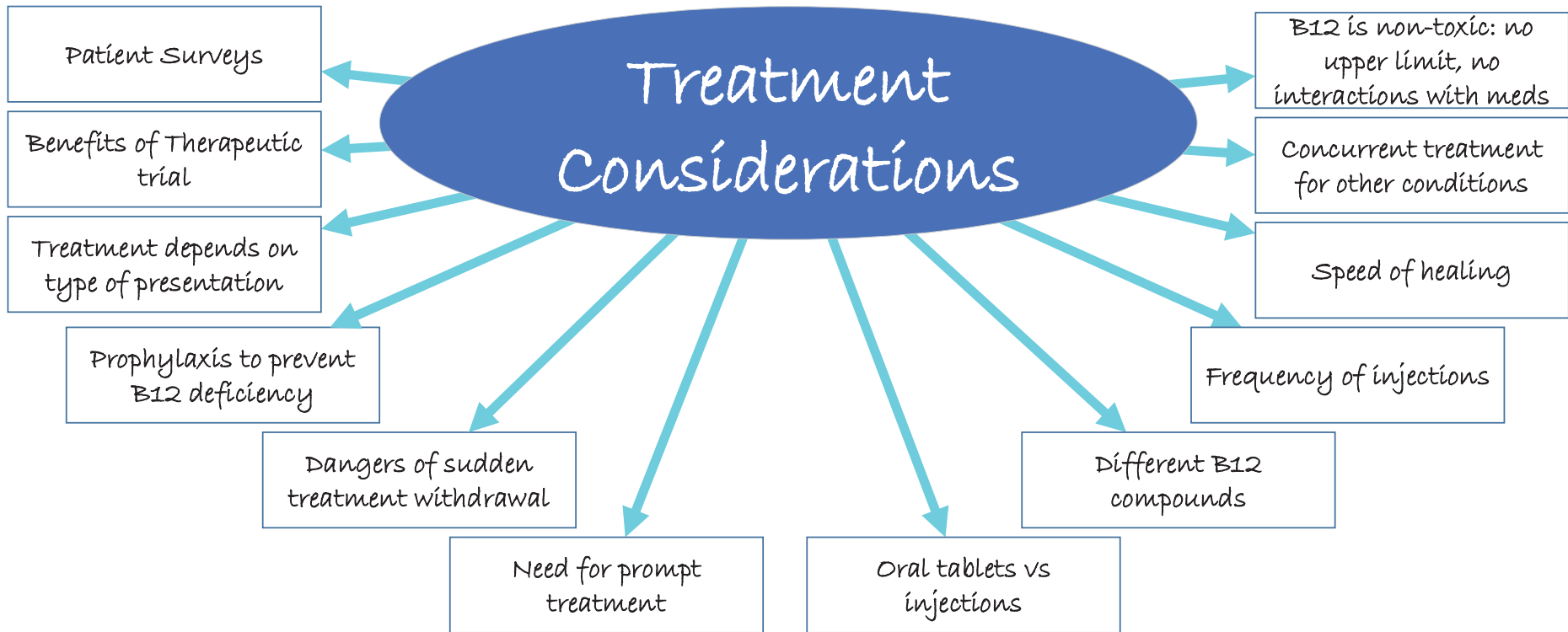


Chapter 3 Treating B12 deficiency

You are the light of the world – like a city on a hilltop that cannot be hidden. No one lights a lamp and then puts it under a basket. Instead, a lamp is placed on a stand, where it gives light to everyone in the house. In the same way, let your good deeds shine out for all to see, so that everyone will praise your heavenly Father.

Matthew 5:14-16

Figure 3-1 Key points regarding treatment



3.1 Vitamin B12-treatment regimes

Management of vitamin B12 deficiency poses a particular challenge because of the wide range of differing presentations and the fact that subtle cobalamin deficiency is non-specific. Correct diagnosis not only of the condition but also of the cause is key to correct treatment which will vary with the individual. Treatment regimes for the main categories of B12-deficient patient presentations are described on the third page of our Appendix 1: Protocol for excluding B12 deficiency (Megaloblastic anaemia/Pernicious anaemia) from adult and child patient presentation which starts on page 267) from adult and child patient presentation. The comments below provide additional and background information.

3.2 A note on safety

Experience has shown that vitamin B12 is completely safe, at any concentration in the diet and in the blood. In more than three decades of treating patients with high doses of vitamin B12 we never had any cases of adverse reactions. In contrast, the consequences of *not* treating a patient with vitamin B12 deficiency, or of treating them with suboptimal dosages, are devastating as described in the rest of this book.

The non-toxicity of vitamin B12 is confirmed by the US National Institute of Health Office of Dietary Supplements which states that the US Institute of Medicine (IoM) has not established any upper limit for vitamin B12 “because of its low potential for toxicity” (NIH ODS, 2018b). The IoM says: “no adverse effects have been associated with excess vitamin B12 intake from food and supplements in healthy individuals” (IoM, 1998c).

Whereas most vitamins have an optimal range (below which is deficiency, and above which would cause a different type of problem) (FAO & WHO, 2001, 2004), there appears to be no upper level of vitamin B12 intake where a problem might occur. Dr John Hathcock, the author of *Vitamin and Mineral Safety* published by the US Council of Responsible Nutrition (the leading trade association representing dietary supplement manufacturers and ingredient suppliers), states (Hathcock, 2014):

“No toxic effects of B12 have been encountered in humans or animals at any level of oral intake (IoM, 1998c; Miller & Hayes, 1982). The overall evidence indicates that vitamin B12 is virtually nontoxic. Doses of 1,000 µg per day were administered to a child by intravenous injection for a year without adverse effect (Merck & Co, 1958).”

Similarly, the European Food Safety Authority (EFSA) states that the European Scientific Committee on Food (SCF) has concluded that “it is not possible to derive an Upper Intake Level, mainly because no clearly defined adverse effect could be identified” (EFSA, 2008). The Dutch charity Stichting Tekort further explains: “It is very clear this fear of overdosing is based on a misunderstanding. For over 60 years high dose vitamin B12 treatment has been used without any signs of the danger of an overdose” (Stichting Tekort, 2018).

Vitamin B12 is safe because:

- It is soluble in water. If there is too much in the blood then it will be excreted rapidly by the kidneys. Note that the fat-soluble vitamins A, D and K may pose a greater risk of toxicity than water-soluble vitamins because of this (JustVitamins, 2014);

- Vitamin B12 is a conveyor and catalyst. If it ceases to be the limiting factor, any extra B12 has no effect;
- From our experience with patients we have seen that the body can use increasing amounts of B12 well beyond the amount normally available to it, to good effect.

However, the same is not true of all the B vitamins. Folate, for example, has an optimal range above which it is thought to cause health problems (Smith et al., 2008), even though folate is often required alongside vitamin B12 in several biochemical processes. Some B vitamins, while needed in deficiency, should not be used at high doses. For example, niacin (vitamin B3) may cause flushing unless the dose is built up gradually, and at high levels of supplementation may cause liver or heart and other problems (NIH ODS, 2019). Similarly, vitamin B6 in high doses from supplements over a long time can cause nerve damage (NIH ODS, 2011a).

3.3 Different types of Vitamin B12

Vitamin B12, also called cobalamin, is the generic name for a family of compounds based on the cobalt atom. As described in Chapter 1, cobalamins consist of cobalt as the central ion in a corrin ring. The cobalt ion can attach to other compounds to create the following forms:

- With CN⁻ (cyanide): cyanocobalamin
- With OH⁻: hydroxocobalamin
- With H₂O: aquocobalamin
- With NO: nitrocobalamin
- With CH₃⁺: methylcobalamin
- With 5-Desoxyadenosyl: adenosylcobalamin

(Gröber et al., 2013)

Hydroxycobalamin and cyanocobalamin are synthetic forms (used for example, in vitamin supplements, pharmaceuticals, or food fortification) which are transformed to methylcobalamin and adenosylcobalamin in the human body. These latter two are the active forms used in metabolism.

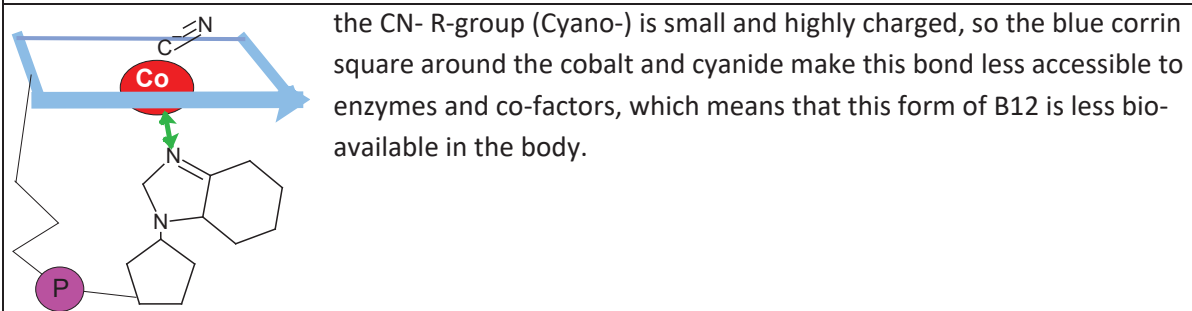
3.3.1 Cyanocobalamin

Cyanocobalamin is the cheapest form of vitamin B12 on sale. It is a very stable form, produced through an industrial process by combining B12 with cyanide (a poison). The main disadvantage of this type of cobalamin is that it is lost from the body very quickly. Because it is linked to cyanide, which the body considers toxic, this form of B12 is one of the targets sought by the kidneys for excretion so body turnover of cyanocobalamin is rapid (IoM, 1998c, p. 307). Since most of the cyanocobalamin is therefore lost to the body shortly after injection, we believe that taking it may not be as effective as taking B12 in other forms.

In our experience, about one in 10 people receiving cyanocobalamin develop mild headaches. Some people also appear to be unable to make use of cyanocobalamin, which may be because the cyano bond is too strong to allow the cyano group to detach (which would free the cobalt ion to attach to another group and create a form more readily used by the body)(see Figure 1-2 Cobalamin molecule on page 26 and Table 1-2 The most commonly used forms of B12 attached to different ions on page 29 which illustrate that the cyano-group could be hidden by the Pyrrole ring from breaking the bond. These patients do derive benefit from other forms of vitamin B12, however.

We note that the BNF does not recommend use of cyanocobalamin in treatment: “Cyanocobalamin solution and Cytamen® injection are not prescribable in NHS primary care” and “Hydroxocobalamin has completely replaced cyanocobalamin as the form of vitamin B12 of choice for therapy...” (BNF, 2017).

Figure 3-2 Cyanocobalamin – illustrating a possible structure which affects bioavailability



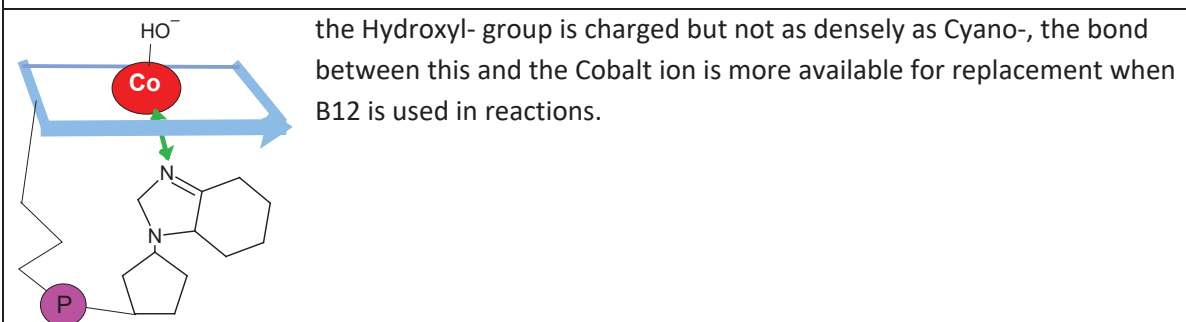
3.3.2 Hydroxocobalamin

Hydroxocobalamin is another artificial form of vitamin B12 (i.e. it is not found in living animals). However, it is rapidly converted to both of the biologically active forms. Hydroxocobalamin is the form of B12 used in injections in the UK and the most usual form of B12 recommended by the B12d.org charity to beneficiaries.

Hydroxocobalamin has a hydroxy- (OH⁻) group attached to the cobalt atom. The hydroxy- group is extremely soluble, and releases the B12 rapidly which frees B12 to interact with other biochemicals.

See the cross-references above.

Figure 3-3 Hydroxocobalamin – illustrating a possible structure which affects bioavailability



3.3.3 Methycobalamin

Methylcobalamin is a biologically active form which is used to transfer methyl groups from one molecule to another in cells and so assist with lipid metabolism and the regulation of DNA (gene switching on and off or epigenetics). The Methyl- (CH₃⁺) group is exchanged in many biological reactions. For example, in the interaction between vitamin B12 and folate (vitamin B9), B12 takes a methyl group from folate, allowing the folate cycle to complete, leading to correct synthesis of DNA.

B12 then donates the methyl group to homocysteine to form methionine. The Methyl-group bond distance is the same as Adenosyl- so it is not illustrated.

Methylcobalamin is also used in treatment and is available in tablet (oral) form and injectable form. An injectable form is used in some countries, such as Japan (see, for example, Kira et al. (1994)). In India, it is available in injectable, oral and sublingual forms (Kamath & Pemminati, 2017).

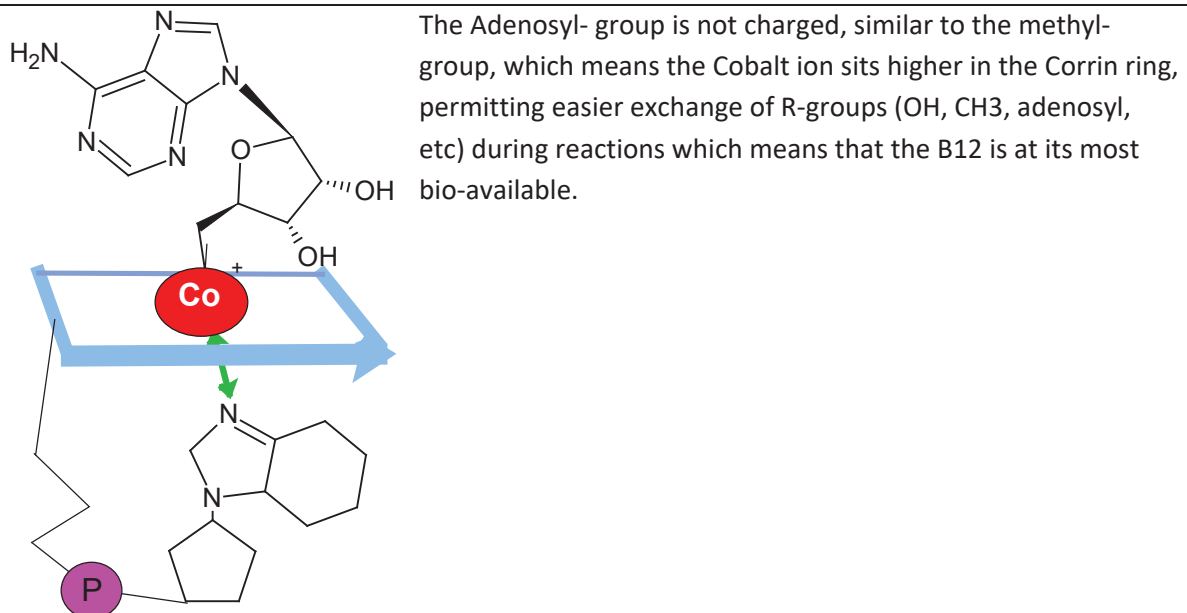
Methylcobalamin appears to be the most important active form in the cell cytoplasm. However, in at least one organelle within the cell, mitochondria, the most important active form appears to be adenosylcobalamin. There are debates about the relative advantages of these two forms. Some suggest that adenosylcobalamin is responsible for myelin synthesis (with deficiency therefore leading to neurological disorders) and cannot be replaced by methylcobalamin. This assertion has been challenged with an alternative hypothesis that the block of the conversion of methionine to S-adenosylmethionine (which depends on methylcobalamin) is responsible for B12 deficiency neuropathy (Kamath & Pemminati, 2017).

We have not encountered any difficulties with hydroxocobalamin but a case where a patient with severe vitamin B12 deficiency responded to treatment with high dose oral methylcobalamin, but not to equally high dose oral hydroxocobalamin, has been reported (Rietsema, 2014).

3.3.4 Adenosylcobalamin – also known as dibenzozide

The other biologically active form is adenosylcobalamin. In this case, adenosine in its active form, adenosyl-, is the active group attached to the reactive site of B12.

Figure 3-4 Adenosylcobalamin – illustrating a possible structure which affects bioavailability



It is possible that this is the form of B12 that is active in the bloodstream when circulating. This appears to be the form that is used to create energy in mitochondria (the active organelles inside each cell).

Adenosylcobalamin needs particular conditions: a particular pH, and accompanying electrolytes, to become soluble. It is usual to take adenosylcobalamin in oral tablets rather than by injection. It is often sold as an athlete performance enhancer because it increases energy and enthusiasm.

3.4 When to start B12 therapy

The best advice when B12 deficiency is suspected is to start treatment straight after taking a sample of blood, even before receiving the results.

Some doctors delay until they have received the results of the blood analysis, to get a base level of serum B12, but the consequence of even such a brief delay is that symptoms could get worse – especially in cases of severe deficiency, whereas there is no risk from providing additional B12 if the body does not actually need it. The *BMJ Best Practice* states that patients with severe haematological or neurological symptoms require immediate treatment with an intensive regime of B12 therapy (BMJ Best Practice, 2018d).

Below (Case 3-1) is an example of the benefit to a patient of a therapeutic trial.

Case 3-1 Benefit of therapeutic trial in a case of Bell's Palsy



Karen Taylor, born 1981, presented with symptoms of Bell's Palsy (facial weakness, visible over her left eye in the photo and causing pain in the left ear). The standard treatment for this condition is large doses of oral steroids. We confirmed via a blood serum B12 test and



signs and symptoms that she could be B12 deficient. Her B12 blood level came back as 345 ng/L on 2 August 2011 which is considered "low normal". As the treatment protocol agreed with the Primary Care Trust stated that therapeutic trials could be started at this level, and with that provisional diagnosis in mind, we commenced treatment with vitamin B12. Within three and a half weeks (by 26 August 2011) the Bell's Palsy resolved without the need for large doses of steroids (which have side-effects).

3.5 How much and how often?

Practices concerning both dose and method of administration of vitamin B12 vary considerably between countries. In most countries, vitamin B12 is given by intramuscular injection (IM) in the form of cyanocobalamin or hydroxocobalamin, although some countries (for example, Sweden) use predominantly oral tablets (Hvas & Nexø, 2006; Nilsson et al., 2005).

Everyone is different and the supplementation needed cannot easily be determined from the symptoms. We have found that in mild cases of B12 deficiency oral tablets may be given but that in moderate and severe cases injections are necessary.

Standard treatment is to give a loading dose of IM injections of 1 mg per 1 ml ampoule of hydroxocobalamin on alternate days for two weeks but in severe cases it may be necessary to give injections for up to eight weeks. This is a matter of clinical judgement. The BNF states that this dose should be continued until there is no further improvement (BNF, 2018) – in our experience some patients may need the loading dose for another month (see, for example, Case 3-2). The BNF recommendation is to follow this up with three-monthly injections. We have found, however, that the three-monthly frequency is not enough and that injections need to be given monthly. If patients have to wait for three months, the benefits of the loading dose may be eroded when there is no fresh B12 in the system. The frequency of injections has to be tailored to patient needs. Our experience based on clinical evidence is that the majority of patients (around 80%) need monthly injections. Also, many patients are ready for a further dose three weeks (rather than three months) after the loading dose has finished.

Hydroxocobalamin is the only form of vitamin B12 supplied for injection by the NHS (2016d). We have found that every patient can be managed on hydroxocobalamin because the body converts it to the usable forms.

Case 3-2 Example of patient needing unusually high number of loading doses



Jane Jermy, born 1965, used to run a creative media company. For ten years she had no strength in her writing hand (photo left) which limited her ability to work and look after her children. She had been diagnosed as suffering from ME, depression, fibromyalgia, joint pain and the psychological disorder Munchausen’s by proxy. In



February 2009 we found her blood serum B12 level to be 172 ng/L. Once treatment



was started she required 33 loading doses (1 mg B12 injections given two days apart), followed by injections every two months until an analysis of her symptoms led to a revision of the schedule to weekly injections. Her symptoms remitted; she became able to write and returned to work.

3.5.1 Oral supplements versus injections

Oral tablets containing vitamin B12 can be purchased from many health food shops and online. They are a convenient way of obtaining B12 supplements, and there are no obstacles to purchasing tablets. However, we do not recommend using tablets containing cyanocobalamin for the reasons given above.

B12 tablets are available which have a mixture of methylcobalamin and adenosylcobalamin, or vitamin B12 along with other associated vitamins and minerals (e.g. B12 and folate, B12 and folate and vitamin B6). These may work better for some.

As a rule of thumb, we have found that 1000 mcg (1mg) of methylcobalamin or hydroxocobalamin is a suitable amount for daily intake orally. This is a much higher dose than the 50-150 mcg indicated by the BNF which also suggests cyanocobalamin for oral intake which we normally would not recommend (BNF, 2017).

If B12 deficiency results from absorption problems in the digestive tract, tablets will be less effective because the B12 cannot be absorbed through this route. Some tablets circumvent this problem by being designed to be placed under the tongue. In this case, the vitamin B12 is absorbed directly into the bloodstream and is not dependent on secretions in the stomach or intestine.

In our own observations, oral supplements will generally stop symptoms getting worse, but for healing a course of injections is often required. Injected vitamin B12 reaches the bloodstream much more quickly than B12 absorbed through the stomach or intestine.

Case 3-3 Oral treatment inadequate: injections needed



Sharon O'Brian presented in 2000, aged 37, with neuropsychiatric symptoms, suffering from falls, facial palsy, paralysis on her right side and a weight of only 5 stone. Because her B12 level was 268 ng/L, which was above the NHS cut-off point for B12 deficiency, we were at that time (due to a PCT embargo) not allowed to treat her with injections. Instead she started oral B12 treatment. Because in reality she was severely B12 deficient – see Chapter 2 for an explanation of the limitations of B12 blood levels as indicators of deficiency - this course of action proved ineffective

and her B12 level fell to 237 ng/L in 2006 and 148 ng/L in 2009. At this point she was referred to a neurologist with an MS-like presentation. The neurologist gave no diagnosis and no treatment. As the embargo on injections was by then lifted, we instituted intensive B12-replacement therapy: her facial palsy and paralysis were totally reversed and she gained weight to 8 stone. We believe that had we been allowed to start treatment when she first presented in 2000 we would have been able to save her 10 years of suffering and the loss of her job. Both her son and daughter have been diagnosed with B12 deficiency and are receiving treatment.



3.5.1.1 Intramuscular injection (IM)

Vitamin B12 for injections is a nutritional supplement, not a medicine. With proper use of sterile technique, there is no reason why individuals should not self-inject. It is usual to inject into the muscle (intramuscular - IM). This is because B12 is water-soluble and flows into the fluids

surrounding the cells of the muscle. It therefore easily transfers into the bloodstream from an intramuscular injection.

3.5.1.2 Subcutaneous injection (SC)

The other common form of self-injection is sub-cutaneous (SC), i.e. into the fatty layer just below the skin. This is ideal for fat-soluble vitamins such as A, D, E and K. Many people self-inject subcutaneously. However, in the case of vitamin B12, the vitamin may not pass into the bloodstream and reach the parts of the body that need it quickly. For example, some people observe a red bruising effect around the injection site, which, unlike a normal bruise, does not change and darken. This may be the B12 (which is red) trapped in the fatty layer, and therefore not circulating in the bloodstream.

3.5.2 Frequency of injections

Chart 3-1 shows the results of a review (part of our Patient Survey – see below) of how often our patients needed injections in order to function optimally which was presented at the IHI/BMJ International Forum *Quality and Safety in Healthcare* conference in Paris (Chandy & Minney, 2014). The vast majority (80%) needed injections monthly or more frequently. (See also the patient comments in Box 3.1 on the effects of prolongation of the time between injections which resulted from the PCT decision to require the Practice to prescribe injections according to guidelines rather than clinical need.) The BNF confirms that during the period that symptoms are improving, alternate-day injections should be continued. The Best Practice guidance from the BMJ website (BMJ Best Practice, 2018d) also confirms that the frequency of injections should be tailored to the severity of the patient’s condition.

Chart 3-1 Frequency of B12 injections required



Source: Patient records and Shinwell Patient Survey 2008-9. Data extracted from 344 individual patient survey forms.

As explained in Chapter 2, the body is recycling vitamin B12 all the time. It is possible that if the body is very efficient at recycling, then improved intake of B12 in the diet or by injection every few months will be quite sufficient, because the body is only using a very small amount each time it cycles B12. However, if it is less efficient at recycling, B12 blood levels could go down quite quickly.

The following chart shows how often injections might be needed for different efficiencies.

Chart 3-2 Effect of vitamin B12 recycling efficiency on frequency of injections

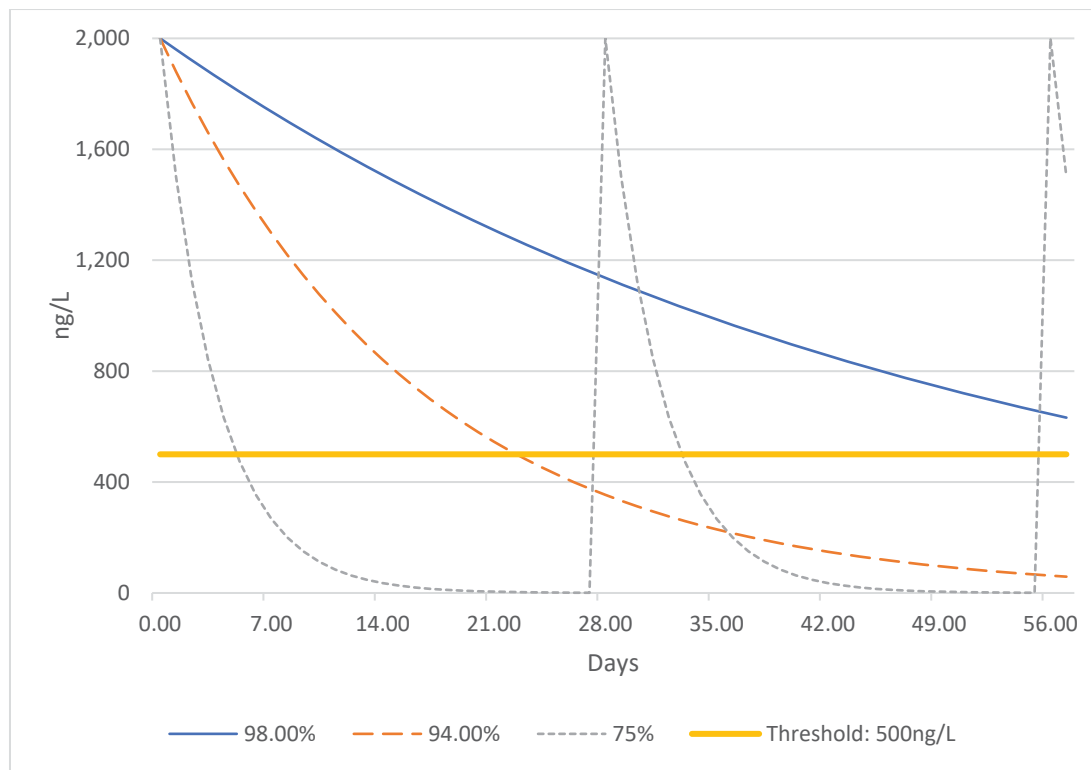


Chart 3-2 shows that, following an injection, the B12 level of a person whose vitamin B12 recycling efficiency is low (grey dotted line) will drop sharply below the 500 ng/L threshold within about 5 days. In contrast, the B12 level of a person whose recycling efficiency is 94% (dashed orange line) will remain above the threshold for about three weeks, and that of a person whose recycling efficiency is 98% (solid blue line) may remain above the threshold for up to three months. The numbers used for recycling efficiency are for illustrative purposes only. Chart prepared by Hugo Minney based on observation at the Shinwell Medical Practice.

The above chart shows the concentration of plasma B12 in the days following an injection. We suggest that where entero-hepatic circulation is reclaiming B12 highly efficiently (and there are no other causes for loss of B12 – such as presence of lead or nicotine toxins which deplete B12), then the level of B12 remains above threshold for longer. So injections every three months may be sufficient to maintain blood B12 above the threshold. However, if the blood serum B12 falls faster, then more frequent injections are needed. At high rates of loss, injections daily or on alternate days may be needed to maintain plasma B12 at a level sufficient for normal function.

This also illustrates why it is more important to inject frequently, than to inject a large dose at each injection.

3.6 Dangers of withdrawing treatment

During the two PCT embargos¹⁹ on B12 treatment, B12 therapy was withdrawn from a number of our patients. We observed that a relapse (the symptoms returned) occurred much more quickly than the textbooks would suggest. Since most patients will have B12 deficiency caused by malabsorption – which is a permanent condition – they will in most cases need lifelong treatment. It is especially important to monitor these patients because symptoms can return rapidly if treatment ceases. The difficulties that cessation of treatment during embargos caused for patients are illustrated in their comments in the Patient Survey questionnaires – see extracts listed in Box 3-1 on page 84.

3.7 Body stores and daily losses

Patients with symptoms of vitamin B12 deficiency which has been caused by insufficient dietary intake (for example, vegetarians) often ask why, if diet is the cause, it has taken so long for their symptoms to manifest (Rizzo et al., 2016). The answer lies in the way the body stores and recycles vitamin B12.

Various studies have been undertaken since the 1950s on the amount of vitamin B12 stored in the body of a healthy adult (for example, Adams et al. (1970)). Such studies are difficult to conduct and use different methods (such as Whole Body Counting (WBC) or vitamin B12 excretion in bile), all of which involve many assumptions and estimates so are not easily comparable. It is generally recognised by medical scientists that more research is needed in this area.

However, a recent overview of the current state of knowledge concerning daily vitamin B12 losses and bioavailability of vitamin B12, which looked at more than 6,000 academic journal articles on vitamin B12, concluded that studies so far conducted had shown a total body store of vitamin B12 ranging on average from 1.06-3.9 milligrams (mg) (Doets et al., 2013 Table 3). For purposes of determining dietary requirements, most estimates of the total body store used by authorities are between 2 and 3 mg (IoM, 1998b). Most of this is held in the liver and appreciable amounts in muscle, bone marrow and the gut, although vitamin B12 is distributed throughout all cells in the body (Chanarin, 1990).

Much of the vitamin B12 held in the liver is recycled, via the bile to the intestines (the process known as entero-hepatic recycling), and reabsorbed into the bloodstream. Depending on the initial size of a person's store of B12, it may take a number of years for daily losses from the body to result in deficiency if their B12 stores are not being replenished.

The study by Doets et al. showed that a summary estimate of the rate of loss based on the WBC method was 0.13% per day. When calculated by measuring vitamin B12 excretion in bile, two studies produced results of 1.1% and 1.5% (Doets et al., 2013). However, much of the B12 excreted in bile is reabsorbed as described in section 2.1.7, although reabsorption may not occur in individuals who

¹⁹ For two periods during the Shinwell Medical Group's treatment of patients with B12 deficiency (12 February 2004 to 3 July 2006 total embargo followed by partial embargo; 14 March 2007 – 1 August 2009 total embargo followed by partial embargo), the medical Practice was forbidden by the PCT to treat patients for B12 deficiency. In both periods, the patient group had to lobby the PCT to have treatment restored. As far as we know, no other doctor or medical practice has been restricted in diagnosing B12 deficiency, or treating with this very safe nutritional supplement.

lack IF which explains why sufferers of pernicious anaemia, for example, experience dramatic B12 losses (IoM, 1998b).

Reports vary on the percentage that is reabsorbed in a healthy individual, but range from 55% (IoM, 1998b) to 90% (EFSA, 2008). Authorities tend to assume a loss rate of 0.1-0.2% of total body vitamin B12 per day (EFSA, 2008; IoM, 1998a). Vitamin B12 is lost mostly through the faeces but also through urine, the skin and metabolic reactions. The losses include unabsorbed B12 from food or bile, shedded cells, gastric and intestinal secretions, and B12 synthesized by bacteria in the colon (IoM, 1998b).

If it is assumed that the smallest B12 body store consistent with health is 300 mcg (derived from Bozian et al. (1963)) with a 0.1 % daily loss rate, no absorption of B12 from food or supplements, and an intact entero-hepatic circulation, then stores of 1 mg would be expected to meet the body's needs for 3 years, 2 mg for about 5 years, and 3 mg for about 6 years. A 1.5 % loss would reduce these estimates to 2, 3.6, and 4 years (IoM, 1998b). This is why it may take several years for symptoms of deficiency to appear.

3.7.1 How much B12 (and in what form)?

Patients may ask why it is necessary to take oral supplements (or have injections): could their symptoms not be rectified by an improved diet containing more vitamin B12?

Many patients will have malabsorption problems that prevent vitamin B12 being absorbed from food in sufficient amounts to maintain health. Or they may have congenital defects that interfere with B12 metabolism. Large doses, whether through tablets or injection, are needed to overcome these barriers.

These amounts are not easily obtained from food. The amount of vitamin B12 in any meal is very small compared with injected doses or supplements. In Europe, the average daily intake of vitamin B12 from a normal diet has been found to be 2-6 mcg although individual intakes may be as high as 32 mcg (EFSA, 2008). A vegetarian diet, however, may provide only 0.5 mcg per day (Chanarin, 1990).

It has also been shown that there is a limit to the amount of vitamin B12 that can be absorbed from any meal, even in a healthy person, because of saturation of the IF-receptors (Doets et al., 2013). Also, not all vitamin B12 in a portion of food is absorbed – estimates show that absorption varies widely from different B12-containing foods (IoM, 1998b Table 9-1; Tucker et al., 2000).

However, some vitamin B12 (about 1-5% of a dose) is absorbed through passive diffusion, that is it bypasses the need for binding to IF (Andrès et al., 2004). This percentage is insignificant when amounts of vitamin B12 are small, as in a single meal, but may become more influential when a large dose is taken, for instance through a tablet. Tablets placed under the tongue, and injections which send vitamin B12 directly into the muscle or bloodstream, are likely to be more effective in most cases.

Carmel provides figures to show that the *percentage* of B12 absorbed from oral doses decreases as the dose increases in healthy people (although the actual amount does increase a little). For instance, from a dose of 1 mcg, 56% (0.56 mcg) would be absorbed, but from a dose of 1 mg, only about 1.3% (13 mcg) would be absorbed. In patients suffering from malabsorption illnesses, only

1.2% is absorbed – that is, the rate of passive diffusion. From injections, in both healthy and ill people, 97% (9.7 mcg) of a 10 mcg dose is absorbed but the rate decreases to 15% (150 mcg) of a 1 mg dose (Carmel, 2008). This still represents a substantial fraction of the total body store in a healthy person (using the figures given above).

We know from experience that some people seem to need higher levels of B12 circulating in the blood in order for their symptoms to be remitted. This implies that people short of B12 in their cells process B12 less efficiently than healthy people and need higher levels circulating in the blood (Smith & Refsum, 2011).

3.7.2 Recommended dietary intake

Opinions about the amount of vitamin B12 needed per day from a normal diet vary between countries, and researchers have questioned whether the Recommended Dietary Allowance (RDA) of 2.4 mcg for adults set by the US National Institutes of Health Office of Dietary Supplements, or 2.5 mcg set by the European Community, is high enough (Bor et al., 2010).²⁰ The UK uses a lower figure of 1.5 mcg (Doets et al., 2012; Public Health England, 2016 Table 4).

The US RDAs for different age groups are given below.

Table 3-1 Recommended daily amounts of vitamin B12

Life Stage	Recommended Amount, Micrograms (mcg)
Birth to 6 months	0.4 mcg
Infants 7-12 months	0.5 mcg
Children 1-3 years	0.9 mcg
Children 4-8 years	1.2 mcg
Children 9-13 years	1.8 mcg
Teens 14-18 years	2.4 mcg
Adults	2.4 mcg
Pregnant teens and women	2.6 mcg
Breastfeeding teens and women	2.8 mcg

Source: *Vitamin B12 Fact Sheet for Consumers* (NIH ODS, 2011b).

²⁰ Following a new European regulation effective from December 2014, nutritional information on packaging formerly known as the Recommended Daily Allowance (RDA) has been expressed as Nutrient Reference Values (NRV). The European Community NRV for vitamin B12 was set at 2.5 mcg (µg) in May 2016. NRVs are based on current scientific knowledge and state how much of a given nutrient needs to be taken per day to prevent deficiency in healthy people (JustVitamins, 2016).

3.8 How long will it take for symptoms to recover?

B12 is a vital vitamin, and plays a role in many different biochemical functions within the body. The rate of improvement is different in each patient and is unpredictable. We know from experience that there will be improvement but it is not possible to put a specific time limit on recovery.

In our experience, most people seem to notice improvements in their symptoms in the following order:

Table 3-2 How long does it take for symptoms to heal?

Timeframe	Symptoms affected (from observations at the Shinwell Medical Practice)
Within hours	Enjoyment of friends, sociability and mood improvements.
Within a day or so	Fatigue should lessen although patients may expect to feel a general tiredness for some weeks.
Within a week	The Brain Fog should lift and patients should start to want to be more sociable, and to be able to remember better. HOWEVER, note that all symptoms do not improve at once. Numbness and pins and needles should start to remit.
Within two weeks	Some strength may return to muscles and joints. However, progress will be gradual.
Within a month	Some of the longer nerves (e.g. those of the hands and feet) may take up to a month to show signs of recovery. Pains in hands and feet, strength and grip strength may take longer to remit/restore but some improvement should be detected. Cyclical hormones such as those of the fertility cycles and associated disorders should be normalising. Hormone-controlled energy levels, e.g. production of cortisol and thyroid hormones should be normalising. Note that the body may not be responding to them yet even though hormone levels in the blood should be much better.
Longer than a month	Recovery from some conditions takes longer. For example, in relapsing/remitting MS (Sub Acute Combined Degeneration (SACD)/MS- like presentation), muscles will need time to regain their tone even though the nerves may now be functioning correctly.

3.9 Reversing-out syndrome

About one in 10 people have observed that they experience similar symptoms to those experienced from deficiency, as they start a programme of B12-replacement therapy. We term this “Reversing-out syndrome”.

The most obvious such symptoms are neurological. For example, where there was numbness, patients may start to feel pain as the nerves recover. They may experience twitches when the nerve axons that instruct the muscles to move start to work again and transmit random signals. Or they may experience shooting pains, when nerves in hands and feet start to transmit sensations and the brain initially interprets these signals as pain.

Another common symptom is a red rash on the skin, sometimes accompanied by itching. The skin is the largest organ in the human body and plays an important role in eliminating toxins. The human body is able to selectively push substances from the bloodstream outside the skin. The red rash may be caused by the body getting rid of homocysteine, by pushing it through the skin onto the surface. Many people apply skin cream but we are concerned that this may trap the homocysteine next to the skin. It is preferable to wash it away with a wet cloth instead.

Patients may also experience sudden tiredness, which may be caused by low potassium or low magnesium. When the body is performing below par, due to low B12, then low levels of magnesium and potassium may be quite sufficient. Once the B12 level is restored, low levels of other nutrients may make themselves felt.

Other symptoms may also manifest as B12 levels are restored. Unfortunately, some patients think this is a result of taking B12 and cease the therapy. We advise that patients persist with treatment in order to pass through Reversing-out syndrome.

3.10 Other considerations

3.10.1 Anaphylactic shock from injections

It is reassuring to confirm that during the past 37 years since commencing B12 injections in 1981, not a single one of our patients has experienced local or systemic anaphylactic shock. Anaphylactic shock affects the whole body and can cause a sudden feeling of weakness (from a drop in blood pressure), abdominal pain, nausea or vomiting, and collapse and unconsciousness. It is very serious; if a patient has an anaphylactic reaction, they may need an observation period in hospital.

Anaphylactic shock is a hypersensitive reaction to an allergen (something that the patient is allergic to). There is nothing in B12-injectable solutions that patients are allergic to. We must emphasise again that we have never observed such a reaction to B12 injections.

In contrast, reactions such as a stinging sensation from injection are common but this is harmless. It may be caused by temperature difference (e.g. injecting straight from the fridge), or because of injecting an unbuffered solution. We advise anyone who self-injects to keep the ampoule out of the fridge and to let it (or the syringe) reach as close to body temperature as possible before injecting (e.g. hold the syringe in the hand for a few minutes).

3.10.2 Mineral or vitamin deficiencies highlighted by B12 supplementation

Prolonged B12 deficiency can result in low levels of other minerals and vitamins, such as magnesium, potassium and vitamin D, or imbalances in many other vital substances the body needs to function well.

For example, magnesium is needed to maintain health. Adequate amounts can be obtained from a well-balanced diet or by taking multivitamin multi-mineral one-a-day supplements. Following

prolonged B12 deficiency, however, a patient's body levels of magnesium may have dropped. A patient may not have noticed low levels of magnesium because they feel so tired and inactive.

Once the normal level of B12 has been restored it is possible that deficiencies of other nutrients may manifest. In our experience, once the B12 level is sufficient to maintain health, the fundamental metabolism of the body is restored to harmony. We have regularly checked the U+Es of our B12-deficient patients but never found it necessary to prescribe additional nutrients (except in the case of patients who had iron deficiency anaemia or folic acid deficiency).

However, taking a multivitamin multi-mineral one-a-day supplement before the first B12 injection to top all nutrients up will not cause harm.

3.11 Vitamin B12 as a prophylactic measure to avoid deficiency

In the following instances B12-replacement therapy should be instituted as a prophylactic measure (to prevent further deterioration or even development of symptoms) regardless of blood serum B12 concentration: prophylaxis is expected to continue for life.

- 1- **Specific medical history:** renal imbalance, diabetes, >65 years old, or following GI surgery, Crohn's colitis, early onset dementia.
- 2- **Moderate/subtle B12 deficiency with mild signs & symptoms**
- 3- **Moderate/subtle B12 deficiency with severe signs & symptoms:** patient presenting with strong family history of B12 deficiency, presence of other autoimmune conditions, major signs and symptoms which could become irreversible if treatment is not commenced urgently e.g. optic neuritis/neuropathy, sudden onset blindness, Subacute Combined Degeneration (SACD), ME, CFS, MS-like presentation, single limb paralysis, sudden loss of muscle mass (Motor Neurone Disease-like presentation), non-epileptic seizures, dysphagia, Bell's Palsy/Ramsey Hunt syndrome, Parkinson's like presentation, dementia, total alopecia, migrainous headache, temporal arteritis, recurrent miscarriages, dysfunctional uterine bleeding, or psychosis.

3.12 Shinwell Medical Practice Patient Surveys on vitamin B12 therapy

Complying with good medical practice, the Shinwell Medical Group conducted two Patient Surveys on the experience of patients undergoing B12 therapy. The surveys took the form of questionnaires issued to patients:

- Patient Survey 1 took place between December 2005 and January 2006, that is, during the ban on B12 treatments imposed by Easington PCT. There were 225 respondents to this survey.
- Patient Survey 2 was conducted from May 2008 to August 2009, after Professor Pringle's report had been published (see Introduction). There were 344 respondents to this survey.

Patient Survey 1 (2005-6): Seven questions were asked concerning the severity of symptoms on first diagnosis, how patients felt after treatment had started, when treatment was stopped (due to the withdrawal of treatment by Easington PCT), and again when treatment resumed (when the ban was partially lifted). Patients were also asked whether they felt any side-effects during treatment and how often they thought they should receive B12 injections when they were on treatment. The results confirmed the effectiveness of the B12 therapy: 87% of patients responded that they felt

better after treatment started; 75% said their symptoms reappeared when treatment was withdrawn; more than half said their symptoms improved again after treatment was restored. Almost all the group (96% of respondents) said they experienced no side-effects during treatment. Another important finding was that patients' B12 blood serum levels, which were tested to accompany the survey, fell much more quickly than is predicted by the textbooks when treatment was withdrawn.

Patient Survey 2 (2008-9): This survey was carried out after County Durham PCT had ordered a change to the B12 treatment protocol from one based on clinical need to one based on guidelines only (which fails to address all aspects of patient presentation). This resulted in the frequency of injections being reduced (to three-monthly from two-monthly or one-monthly) for some patients and treatment being completely withdrawn for others. Patients were asked to complete a survey during their treatment review. They described their symptoms before diagnosis and after treatment had started on a scale of 0 to 5 where 5 was the most severe. They were also asked whether they consented to the new treatment regime imposed by the PCT. Patients were grouped into two categories: those whose minimum blood serum B12 was below the 200 ng/L guidelines' cut-off point, and those where the level was above 200 ng/L. A total of 344 surveys were collected.

The symptoms described covered the wide range of body systems affected by B12 deficiency. B12 levels were recorded at three points: at diagnosis, during treatment (the highest level reached) and the level reached during the withdrawal period if the patients had been affected by the previous Easington PCT ban. The blood serum levels of those with low levels at diagnosis (typically 160-167 ng/L) rose to a range of 1387-1692 ng/L during treatment but fell to a range of 271-574 ng/L when treatment was withdrawn. The levels of those with initially higher starting points (208-256 ng/L) rose to 1044-1391 ng/L but fell back to 140-479 ng/L during the withdrawal period. Over 71% of patients explicitly did not agree to the change to the PCT-imposed regime. A striking point to emerge from the data was the impact of B12 injections on blood serum B12 levels. It is commonly assumed that the "normal" B12 levels in the UK are 200-900 ng/L but patients receiving supplements have levels substantially above this. At the same time patients reported that their symptoms were mostly remitted. This indicates that the "normal" range for one individual may be different from the "normal" range for another. The "normal" range given by manufacturers of testing assays varies from one manufacturer to another, and there is more variation between one laboratory and another, calling into question whether there is any such thing as a "normal" range.

Box 3-1 Extracts from the Shinwell Medical Practice Patient Survey 2008-9

Patient descriptions (in their own words) of the effects of B12 treatment, cessation of treatment or prolongation of time between injections, and symptoms during treatment.

All clear, able to swallow. Dizziness improved; more energy; no cramp; no hair falling out.

Much improvement. When treatment stopped became worse; much improvement since treatment re-commenced.

A lot better when getting monthly injections; tingling still in hands.

Patient can taste food (without salt); hair stronger; a lot fitter; health in general very good; no symptoms reappearing.

A lot better; even got a job; could drive again; could walk in a straight line; whole life has improved; feel and look healthy; not depressed; occasionally feel memory loss when B12 is due.
Patient feels a totally different person; he is 76 in August: I feel much healthier and a happier person than when I was 72.
Feel much better; all of the symptoms have gone.
Big improvement on all symptoms while have regular treatment. But now the time [is greater] between treatments, symptoms have returned and feel much worse.
Though diagnosed with MS she has found that from the initial treatment her symptoms have been reduced in severity, and her condition only declined when on two occasions her treatment was stopped. The treatment improves [her condition] at every level as well as slowing the onset of MS.
On monthly injections symptoms cease. Since going on 2-monthly in January, she feels like she did before the injections started - all the symptoms return. 2-monthly injections - she only feels better for the first 2 weeks then she has another 6 weeks where she spends most of the time in bed with severe exhaustion.
Lack of energy; other symptoms start to reappear as time between injections passes.
Much better; no tiredness; twice tried - monthly + by 6th week dropping and bad tempered; most of the symptoms return; no interest in anything; could not tolerate oral medication.
Much better; mild symptoms at the end of the month when needing another injection.
Much better whilst on treatment. On stopping or reducing the interval to 2- or 3-monthly old symptoms return - mainly tiredness.
Much better after he gets the injection; in the 3rd week the symptoms come on and wife notices it.
Less tired; hasn't fainted; pins and needles gone; not confused.
Improves after treatment, but after 4 or 5 weeks symptoms come back.
She felt very well as she was on the B12 injections every 2 weeks in the beginning then monthly injections were stopped for about a year, and she completely fell apart again having her original symptoms. Injections were started again every month as then they had to be 2-monthly; 2-monthly are no good as she starts having symptoms again. She would like to go back to monthly injections as she feels this is more beneficial
Her health improved over a number of years; then injections stopped for 2 years and she deteriorated really bad to the point when the injections started again - by then her level was really low.
Monthly injection everything was 90% better; when changed to 2-monthly symptoms would reappear in-between injections - tiredness, headache, unable to concentrate at about 5 to 6 weeks, numb feeling in arm at some time, gradually symptoms start reappearing one at a time. She cannot manage on 2-monthly treatment, as cannot cope at work or at home; she needs monthly injections to feel like she can work and take care of her family.
Since changing to 2-monthly injections the patient feels very tired, always wanting to sleep, irritableness, tingling feet, ratty, feeling drawn, weepy, pressure on head. Feeling ok up to 2/3/weeks after injection, then after that goes back downhill. Feels better getting injection on a monthly basis as after the 3rd week she knows she is ready for it again. However, getting injection 2-monthly she feels terrible, miserable, weepy, and all the symptoms start again.

Tired, feeling down the same as before he started the injections. Felt much better with injections monthly, going into the second month he could feel himself going back to the way he felt before the injections started.
One-monthly injections no symptoms (2nd time injections have stopped); 2-monthly very tired, numbness in arms, twitching in face, aches all over, physically drained.
The patient was so well on monthly injections, then felt unwell on 2-monthly; lost weight - 4.5 stone in the last year; couldn't eat, tiredness, sleeping all the time, right forefinger partially paralysed.
When receiving monthly injections she felt very well in herself and had none of the symptoms. Then started 3-monthly and has gone back to suffering all symptoms. Having tried 3-monthly injections she feels she is unable to manage this; she feels that she needs the supplement at around the 4th/5th week.
When she was getting the injections every 2 weeks she felt better than she had done for a lot of years. But since they went to 2-monthly her symptoms come back just as bad after about 3 weeks. She states she needs the injection at least monthly to function properly and lead a normal life.
When she had monthly B12 injections she was fine, but since having the injections every 3 months she feels a lot worse. She now has blurred vision, constant tiredness, no energy, neuropathic pain and numbness down her right leg.
A lot better, not as tired, no other symptoms are there.
Left-sided headache, shooting pain from back to the head, left orbital pain, palpitations, panic attack, tiredness, going to bed at 8.30pm, pins and needles and numbness in hands, burning sensation in fingers, hair falling. Since 2-monthly injections many of the signs and symptoms returned but much worse, especially palpitation, shooting pain and headache on left side of head and left eye, tiredness.
Was initially on B12 injection (monthly), then it stopped and she was on oral OC Vit B12 tablet. She is a lot better, left side weak, left knee locks, using a walking stick. She was very well on B12 injections. However, she can manage reasonably well on oral OC B12 tablets 100mg.
Oral medication - did not respond; whilst having regular injections feel much better.
Feel well after injection but towards needing next dose she begins to feel tired, dizzy, feeling of choking, unable to swallow.
A lot better, feel well when getting monthly injections, and since 3-monthly injections tiredness, swaying, palpitations.
Felt much better with injections; all symptoms back since treatment stopped.
Since the treatment stopped she is back to square one. When she did have treatment she was so much better, she does not think she should have to be taken off the B12.
Yes, definitely, when stopped symptoms returned. She was really worried.
When she was getting 1 monthly injections she was so much better, able to go to work and lead a normal life at work and home. When stopping injections on 21/10/2008 she has started to have all the symptoms if not worse.
When she was getting regular injections she felt a lot better but when she stopped having injections in 2004 her symptoms came back again, also when in 2008 injections stopped severe symptoms came back.