

# Geriatric Evidence Based Cobalamin Deficiency Management and Cyanocobalamin Injection Rate

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## Abstract

*Cobalamin deficiency is common in geriatric populations. Despite the proven oral cobalamin efficacy, many clinicians still over utilize intramuscular injections. Traditionally cyanocobalamin injection was the only way to treat cobalamin deficiency. Cochrane review and other published studies have shown oral high dose cyanocobalamin to be an effective, safe, pain free and cost efficient alternative to the parenteral injections. We were able to provide providers and patients with the current literature on geriatric causes of cyanocobalamin deficiency and remove the knowledge gap, thus reducing the rate of unnecessary cyanocobalamin injections.*

**Key words:** cobalamin, geriatrics, cyanocobalamin, B12 Injection

## Introduction

Vitamin B12 deficiency is common in geriatric populations with the prevalence in some studies as high as 14.5%.<sup>1,2</sup> In geriatric patients, some of the precipitating factors are achlorhydria, pernicious anemia, use of proton pump inhibitors, use of metformin, poor dietary intake, and atrophic gastritis.<sup>3,4</sup> As geriatricians and primary care providers we often see multiple other causes of B12 deficiency such as malnutrition, polypharmacy, high alcohol intake, recent hospitalization, recent gastrointestinal bleeding requiring high dose intravenous proton pump inhibitor (PPI) followed by an oral PPI leading to significant iatrogenic achlorhydria compounding the age related parietal cell proton pump function decline leading to significant cobalamin malabsorption. Although the classic autoimmune antibody induced “pernicious anemia” is present in elderly patients, a majority of our geriatric patients are suffering from multiple causes of B12 deficiency as mentioned above. The efficacy of high dose oral cobalamin administration is well documented in the literature. Most elderly patients respond well to the high dose oral administration and their symptoms decrease as their lab values are restored to normal.<sup>6</sup>

Despite the proven oral cobalamin efficacy, many clinicians and patients still over utilize cyanocobalamin intramuscular (IM) injections for cobalamin deficiency management. This practice sometimes leads to years of unnecessary B12 injections. Traditionally cyanocobalamin injection was the only way to treat cobalamin deficiency since high dose oral administration was not available and low dose oral B12 is not efficient. A significant number of elderly cobalamin deficiencies managed using cyanocobalamin injections rather than high dose oral cobalamin preparations. Unnecessary cyanocobalamin injections lead to increased healthcare burden by increasing office visits, injection associated complications and increased cost of care.<sup>7</sup>

High dose oral supplementation of cobalamin such as 1000 microgram or more daily instead of cyanocobalamin injections has been proven to be effective, safe, cost efficient and without pain or complications.<sup>3</sup> A sublingual dose of 500 µg of cobalamin given either sublingually or orally is effective in correcting cobalamin deficiency as well.<sup>8</sup> Cochrane review studies and other published studies have shown oral high dose B12 to be effective, safe, pain free and less costly alternative to parenteral B12 injections.<sup>6,7,11</sup>

## Objective

Our objective was to decrease the rate of unnecessary intramuscular cyanocobalamin injections in our primarily outpatient geriatric patients to reduce regular monthly injection visits, injection related pain, and increase facility appointment availability. Research has shown that lack of physician knowledge on current literature and concerns about oral cobalamin effectiveness could be the barrier.<sup>9</sup> We implemented a plan to educate our primary care providers as well as our patients on appropriate available B12 treatment options. Treatment options included high

dose oral or sublingual versus parenteral B12 injection. After providers completed an educational training session, they were encouraged to reassess their patients and discuss treatment options, the decision on appropriate route (oral vs IM Injection) and dose of treatment of B12 deficiency was left to the treating physician and patient's preference.

## Setting and Methods

### Setting

The setting was a multispecialty outpatient clinic with a large Medicare Advantage population in the Phoenix metropolitan area. The clinic has 6 adult medicine providers including 1 Geriatrician, 4 Internal Medicine physicians and 1 Nurse Practitioner. Additional services offered onsite are: pharmacy, laboratory, radiology, ultrasonography, warfarin anticoagulation clinic, diabetic educator, and chronic disease management programs.

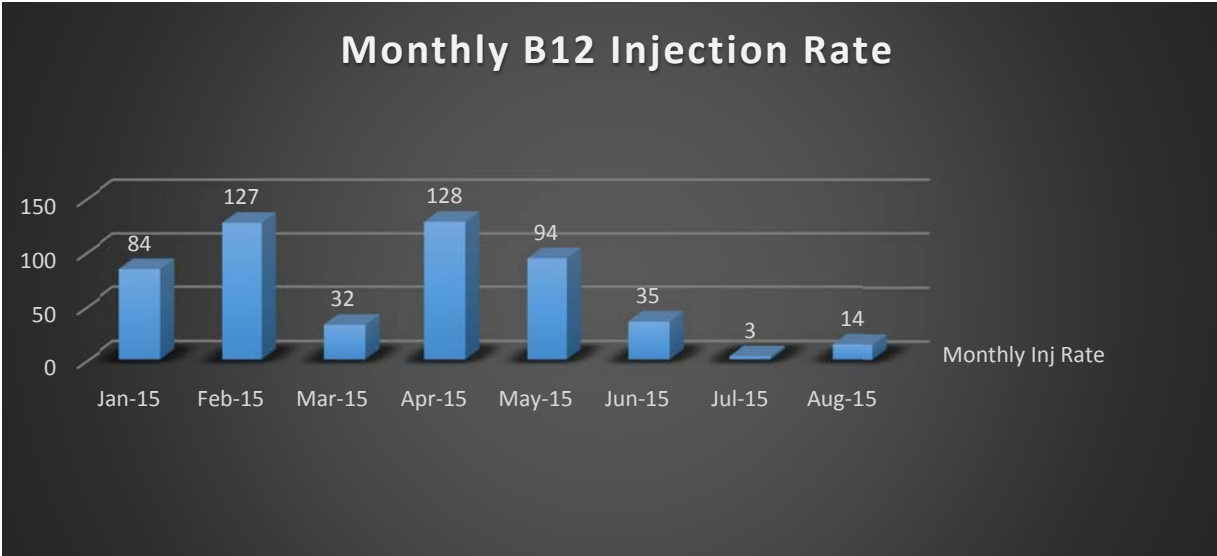
### Methods

We monitored the monthly cyanocobalamin injection rate being dispensed by the pharmacy to the adult medicine office for Medicare Advantage patients. A monthly average baseline of 93 B12 injections was being dispensed which equated to more than 1000 injections per year. (Table 1) Physicians were educated on high dose oral and sublingual cobalamin supplementation in appropriate patients based on current available practice guidelines. Physician education was provided using geriatrics evidence based medicine PowerPoint presentations during provider meetings which included a question and answer session. Providers were given patient education materials to share with patients to aid in informing them of their treatment options. Training materials were derived from the American Academy of Family of Physician's patient education on B12 management and explained during an office visit with the provider.<sup>10</sup> Patients were asked to make an appointment with their providers to review and reevaluate their cobalamin deficiency treatment plan and choose an appropriate treatment option. Physicians and patients discussed the specific clinical attributes of their B12 deficiency to determine an appropriate course of action whether to switch to high dose oral/sublingual cobalamin or continue the parenteral cyanocobalamin injection. Patients were empowered to make an educated decision in regards to their treatment and the provider honored their decision. Patients were also provided regular opportunities to reevaluate their decision and were free to switch from oral to injection or injection to oral at any time. Regular primary care provider updates were provided during twice a month office staff meeting debriefs over the course of 3 months follow up.

### Results

Prior to the implementation of geriatrics B12 management, between 90 to 100 vials of cyanocobalamin injections were being used on a monthly basis. This translated to more than 1000 B12 injections at our office. We calculated the average rate of B12 injections provided from January 2015 through May 2015 (Table 1). The evidence based cyanocobalamin treatment guideline educational intervention started June 1, 2015. By August 2015, a significant number of patients switched to high dose oral/sublingual cobalamin supplementation by their providers after appropriate evaluation and offered all treatment options. This led to a decreased rate of unnecessary cyanocobalamin injection by more than 81 percent within 3 months from June 2015 to August 2015. (Graph 1)

Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15
84	127	32	128	94	35	3	14



**Graph 1**

**Table 1**

<i>January-May Average Monthly B12 Injection Rate</i>	<i>93</i>
<i>June - August Average Monthly B12 Injection Rate</i>	<i>17.3</i>

### **Discussion**

Several studies have shown the effectiveness of high dose oral and or sublingual cobalamin treatment instead of cyanocobalamin parenteral injection.<sup>3,7,11</sup> Studies also show that lack of provider’s knowledge and comfort could be a barrier in not using oral vs parenteral B12 treatment.<sup>9</sup> When considering the direct (e.g. copay) and indirect (e.g. transportation expenses) patient costs associated with monthly cyanocobalamin injections, oral B12 therapy is likely to be a cost effective treatment with similar efficacy to intramuscular injections. We were able to provide both providers and patients with the current literature, geriatrics guidelines and remove the knowledge and comfort gap thus reducing the rate of unnecessary cyanocobalamin injection by more than 81 percent in 3 months.

Vitamin B12 deficiency is common in geriatric patients. Studies have estimated its prevalence to be as high as 14 %. Many factors contribute to this high prevalence, including some that may contribute to a deficiency over an extended period of time. Vitamin B12, or cobalamin, is not synthesized by the body and thus adequate dietary intake is essential.<sup>12</sup> Cobalamin is found in animal products therefore Vitamin B12 fortified foods or supplementation are necessary to prevent deficiency in vegetarians. Individuals with gastrointestinal diseases, including Crohn’s disease or celiac disease, may also be at increased risk of cobalamin deficiency due to malabsorption.<sup>12</sup> The use of certain medications may also precipitate cobalamin deficiency. Metformin, a medication commonly used in the treatment of type two diabetes, has been associated with reductions of Vitamin B12 in the body.<sup>12</sup> Proton pump inhibitors, a class of medications commonly used to reduce heartburn or dyspepsia, has also been implicated in reducing the absorption of Vitamin B12.<sup>12</sup> While some factors may contribute to cobalamin deficiency for several decades, other factors are more specific to onset during advanced age.

In older adults, malabsorption of Vitamin B12 is a major contributor to cobalamin deficiency.<sup>13</sup> One cause of malabsorption may be atrophic gastritis, a condition of chronic inflammation of the mucous membrane layer of the stomach. Atrophic gastritis is thought to affect up to thirty percent of older adults.<sup>12</sup> Atrophic gastritis results in decreased hydrochloric acid secretion by the parietal cells which leads to a more basic environment ultimately resulting in malabsorption of vitamin B12. The parietal cells ability to secrete intrinsic factor, another component necessary for proper vitamin B12 absorption, is also impaired by atrophic gastritis. Similar malabsorption issues are

noted with achlorhydria and pernicious anemia due to insufficient secretion of hydrochloric acid and intrinsic factor, respectively. Pernicious anemia is thought to occur in up to two percent of older adults.<sup>12</sup> While there are many characteristic causes of cobalamin deficiency, the majority of our geriatric patients are suffering from multiple causes of vitamin B12 deficiency.

Removing the barriers of provider comfort and improving the knowledge gap coupled with patient education and proper decision on personalized B12 management could lead to significant reduction of unnecessary parenteral cyanocobalamin injections.

### Study Limitations

Several opportunities exist for future research. Additional studies are needed in long-term effectiveness of oral cobalamin treatment versus intramuscular cyanocobalamin injections. Studies of longer duration will also be advantageous to eliminate any potential for a seasonal bias of the data.

### References

1. Pennyacker LC, Allen RH, Kelly JP, Matthews LM, Grigsby J, Kaye K, Lindenbaum J, Stabler SP. High prevalence of cobalamin deficiency in elderly outpatients. *J Am Geriatr Soc.* 1992 Dec and 40(12):1197-204. PubMed PMID: 1447433.
2. Lindenbaum J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH. Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr.* 1994 and 60(1):2-11. (n.d.).
3. Andrès E, Fothergill H, Mecili M. Efficacy of oral cobalamin (vitamin B12) therapy. *Expert Opin Pharmacother.* 2010 Feb and 11(2):249-56. doi: 10.1517/14656560903456053. Review. PubMed PMID: 20088746.
4. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ.* 2010 and 340:c2181.
5. Metformin With Either Histamine H2-Receptor Antagonists or Proton Pump Inhibitors: A Polypharmacy Recipe for Neuropathy via Vitamin B12 Depletion. Zdilla MJ. *Clin Diabetes.* 2015 Apr; 33(2):90-5.
6. Vidal-Alaball J, Butler CC, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database Syst Rev.* 2005 and (3):CD004655.
7. 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 Jan, 47:79-86. PubMed PMID: 11212437 and PubMed Central PMCID: PMC2014701
8. Sharabi A, Cohen E, Sulkes J, Garty M. Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route. *Br J Clin Pharmacol.* 2003 Dec, 56(6):635-8. PubMed PMID: 14616423 and PubMed Central PMCID: PMC1884303
9. Sep, Lederle FA. Oral cobalamin for pernicious anemia: back from the verge of extinction. *J Am Geriatr Soc.* 1998 and 46(9):1125-7. PubMed PMID: 9736106.
10. Oh R, Brown DL. Vitamin B12 deficiency. *Am Fam Physician.* 2003 Mar 1;67(5):979-86. Review. PubMed PMID: 12643357.
11. Rabuñal Rey R, Monte Secades R, Peña Zemsch M, Bal Alvaredo M, Gómez Gigirey A. [Should we use oral replacement for vitamin B12 deficiency as the first option of treatment?]. *Rev Clin Esp.* 2007 Apr;207(4):179-82. Spanish. PubMed PMID: 17475180.
12. National Institutes of Health, Office of Dietary Supplements. Vitamin B12 Dietary Supplement Fact Sheet. <https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional>. Published February 2016. Accessed February 2, 2017
13. Devalia V, Hamilton M S, Molloy A M, et al. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. *British Journal of Haematology.* 2014;166(4):496-513. Published June 2014. Accessed February 2, 2017