Analysis

The data was cleaned by removing ambiguous or duplicate entries and converting dosage units to micrograms. Topical and nasal administration routes had insufficient data and were therefore removed from the analysis. Mean symptom number and severity were calculated for each individual at baseline (i.e. estimates of symptoms prior to any treatment) and for each reported epoch.

For each reported epoch participants could choose from 10 frequency values. Due to relatively few cases for certain options (i.e. three times daily), data were binned to produce four meaningful categories with roughly equal numbers of epochs. Daily (DLY), encompassing every other day, daily, and 2 or 3 times a day. Weekly (WKLY), encompassing once or twice a week. Monthly (MNTH), encompassing once or twice a month. Finally monthly plus (MNTH+), encompassed once every 2 or 3 months.

The primary analysis was conducted with the mean symptom severity change score (from baseline) as the dependent variable in order to assess overall trends and reduce the number of independent tests being performed. SPSS (v21) was used to run linear mixed models. Participant ID was always included as a random factor to account for repeated measurements. Diagnosis (e.g. pernicious anaemia), was not a significant predictor itself but was included in all models as a covariate. Secondary exploratory analyses

using factor scores and individual symptom ratings will be freely available at Mendus.org

3. RESULTS

3.1 Influence of B12 Administration Route

To assess the effectiveness of orally administered B12, versus injections, we first restricted the dataset to epochs where either administration route was exclusively reported. Oral B12 was associated with less mean symptom improvement, from a baseline severity of 6.99 to 6.42, whereas injections resulted in a change from 6.96 to 5.51. This difference was significant, $F(1,181)=6.5$, $P=0.01$ (Fig. 2) and translates to 8% and 21% symptom decrease for oral and injections respectively. Including dosage and frequency into the model resulted in an even greater difference $F(1,155)=11.4$, $P<0.001$ (Fig. 2) with oral B12 increasing symptom severity by ~9% versus a ~20% decrease for injections.

Individuals frequently reported using injections and oral B12 simultaneously. This allowed a second test of the effectiveness of oral B12, by comparing epochs where injections were use alone with epochs where both oral and injections were reported. The combination of injections and oral B12 was associated with significantly greater symptom reduction (~35%) compared to injections alone (~20%)($F(1,250)=14.0$, $P<0.001$)) (Fig. 3).

3.2 Influence of Form of Cobalamin Used

Restricting the dataset to epochs where injections were the primary source of B12 revealed no significant differences between cyanocobalamin, hydroxocobalamin and methylcobalamin on the effectiveness of reducing mean symptoms, $F(2,218)=1.6$, $P=0.2$. Adding dosage, frequency and a secondary source of B12 to the model did not reveal any differences. The results from Methylcobalamin should be interpreted cautiously as there were many fewer data points.

3.3 Influence of Injection Frequency

A main effect was observed for the influence of injection frequency on mean symptom rating, $F(3,242)=9.3$, $P<0.001$. Receiving DLY or WKLY injections did not differ in terms of mean symptom reduction, $t(251)=0.13$, $P=0.9$. However, monthly (MNTH) and every 2-3 months (MNTH+) were associated with significantly lower

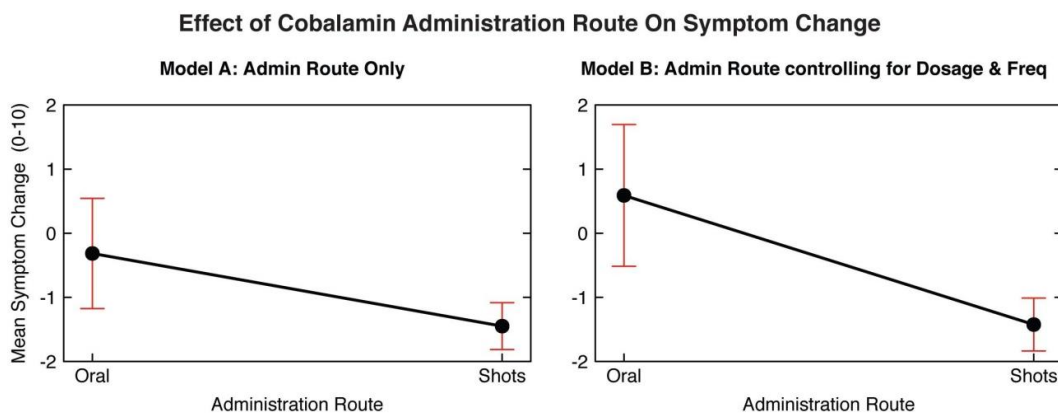


Fig. 2. Oral B12 is associated with less symptom improvement compared to B12 injections in a simple model (left) $F(1,181)=6.5, P=0.01$, as well as when controlling for dosage and frequency of the treatment (right) $F(1,155)=11.4, P<0.001$). Both models control for diagnosis and do not include self-diagnosed individuals

symptom improvement, $t(234)=2.9, P=0.004$ and $t(244)=4.4, P<0.001$. The presence of additional oral B12 (Fig. 4) had the largest effect on MNTH injections, increasing symptom reduction from 11% to 38% while DLY and WKLY were increased to 39% and 40% from reductions of 28% without oral B12. However, oral B12 did not substantially increase the effectiveness of MNTH+ injections which increased at ~12% to 15% symptom reduction.

Effect of Combining Oral and Parenteral Cobalamin

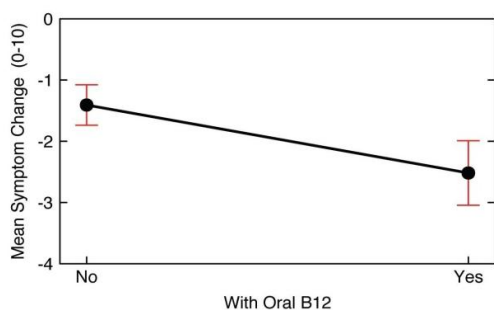


Fig. 3. Oral B12 was often taken in addition to injections. The combination of oral and parenteral cobalamin was associated with greater symptom reduction than injections alone ($F(1,250)=14.0, P<0.001$)

3.4 Influence of Folate and Iron

Considering epochs where injections were listed as the primary source of B12 we next assessed whether supplementing with any form and dosage of folate and/or iron reduced mean symptom severity. Taking folate increased

symptom reduction to 31% compared to not taking Folate (19%), $F(1,251)=20.5, P<0.001$. Iron did not significantly impact mean symptom severity.

Effect of Injection Frequency On Symptom Change

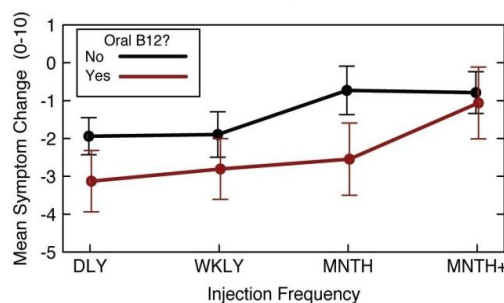


Fig. 4. For epochs containing only B12 injections (black line) there was a main effect of frequency with more frequent shots associated with greater symptom improvement ($F(3,242)=9.3, P<0.001$). Weekly injections did not differ from Daily injections ($t(251)=0.13, P=0.9$), whereas shots delivered every 2-3 months (MNTH+), or monthly (MNTH), were associated with significantly lower symptom improvement than Daily, $t(234)=2.9, P=0.004$ and $t(244)=4.4, P<0.001$. Adding oral B12 (red line) increased the effectiveness of all injection frequencies except monthly+

4. DISCUSSION

The present investigation revealed several important results, which, considering the

potentially disastrous consequences of under-treating vitamin B12 deficiency, call for further investigation.

- 1) Contrary to previous work using biomarkers to assess improvement, symptom reports suggest oral cobalamin is less effective than injections.
- 2) The combination of injections and oral cobalamin was more effective than either alone.
- 3) Injections delivered every two to three months were associated with far less symptom improvement than daily and weekly injections.
- 4) Folate had a beneficial impact on symptoms.

4.1 Oral versus Parenteral Cobalamin

The current results suggest, in terms of symptoms improvement, that B12 injections are superior to oral cobalamin. Holding all other treatment parameters constant, across 413 discreet periods of B12 use, injections resulted in ~25% mean symptom reduction compared to ~11% for oral B12. This is at odds with several small trials reporting equivocal results for the two administration routes [3,8-10]. There are several reasons for this discrepancy.

First, each of the trials conducted to date [3,8-10] assessed improvement using either serum B12 levels or hematological markers. While it is clearly important that these biomarkers return to normal, it does not necessarily indicate improvement in patient symptoms. It has been shown that the serum B12 test is unreliable [14,15] and further, insufficient to detect possible functional B12 deficiency [19-22]. Of the two trials to employ more informative tests of B12 deficiency (homocysteine and methylmalonic acid) one did not report any symptom measures⁹ while the other reported 'improvement' for 8 of 33 individuals [3].

Second, individuals with pernicious anaemia (PA) or B12 malabsorption issues were heavily under-represented in the past trials [3,8-10]. Pernicious anaemia involves a lack of intrinsic factor required for absorption of B12 [7] and thus by under-representing PA previous trials may have over-estimated the effectiveness of oral cobalamin. In the current study, 59% of the sample had a diagnosis of PA (n=114). Indeed, several notable specialists have warned against the use of oral cobalamin [5-7,11,16,23]. According to Solomon [6], oral cobalamin may be

adequate for many patients but its benefits for the reversal of neurological presentations have not yet been established [16].

Interestingly, when taken alongside injections, oral B12 was associated with significantly more symptom improvement than injections alone. However, given the significantly lower symptom improvement for oral compared to injections, and, the lack of symptom assessments previous trials we suggest further research is needed.

4.2 Frequency of Parenteral Treatment

When examining periods where patients reported only using injections, frequency had a big impact on symptom improvement. Daily and weekly shots were statistically indistinguishable from one another but clearly superior to monthly and monthly+ injections (every 60-90 days). Taking oral B12, in addition, improved the effectiveness of daily, weekly and monthly injections but failed to improve the already poor performance of monthly+ injections. These results are worrying given the large percentage of individuals in the current dataset (55%) and Hooper et al. [4] (50%) who reported receiving injections every 2-3 months. Unfortunately, these results would be consistent with the high number of dissatisfied patients (64%) reported by Hooper et al. [4].

One could certainly argue that the failure of infrequent injections to improve symptoms is to be expected. That is, treatment guidelines in the UK (and Ireland) suggest a patient with neurological symptoms should only be placed on a maintenance dosage, of one injection every 2-3 months, once symptom improvement has ceased on loading doses [17]. In theory this seems reasonable, assuming physicians rely on more than just a biomarker of B12 when assessing improvement. Unfortunately, the vitamin B12 deficiency support groups [12,13] are rife with individuals forced to self-inject to keep their symptoms at bay, while their physicians tell them their B12 levels are normal as in a recent case study [16].

Quite remarkably, when consulting the literature it is unclear what evidence the recommendation for a maintenance dose of once every 2-3 months is even based on. A report outlining treatment recommendations for the UK confirmed that studies investigating the clinical benefit of injection frequency are 'absent' [17]. Furthermore, consistent with the present observations, several prominent B12 specialists seem to advocate for no fewer than monthly

maintenance injections [5-7,11] (Dr. Robert Allen, written communication, August 2016). A sentiment consistently iterated by these specialists is that, considering the grave consequences, it is better to err on the side of administering too much B12 than too little.

4.3 The Importance of Adding Folate

Finally, our survey revealed that the addition of folate to treatment regimens greatly improved symptom severity. This was not surprising given the overlap in the chemical pathways of the two B-vitamins. Both must be present in adequate amounts for the production of the active forms of vitamin B12 (methylcobalamin and adenosylcobalamin) [24]. However, the fact that only 34% of individuals reported taking folate suggests awareness needs to be raised concerning the use of folate in B12 deficient patients.

5. LIMITATIONS

The present study has several clear limitations. Perhaps most significant is the potential bias of the sample. Respondents were members of support groups that advocate for the issues being examined here and who, rightly or wrongly, believe in the observed outcomes. This cannot be denied. Nonetheless, several findings suggest the data is reliable. For example, the importance of taking folate and iron are heavily discussed topics in these groups. However, only folate showed an association with symptoms. Had the data been influenced, knowingly or unknowingly, to be consistent with beliefs both iron and folate should have been associated with benefit. Why iron intake was not linked to symptom improvement is not clear.

The study was also retrospective, lacked 'objective' biomarkers of B12 and relied on the long-term memory of patients. While a limitation, these data fill a void left by previous work, which failed to adequately assess symptoms when assessing recovery [3,8-10]. Future work is certainly needed which will combine accepted and accurate biomarkers of B12 deficiency with patient symptom reports. This is already in development at Mendus.org as an extension of the current work.

6. CONCLUSION

The present survey suggests better symptom relief is attained using injections than oral B12. The optimal injection frequencies were far more

frequent than is often prescribed and much more effective if oral B12 and folate were also taken. Our results are consistent with the recommendations of many experts [5-7,11,16,23] but suggest maintenance dosages of once every 2-3 months are insufficient. The recommendations advocated by the National Institute for Health and Care Excellence (NICE) and the British Committee for Standards in Haematology (BCSH) [17] and reflected in the British National Formulary 2016 [25] would only seem to be appropriate if physicians actually included patient symptom reports in their assessments, rather than relying solely on biomarkers of vitamin B12.

CONSENT AND ETHICAL APPROVAL

Upon registration, when the anonymous data tracking IDs were administered, informed consent was provided by each participant, including to the sharing of anonymous data for publication if applicable. Personal identifiers were not collected rendering the data anonymous and, as per the World Health Organization guidelines, the project did not meet the criteria for 'Research involving human participants'. The study also met the second criterion commonly used for determining exemption from IRB review, namely, minimal risk.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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