

**Understanding Dosage Acceptance of High Dose Methylcobalamin
– An Exploratory Survey**

**Internship Training at
BestoChem Formulations (I) Ltd
Laxmi Nagar, Vikas Marg, Delhi**

**By
Sanchit Rajawat**

**Under the Guidance of
Dr. Sandeep Narula**

**Post Graduate Diploma in Pharmaceutical Management
2012-2014**



**Institute of Health Management Research,
Jaipur
2014**

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TO WHOMSOEVER IT MAY CONCERN

This is to certify that **Mr. Sanchit Rajawat** student of Post Graduate Diploma in Pharmaceutical Management (PGDPM) from Institute of Health Management Research, Jaipur has undergone dissertation at **Bestochem Pharmulation (I) Ltd.** from **March 2014 to May 2014.**

The candidate has successfully carried out the study designated to her during dissertation and her approach to the study has been sincere, scientific and analytical.

The internship is in fulfilment of the course requirements.

I wish him all success in all his future endeavours.



Dr. Ashok Kaushik
Dean, Academics and Student Affairs
IIHMR, Jaipur



Dr. Sandeep Narula
Associate Professor
IIHMR, Jaipur

24-05-2014

TO WHOM SO EVER IT MAY CONERN

This is to certify that Mr. Sanchit Rajawat, student of Indian Institute of Health Management & Research, Jaipur has completed his dissertation on "Research study on Perception Mapping of Doctors towards High Dose of Methylcobalamin".

He is in Product Management Team and handling the marketing and clinical profiles of Methylcobalamin.

The study and its findings are solely for Company's product planning. And not to be used anywhere else apart from his academic purpose.

The work done by him was found to be good. We wish him all the best for his future endeavors.

For *BestoChem Formulations (I) Ltd.*


(AMIT KR SHARMA)
Marketing Manager

BestoChem Formulations (I) Ltd.®

CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled Research study on
Understanding Dosage Acceptance of High Dose Methylcobalamin
– An Exploratory Survey

and submitted by

Sanchit Rajawat

Enrollment No. 188

Under the supervision of

Dr. Sandeep Narula

for award of Postgraduate Diploma in Pharmaceutical Management of the Institute carried out during the period from 10-March-2014 to 24-May-2014 embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other Institute or other similar institution of higher learning.

Sanchit
26/05/2014

Signature

24-05-2014

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ACKNOWLEDGEMENT

“Successful passage and outcome of every work comes with dedication determination and team work. All these turn futile in the absence of visionary guidance.”

I wish to take this opportunity to convey my sincere gratitude to all those who has helped me in the successful completion of this project.

My heartiest thanks to **Mr. Amit Kr. Sharma, Mr. Ashish Narang, Mr. Divyesh Tewari** and **Mr. Sushil Kaushal** our project assistance for carrying out the project, without whose constant guidance, co-operation and encouragement my entire project would have remained a distant dream.

I am extremely grateful to my dissertation mentor, **Dr. Sandeep Narula** for his guidance and support during the project.

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I would also like to express my gratitude and thanks to all the doctors for giving me attention and time.

My heartiest thanks to *BestoChem Formulations (I) Ltd.* team for mailing and calling me from time to time and keeping us update with all the latest updates and instructions on behalf of the company.

Last but not least, I would like to thanks my mother, brother, friends and all my well-wishers for their support and guidance in the successful completion of the project.

ABSTRACT

Methylcobalamin is neurological active form of Vitamin B₁₂ which supports the healthy structure and function of the nerves and brain. Several studies have found that people can have neurological signs and symptoms of a specific methylcobalamin deficiency, even when serum B₁₂, and blood tests which measure adenosylcobalamin activity, are perfectly normal. While healthy people need just a tiny trace of methylcobalamin to avoid a normal deficiency, a massive body of evidence powerfully supports with high dose Methylcobalamin and not regular B₁₂ can protect brain and nerve cells against toxins, help the healing of damaged neurons, and even provide powerful nutritional support in serious neurodegenerative diseases. Moreover, most studies show there is no adverse effect, harmful reaction or known toxicity of dose up to 6000 mcg/day. Urinary loss of methylcobalamin is low due to renal uptake and reabsorption by kidneys.

This market research study on doctors is intended to map the perception of Indian doctors on high dose of methylcobalamin (≥ 1500 mcg) and need of high dose in Indian market. Survey was conducted on 50 doctors. Research has given commendable insight of dosage form, strength, dosage schedule, indications and awareness level. Result of study is very helpful for launching high dose methylcobalamin in Indian market.

Key words:- High dose Methylcobalamin (≥ 1500 mcg), Doctors Perception

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INTERNSHIP REPORT

INTRODUCTION

Internship is the part of second year program where the students learn by observing and learning. Observation is the key to learning the minute details with which the organization carry out its day to day works. Orientation with different department and their activities is a part of internship.

Internship is the process, through which we can understand process of work and thereafter be able to involve in decision making.

I am appointed as Product Executive in Bestochem Pharmulation (I) Ltd. It deals with Pharmaceutical Marketing and Pharmulation.

OBJECTIVE OF INTERNSHIP

- (a) To understand the work of Pharmaceutical Marketing.
- (b) To learn various managerial and administrative skills needed to work in a Product Management Team.
- (c) To learn various functions like Visual ate designing, leave behind literature designing, Sales analysis etc.

ORGANISATIONAL STRUCTURE

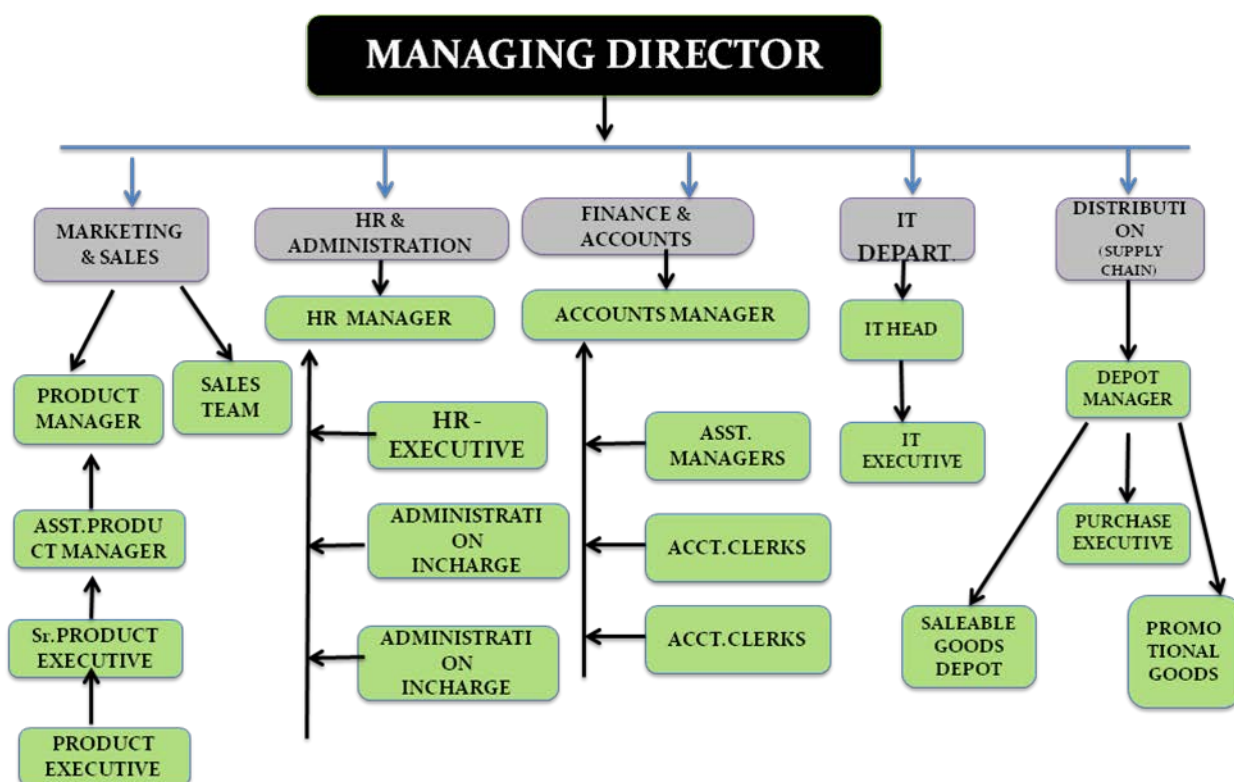
THE ORIGIN:-

ESTABLISHED IN : 1992

PROMOTERS : Mr. GIRISH JUNEJA & Mr. VIJAY PRAKASH

Pharmaceutical Company of India with ISO 9001:2008 certification.

- 1992 Bestochem launched.
- 2008 Manufacturing unit establishment –SALUTE BESTOCHEM.
- 2008 Quality Bestochem(FRANCHISE) launched.
- Holding MS 0.19% with rank of 75 out of 200 domestic pharma companies.
(As per ORG MAT DEC'13 Indian pharma market)
- Collaboration with 7 GMP/WHO recognized manufacturing associates.



BUSSINESS:-

Domestic Pharmaceuticals Products

Consistent Track Record:	Profitable growth in last four years
Products established in Indian domestic market	More than 150 SKU wise
Strong Relationships	Top tier DOCTORS in key markets.
Add Strategic Value	To the patient health.
Core Platform	Provides high degree of vertical integration & cost advantage.
Strong Customer Base	Servicing more than 90,000 customers spread over country.

REVENUE:-

FY 2011-12 (Up to 31.3.2012) - 9,924.81 Lacs

FY 2012-13 (Up to 31.3.2013) - 10,240.08 Lacs

DISTRIBUTION:-

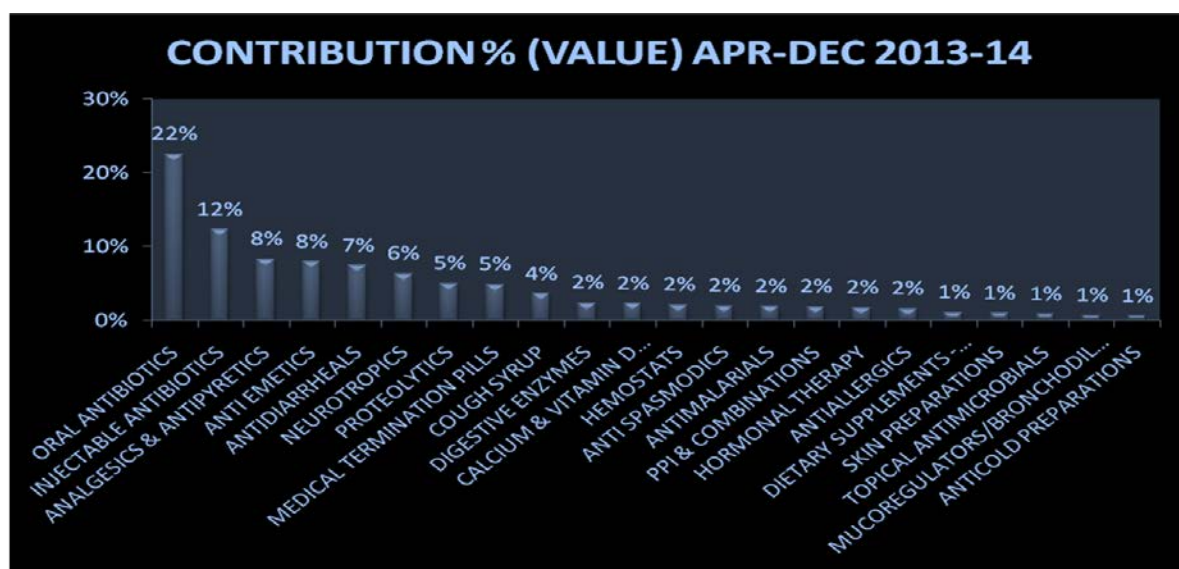
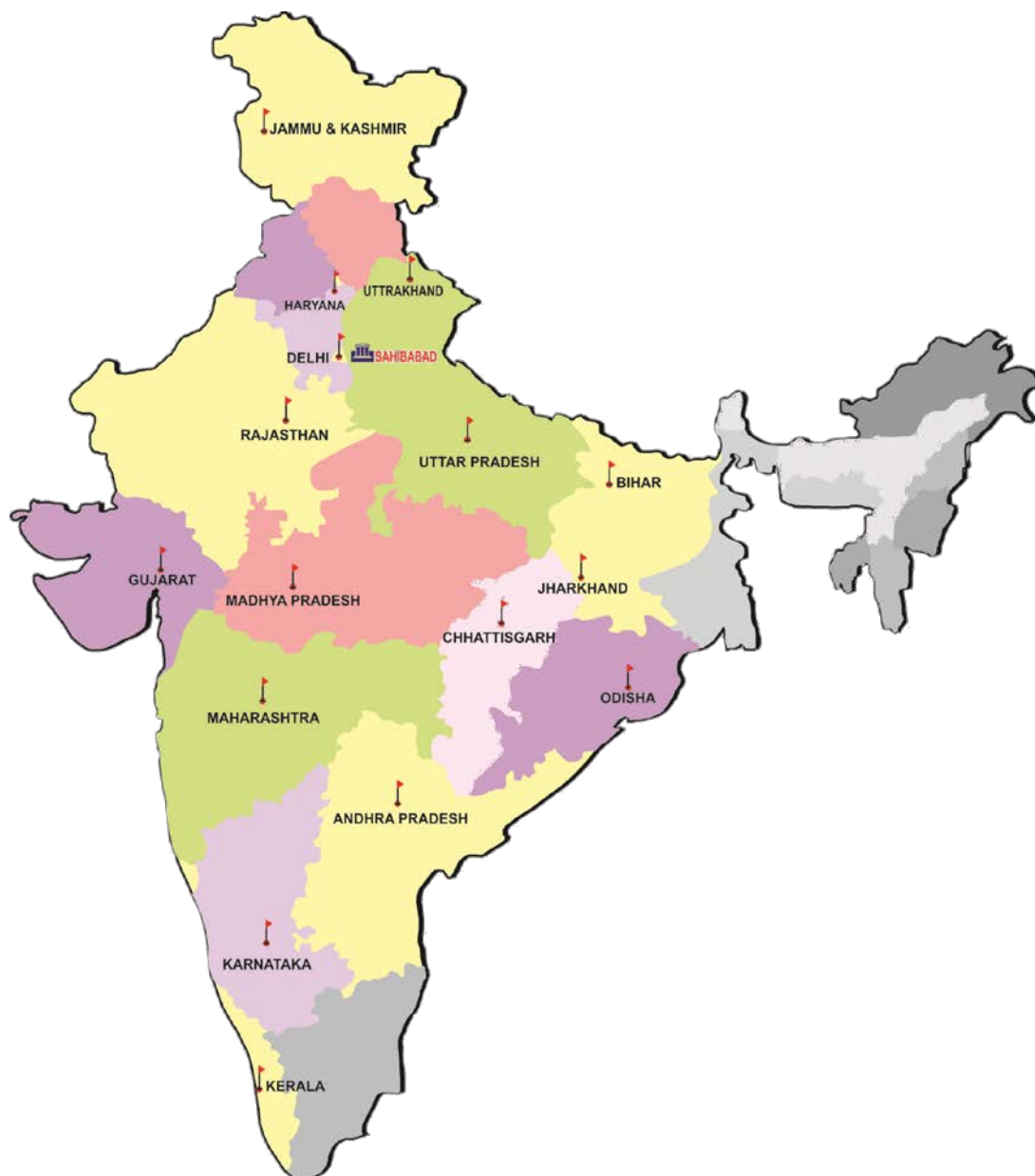
Having strong distribution channel operated by 05 C&F , 18 C&A and 04 Distributors all over INDIA.

Operated from various locations :-

Meerut (W.UP), Agra (W.UP), Jhansi (W.UP), Lucknow (E.UP) , Varanasi (E.UP) , Gorakhpur (E.UP) , Kanpur (E.UP) , Roorkee (UK), Rudrapur (UK), Delhi, Ambala (HARYANA), Jaipur (RAJ), Indore (MP), Ahmedabad (GUJRAT), Bhiwandi (MH), Pune (MH), Nagpur (MH), Bangalore (KARNATAKA), Hubli (KARNATAKA), Ernakulam (KERALA), Hyderabad (A.P), Cuttack (ODISHA), Raipur (CHHATTISGARH), Ranchi (JHARKHAND), Patna (BIHAR).

Having more than 1000 stockist & super stockist.

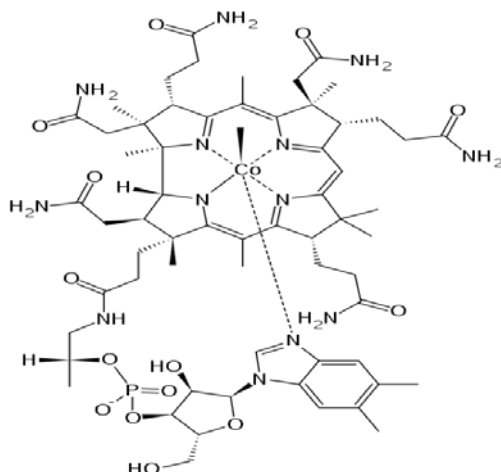
OPERATIONAL STATES:-



DISSERTATION REPORT

INTRODUCTION METHYLCOBALAMIN

Methylcobalamin (mecobalamin, MeCbl, or MeB₁₂) is a cobalamin, a neurologically active form of vitamin B₁₂. It is dark red crystals or a crystalline powder, odour less and has little taste. Slightly soluble in water, hygroscopic, affected by light and differs from cyanocobalamin in that the cyanide is replaced by a methyl group. ⁽¹⁾



Chemical Name: Co α -[α -(5,6-dimethylbenz-1H-imidazolyl)]-Co β methylcobamide

Molecular Formulae: C₆₃H₉₁CoN₁₃O₁₄P

Molecular Weight: 1344.40

Methylcobalamin is the most potent form of Vitamin B₁₂ found in nature. We need methylcobalamin for the healthy development and sustenance of our nervous, circulatory, and immune systems.

Methylcobalamin is the only active form of Vitamin B₁₂ in the brain outside the mitochondrion. The liver must convert cyanocobalamin to methylcobalamin in order for Vitamin B₁₂ to do its biochemical work in the brain. ⁽²⁾

Recommended Dietary Allowance

Extraordinarily small amounts of vitamin B₁₂ suffice for daily nutritional needs. The official USA and Canadian recommendations for daily intake are as follows. ⁽³⁾⁽⁴⁾

Infants

- 0-6 months: 0.4 mcg
- 7-12 months: 0.5 mcg

Children

- 1-3 years: 0.9 mcg

- 4-8 years: 1.2 mcg
- 9-13 years: 1.8 mcg

Males and Females 14 years and older: 2.4 mcg

Pregnant Women 2.6 mcg

Nursing Women 2.8 mcg

Sources:-

Dietary vitamin B₁₂ is found mostly in animal foods. Eggs, dairy products, fish and meat, especially organ meat like liver, are good sources of Vitamin B₁₂. Clams and beef liver have extremely high amounts of this vitamin. Vegetarian sources include Cheese, milk, yoghurt, etc.

Pharmacology: -

Methylcobalamin is a kind of endogenous co-enzyme of Vitamin B₁₂. It plays an important role in transmethylation as a co-enzyme in the synthesis of methionine from homocysteine. Methylcobalamin is well transported to nerve cell organelles than cyanocobalamin promotes nucleic acid and protein synthesis. It promotes axonal transport and axonal regeneration. It also normalizes axonal transport in sciatic nerve cells. Methylcobalamin promotes myelination (myelin sheath synthesis), synthesis of lecithin which is the main constituent of medullar sheath lipids and increases myelination of neurons. Methylcobalamin restores delayed synaptic transmission and diminished neuron transmitters to normal. ⁽⁵⁾

Pharmacokinetics:-

Serum and Cerebrospinal Fluid (CSF) contain large quantities of Methylcobalamin as follows

Absorption of Methylcobalamin is Dose dependent.

Peak plasma concentrations after- 3 hr (oral), 0.9 hr (IM), 3 min (IV).

Half Life: 12.5 hrs with 1500 mcg if concentration increases, half life also increases

Excretion of Methylcobalamin is through urine ⁽⁵⁾ ⁽⁶⁾

Methylcobalamin can be given to 1500 mcg to 6000 mcg/day.
Maximum dosage 500 mcg/kg body weight/day can be given.

Methylcobalamin dependent pathway for metabolism of homocysteine to methionine, cobalamin in the form of Methylcobalamin (CH₃Cbl) serves as a coenzyme for the conversion of homocysteine to methionine.

The diagram illustrates the Methionine Cycle, a metabolic pathway involving folate and cobalamin. Folic Acid is converted to Methyl Tetrahydrofolate ($\text{CH}_3\text{-THF}$), which then becomes THF. THF is converted to Methylene THF, which leads to DNA formation and protein synthesis. Methylene THF is formed by the transfer of a methyl group (CH_3) from Methyl Tetrahydrofolate to Homocysteine. Homocysteine is converted to Methionine, which is then converted to Lecithin and finally to Myelin sheath / Nerve Regeneration. Methionine Synthase is the enzyme that converts Homocysteine to Methionine, using Mecobalamin (the active form of Cobalamin) as a cofactor. Mecobalamin is converted from Cobalamin to Methylcobalamin, which is then converted to Mecobalamin. The methyl group (CH_3) is transferred from Methylcobalamin to Mecobalamin.

```
graph TD
    FA[Folic Acid] --> MT[MTetrahydrofolate<br/>(CH3-THF)]
    MT -- "(CH3)<br/>Methyl" --> MC[Methylcobalamin]
    MC --> Mec[Mecobalamin]
    Mec -- "Methionine Synthase" --> H[Homocysteine]
    H -- "Methyl (CH3)" --> M[THF]
    H --> Me[Methionine]
    Me -- "Methyl" --> L[Lecithin]
    L --> MS[Myelin sheath /<br/>Nerve Regeneration]
    M --> MTHF[Methylene THF]
    MTHF --> D[DNA formation &<br/>protein synthesis]
```

Indications:-

Hyperhomocysteinemia:-

- ✓ Sulfur-containing amino acid
- ✓ Formed exclusively by demethylation of methionine.
- ✓ Elevated levels cause damage to artery walls = increased the oxidation of LDL
- ✓ Elevated homocysteine levels are significantly correlated with increased risk to heart disease.

Polyneuropathy (Diabetic, Alcoholic, Drug Induced, Peripheral Neuropathy):-

- ✓ Neuropathy is damage to a single nerve or nerve group, which results in loss of movement, sensation, or other function of that nerve.
- ✓ Diabetic neuropathies are nerve disorders caused by many of the abnormalities common to diabetes such as high blood glucose.
- ✓ Alcoholic neuropathy is a disorder involving decreased nerve functioning caused by damage that results from excessive drinking of alcohol
- ✓ Substance called Neurotoxins causes severe damage to peripheral nerves and destroy axon or myelin sheath.
- ✓ Peripheral Neuropathy is a collection of disorders that occurs when nerves of the peripheral nervous system are damaged

Atherosclerosis / CVD:-

- ✓ Atherosclerosis is a disease in which plaque builds up inside the arteries.

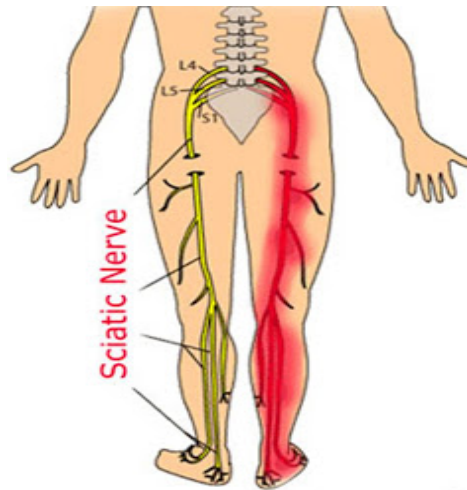
Neuralgia:-

- ✓ Neuralgia is pain in one or more nerves that occurs without stimulation of pain receptor cells. Neuralgia pain is produced by a change in neurological structure or function rather than by the excitation of pain receptors that causes nociceptive pain.



Sciatica Pain:-

- ✓ The term sciatica is used to describe a symptom rather than a specific disease. Some use it to mean any pain starting in the lower back and going down the leg. Others use the term more specifically to mean a nerve dysfunction caused by compression of one or more lumbar or sacral nerve roots from a spinal disc herniation. The pain typically occurs in the distribution of a dermatome and goes below the knee to the foot. It may be associated with neurological dysfunction such as weakness.

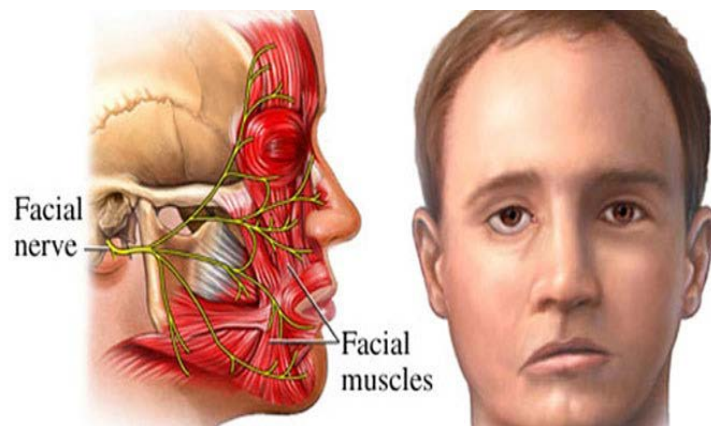


Parkinson's disease:-

- ✓ Parkinson's disease belongs to a group of conditions called motor system disorders, which are the result of the loss of dopamine-producing brain cells.

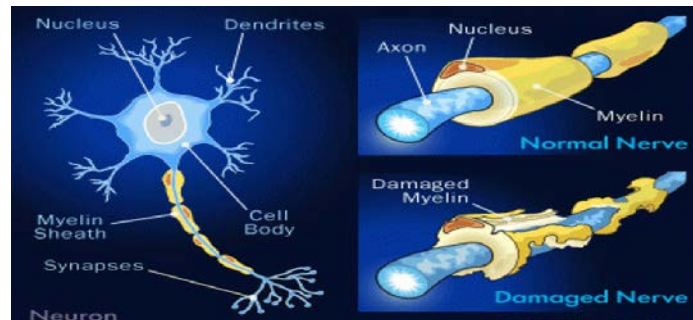
Bell's Palsy:-

- ✓ Bell's palsy is a form of temporary facial paralysis resulting from damage or trauma to the facial nerves. The facial nerve-also called the 7th cranial nerve-travels through a narrow, bony canal (called the Fallopian canal) in the skull, beneath the ear, to the muscles on each side of the face. For most of its journey, the nerve is encased in this bony shell.



Multiple sclerosis:-

- ✓ Multiple sclerosis is a nervous system autoimmune disease that affects brain and spinal cord. It damages the myelin sheath, the material that surrounds and protects nerve cells. This damage slows down or blocks messages between brain and body.



Dementia:-

- ✓ Dementia is the loss of mental functions such as thinking, memory and reasoning that is severe enough to interfere with a person's daily functioning. Dementia is not a disease itself, but rather a group of symptoms that are caused by various diseases or conditions.

REVIEW OF LITERATURE

Healthy people need just a tiny trace of methylcobalamin to avoid deficiency, a massive body of evidence powerfully supports the conclusion that supplementing with mega dose levels of methylcobalamin and not regular B₁₂ can protect brain and nerve cells against toxins, help the healing of damaged neurons, and even provide powerful nutritional support in serious neurodegenerative diseases.

Several researchers have found that people can have neurological signs and symptoms of a specific methylcobalamin deficiency, even when serum B₁₂, and blood tests which measure cobalamin activity, are perfectly normal. In the Holistic Life Style (2001 May; issue 6, Vol 1; 1-9.) high dose B₁₂ therapy is perfectly safe. In other words, the risk of overdose is virtually not (Med Hypotheses. 1991; 34:131-40) and the most direct method for adding these high doses of B₁₂ is through intramuscular (IM) or intravenous (IV) injection (Anti-Aging Medical News. 1999).

The renal uptake of both folate and vitamin B₁₂ involves glomerular filtration followed by tubular reabsorption. Significant amounts of vitamins are filtered daily, and because urinary excretion of B₁₂ and intact folate is low, both are reabsorbed within the renal tubular system to prevent urinary loss. In a research study published in Am J Physiol Renal Physiol in 2006, the injection of a single dose of radio labeled B₁₂ was followed by injections of large doses of B₁₂, more vitamins was retained in the kidneys up to 30 days after injection. This may indicate that the release from the kidneys is negatively regulated by vitamin status, but it may also reflect reabsorption of increased amounts of filtered, labeled B₁₂ by the constitutive high-capacity, megalin-mediated mechanism. One more study shows that Human urinary excretion of methylcobalamin is about one-third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention (J Lab Clin Med 1973; 81:557-567).

The dosage for clinical effect is 1500-6000 mcg per day and methylcobalamin has excellent tolerability and no known toxicity (Alternative Medicine Review, Volume 3, Number 6 1998, Page 461-63).

High dose of Methylcobalamin used in various diseases like.

Regenerating Nerves:-

Few substances have been shown to regenerate nerves in humans with peripheral neuropathies. However, a study in the Journal of Neurological Science (1994 Apr. 122[2]:140-143) postulated that methylcobalamin could increase protein synthesis and help regenerate nerves. The scientists showed that very high doses of methylcobalamin produce nerve regeneration in laboratory rats.

The scientists stated that high doses of methylcobalamin might be of clinical use for patients with peripheral neuropathies. The human equivalent dose the scientists used is about 40 mg of sublingually administered methylcobalamin.

In humans, sub acute degeneration of the brain and spinal cord can occur through the demyelination of nerve sheaths caused by a folic acid or vitamin B₁₂ deficiency. In A study in Journal of Inherited Metabolic Diseases (1993; 16[4]:762-770), it was shows that some people having genetic defects that preclude them from naturally producing methylcobalamin.

Bell's palsy:-

Bell's palsy is non-lethal paralysis of the facial nerve. Any or all branches of the nerve may be affected, and, in fact, Bell's palsy victims may not be able to open an eye or close one side of the mouth. To assess the benefits of methylcobalamin, 60 patients with Bell's palsy were divided into three groups. One group was given standard steroid drug therapy, the second group was given methylcobalamin plus steroid therapy, and the third group was given methylcobalamin by itself. The comparison among the three groups was based upon the number of days needed to attain complete recovery of nerve function, facial nerve scores, and improvement in symptoms. The results: It took an average of 7.79 weeks for the group given the steroid drug to recover completely. In contrast, the group given the steroid drug and methylcobalamin took just 1.23 weeks to recover, and the group receiving the methylcobalamin by itself enjoyed complete recovery after just 5.1 days. The facial nerve score was significantly more severe in the steroid group compared with the methylcobalamin groups, and improvement in symptoms was better in the methylcobalamin groups compared with the group treated with the steroid drug. The results of this study, published in Methods and Findings of Experimental Clinical Pharmacology (17[8]:539-44 1996 Oct), showed that methylcobalamin was 10 times more effective than the steroid drug approved by the Food and Drug Administration. For those debilitated by Bell's palsy, a dose of 40 to 60 mg a day of methylcobalamin could be a safe and effective therapy.

Parkinson's disease:-

At its current rate, Parkinson's disease strikes one in every 100 people over the age of 65. Almost every human suffers Parkinson's-like symptoms as they age. Methylcobalamin may help to prevent Parkinson's disease and slow the progression in those who already have it. Here's how: Dopamine is a neurotransmitter that controls motor functions. Dopamine transmits messages through different regions of the brain and along nerve pathways in order to coordinate muscle movement. Proper dopamine metabolism also is required to maintain a state of psychological well-being. Aging humans suffer a progressive disruption of dopamine metabolism that can cause muscle weakness, loss of coordination, and depression. Parkinson's disease is caused by the premature destruction of specialized brain cells that produce dopamine. When 80 percent of dopamine-producing brain cells have died, Parkinson's disease is usually diagnosed. It is therefore desirable to protect dopamine-producing brain cells and maintain youthful dopamine metabolism throughout life. Dopamine is formed from the amino acid L-dopa. The more L-dopa that enters the brain, the more dopamine is produced, but the problem is that L-dopa itself is toxic to brain cells and is a direct cause of cell death. The mechanism of L-dopa toxicity is excessive release of glutamate from neurons (Brain Research 1997 Oct 10; 771[1]: 159-162), which injures and kills brain cells. This could be why the drug Sinemet, which provides significant amounts of L-dopa to the brain, only works for several years before its effects wear off and the Parkinson's patient deteriorates rapidly. The types of brain cells that are most vulnerable to glutamate-induced toxicity are the very cells involved in dopamine metabolism and neural-motor control. Methylcobalamin has been shown specifically to protect against glutamate-induced neural toxicity caused by L-dopa. This means that supplementation with methylcobalamin could protect those patients with Parkinson's disease from glutamate-induced toxicity caused by the high amount of L-dopa they are putting into their brains by taking Sinemet. If brain cells that control motor function were protected against L-dopa-induced glutamate toxicity, it could mean that Parkinson's patients who take methylcobalamin could continue benefitting from the dopamine-enhancing effects of Sinemet for a much longer period of time. Late-stage Parkinson's patients for whom Sinemet therapy no longer works may have already suffered too much glutamate-induced brain cell damage to benefit from methylcobalamin. The Parkinson's patients who are still benefitting from Sinemet may be able to protect their striatal neurons by taking 5 to 20 mg a day of methylcobalamin sublingually (under the tongue), along with

Sinemet. The combination of methylcobalamin and Sinemet therapy could be a medical breakthrough, but this can only be proven by controlled studies. Today's Parkinson's patients cannot wait for the completion of clinical studies and may want to start sublingual intake of 5 to 20 mg a day of methylcobalamin immediately.

Alzheimer's disease:-

A study in *Clinical Therapeutics* (1992 May;14(3):426-437) showed that the intravenous administration of large doses of methylcobalamin to Alzheimer's patients improved the patients' intellectual functions such as memory, emotions and communication with other people. The scientists concluded that methylcobalamin is a safe and effective treatment for psychiatric disorders in patients with Alzheimer-type dementia.

Multiple Sclerosis:-

A study in the journal *Internal Medicine* (1994 Feb. 33(2):82-86) investigated the daily administration of 60 mg of methylcobalamin to patients with chronic progressive multiple sclerosis (MS), a disease that has a poor prognosis and features widespread demyelination in the central nervous system. Although motor disability did not improve, there were clinical improvements in visual and auditory MS-related disabilities. The scientists stated that methylcobalamin might be an effective adjunct to immunosuppressive treatment for chronic progressive MS. Those with less serious forms of MS may consider adding methylcobalamin to their daily treatment regimen. The effects of methylcobalamin were studied on an animal model of muscular dystrophy. This study, published in *Neuroscience Letters* (1994 Mar 28; 170[1] 195-197), looked at the degeneration of axon motor terminals. In mice receiving methylcobalamin, nerve sprouts were more frequently observed and regeneration of motor nerve terminals occurred in sites that had previously been degenerating.

Sciatica:-

The scientists stated that a deficiency of methylcobalamin causes demyelination disease in people with this in-born defect. An early study published in the Russian journal *Farmakol Toksikol* (1983 Nov; 46[6]: 9-12) Nov 1983) showed that the daily administration of methylcobalamin in rats markedly activated the regeneration of mechanically damaged axons of motor neurons. An even more-pronounced effect was observed in laboratory rats whose sciatic nerves were crushed mechanically. Two

studies published in the Japanese journal *Nippon Yakurigaku Zasshi* (1976, Mar, 72,[2]: 269-278) showed that the administration of methylcobalamin caused significant increases in the *in vivo* incorporation of the amino acid leucine into crushed sciatic nerves, resulting in a stimulating effect on protein synthesis repair and neural regeneration.

Diabetic neuropathy:-

Clinical usefulness of intrathecal injection of methylcobalamin in patients with diabetic neuropathy checked in (Ide H Fujiya S Asanuma Y Tsuji M Sakai H Agishi Y, *Clin Ther* (1987) 9(2):183-92) Seven men and four women with symptomatic diabetic neuropathy were treated with methylcobalamin (2,500 micrograms in 10 ml of saline) injected intrathecally. Treatment was begun when patients had good metabolic control, as determined by measurements of plasma glucose and hemoglobin, and was repeated several times with a one-month interval between injections. Three patients were re-treated one year after the last intrathecal injection. Symptoms in the legs, such as paresthesia, burning pains, and heaviness, dramatically improved. The effect appeared within a few hours to one week and lasted from several months to four years. The mean peroneal motor-nerve conduction velocity did not change significantly. The mean (+/- SD) concentration of methylcobalamin in spinal fluid was 114 +/- 32 pg/ml before intrathecal injection (n = 5) and 4,752 +/- 2,504 pg/ml one month after intrathecal methylcobalamin treatment (n = 11). Methylcobalamin caused no side effects with respect to subjective symptoms or characteristics of spinal fluid. These findings suggest that a high concentration of methylcobalamin in spinal fluid is highly effective and safe for treating the symptoms of diabetic neuropathy.

Anemia:-

According to National Formulary of India, "Government of India Ministry of Health and Family Welfare", (2011, 4 th Edition, p.n. 609-610) Initially 1000 µg 3 times a day for 2 weeks, thereafter 1000 µg every 3 months by intramuscular injection in case of pernicious anaemia and other macrocytic anaemia. In case with neurological involvement, initially 1 mg on alternate days. Until no further improvement, thereafter 1000 µg every 2 to 3 months. Prophylaxis: 1000 µg every 2 to 3 months.

Male Impotence:-

In one study, methylcobalamin, at a dose of 6 mg/day for 16 weeks, improved sperm count by 37.5 percent. In a separate investigation, methylcobalamin, given at a dose of 1,500 micrograms per day for 4-24 weeks, resulted in sperm concentration increases in 38 percent of cases, total sperm count increases in 54 percent of cases, and sperm motility increases in 50 percent of cases (Hinyokika Kyo 1984; 30:581-586).

RATIONAL OF STUDY

Largely prescribed dose of methylcobalamin is 500 mcg to 1500 mcg. According to review of literature, methylcobalamin single dose high strength dose preparations can be used for indications of various neurological problems. High dose Methylcobalamin is very helpful in faster neuron regeneration and recovery. According to many studies there is no adverse effect, harmful reaction or known toxicity of dose up to 6000 mcg as a single dose. Moreover, urinary loss of methylcobalamin is not much unlike other vitamins, due to renal uptake and reabsorption by kidneys. In developed countries Methylcobalamin 5000 mcg is available Over the Counter. Yet, Indian Pharma market has limited number of preparation available above 1500 mcg as a single dose.

RESEARCH QUESTIONS

- What is the acceptance of doctors for high dose of Methylcobalamin?

OBJECTIVES

- To Analyze the Need of Single Dose - High Strength Preparation of Methylcobalamin.

RESEARCH METHODOLOGY

The project was all about conducting a survey of doctors and determines their perception for high dose of methylcobalamin. This data was recorded, analysed and interpreted within the scope of the specified objective.

Research Design:-

The study was qualitative research.

Sampling Frame:-

Target population-

Respondents include Doctors who prescribe methylcobalamin in their clinical practice.

Sampling Element-

Individual respondents of questionnaire were used as a sampling element for the study.

Sampling Technique-

Purposive sampling technique was used for the study.

Sampling size-

Sample size for the study was 50.

Data Collection Tools and Technique-

Tool-

Semi structured questionnaire that include both open ended and close ended questions was designed considering the various factors identified, so that the data collected would be in compliance with the information needed.(Copy Enclosed in annexure)

Technique-

Survey method was used by the help questionnaire.

ANALYSIS AND INTEROPERATION OF DATA

A primary research on data obtained from the questionnaire was performed in Microsoft office excel 2007 and coding method was used for the purpose of data entry.

The analysis gave a series of results has been discussed below with interpretation.

Doctors (subjects) prescribing methylcobalamin were the respondents of the questionnaire and sample size.

Out of 50 respondents, all were prescriber of methylcobalamin.

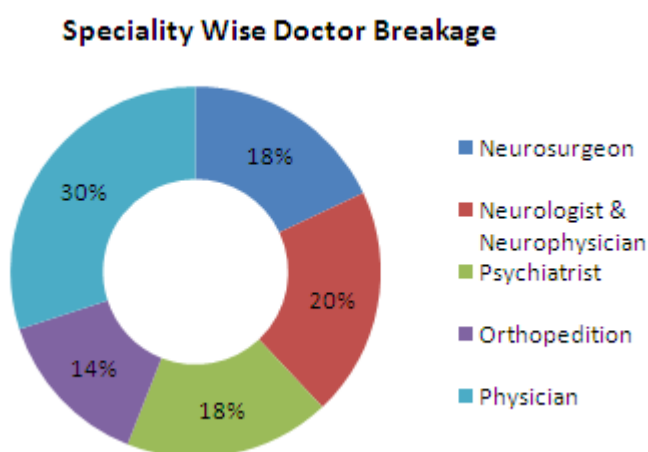


FIGURE 1. SPECIALITY WISE BREAKUP OF DOCTORS

Prescribing Habit of Doctors for Methylcobalamin:-

Data shows maximum numbers of respondents who are prescriber of methylcobalamin were prescribing methylcobalamin depending on the need of patient 60%, followed by regularly 36% and occasionally 4%.

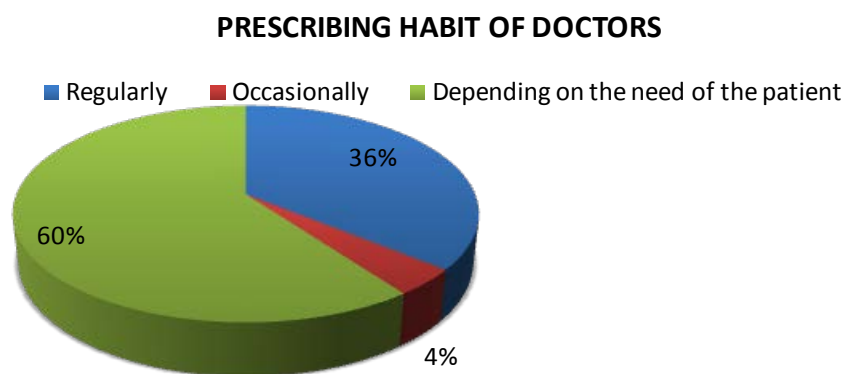


FIGURE 2. PRESCRIBING HABIT OF DOCTORS

Awareness of High Dose Methylcobalamin and Its Effects:-

A preliminary examination of data shows that 56% of respondent subjects were aware about high dose of Methylcobalamin and its effects. 40% of subjects were not aware about higher dose and rest 4% subjects had heard somewhere about high dose but were not sure about its usage and effects.

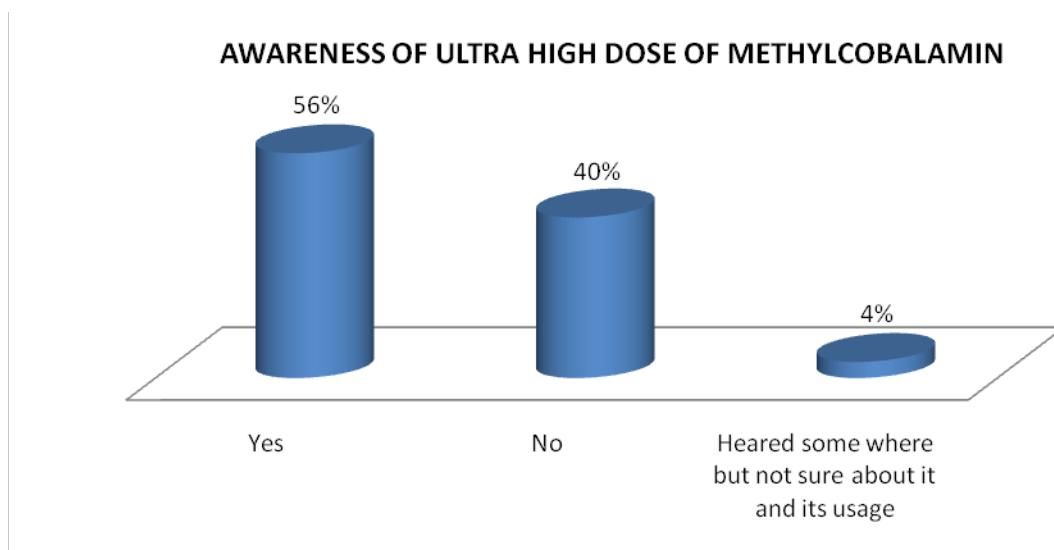


FIGURE 3. PERCENTAGE AWARENESS OF HIGH DOSE OF METHYLCOBALAMIN

Perception of Doctors on High Dose:-

According to data obtained, 28% subjects had opinion that high dose of methylcobalamin is advantageous over regular dose. 64% of doctors unable to say anything and needed more scientific literature and clinical evidences on indications where high dose of methylcobalamin is useful. Rest 8% of respondent had opinion that there is no advantage of high dose over regular dose.

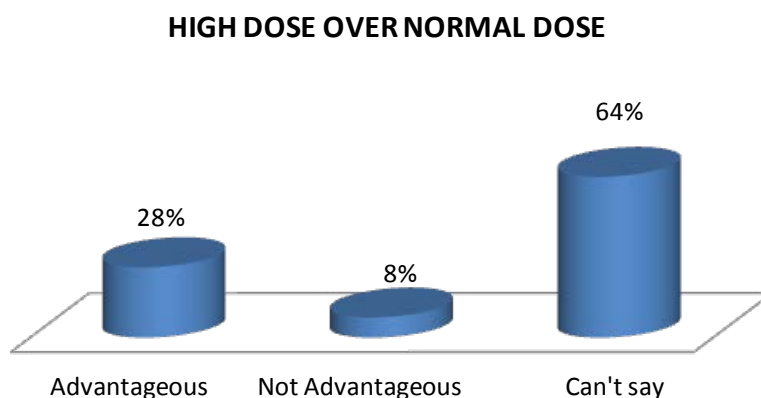


FIGURE 4. PERCENTAGE OF COMPARE BETWEEN HIGH DOSE AND NORMAL DOSE

Respondent comments on high dose therapy above 1500 mcg over regular dose therapy.

NUMBER OF RESPONDENT COMMENTED

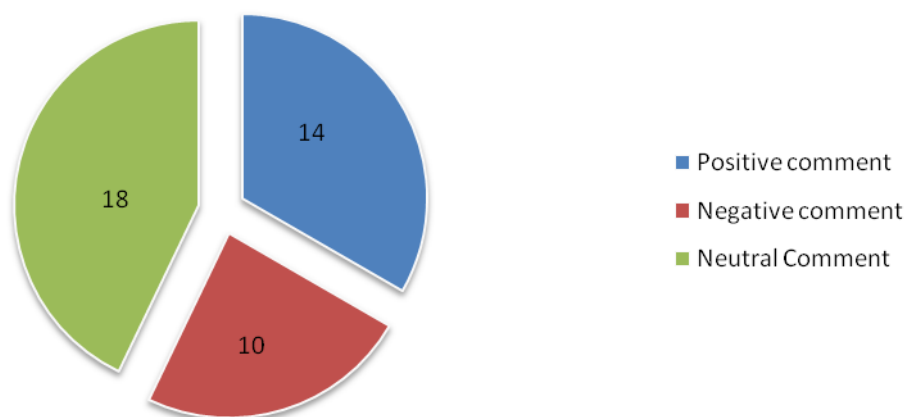


FIGURE 5. BREAKUP OF NATURE OF COMMENT AND NUMBER OF RESPONDENT

ASPECT OF COMMENTS	COMMENT GROUP	NUMBER OF COMMENT
POSITIVE	Used in past	2
	Always show better result over regular dose	2
	Excellent result	3
	Dose convenience	3
	Faster Recovery and good improvement	6
	Best Result in-	
	Neuropathy	4
	Drug induced neuropathy	1
	Diabetic Neuropathy	2
	Sciatica pain and Sciatica pain without herniated disc	3
	Tingling, Radial pain with low back pain	1
	Lumber Radiculopathy	1
NEUTRAL	Heard somewhere but not sure on use of high dose	7

	Not have any idea on use of high dose	8
	Use 750 to 1500 mcg	2
	Depend on B ₁₂ level	1
	Not useful in my practice	2
NEGATIVE	Seen Side effect dizziness, difficulty in walking with 1500 mcg	2
	Not required	3
	Result can't be judged	3
	Absorption is not more than 1500 mcg	2
	In Harrison medical book dose up to 1000 mcg only	1
	Not seen any out come from high dose	1
	Storage capacity of body is only up to 2-3 milligram	1

TABLE 1. DOCTORS COMMENT ON HIGH DOSE OVER REGULAR DOSE METHYLCOBLAMIN

Prescriber of High Dose of Methylcobalamin:-

Only 26% of all respondents were prescriber of high dose of Methylcobalamin. In other words out of all aware respondents of high dose of Methylcobalamin is only 46% were prescriber of Methylcobalamin. Schedule, dosage form and indication where respondents use high dose of Methylcobalamin is summarized in table below.

INDICATION	SCHEDULE			Number of Respondent
	STRENGTH	DOSAGE FORM	DURATION	
NEUROPATHY	2500 mcg	IV/IM	Once a week up to 5 time	5
DIABETIC NEUROPATHY	2500 mcg	IV/IM	Once in a week up to 5 time	3
MALE INFERTILITY				
LOW BACK PAIN	2500 mcg	IV/IM	Once in a week up to 5 time	1
TRAUMATIC NERVE INJURY	2500 mcg	IV/IM	Once in a Month	1
SCIATICA PAIN	2500 mcg	IV/IM	Once per week	3

			up to 5 time	
NEURALGIA				
DEMENTIA	2500 mcg	IV/IM	Once in alternate day up to 7 times	1
PARALYSIS				
BELL'S PALSY	2500 mcg	IV/IM	Once in alternate day up to 7 times	2
VERTIGO				
MULTIPLE SCLEROSIS				
ALS				
PARKINSON'S DISEASE				

TABLE 2. INDICATION AND RESPONDENTS OF HIGH DOSE METHYLCOBALAMIN

Overall Comment for High Dose Methylcobalamin therapy:-

58% of respondents were given their comment from total respondent. 24.13% were positive in nature, 68.96% neutral in nature and 6.89% were negative in nature.

ASPECT OF COMMENTS	COMMENT GROUP	NUMBER OF RESPONDENT
POSITIVE	Good information or new information	4
	Show Good Result	2
	Searched on net in past, need clinical evidence	1
NEUTRAL	Evidence based use in particular indication	9
	Prescribe after text book reference	1
	Need more information	10
NEGATIVE	No rational of high dose	1
	Storage Capacity is not more then 2-3 milligram	1

TABLE 3. OVERALL COMMENT OF DOCTORS ON HIGH DOSE THERAPY

CONCLUSION

1. All the doctors in the sample prescribed Methylcobalamin on a regular basis. Methylcobalamin prescribing habit of doctors was frequent; only 4% of doctors prescribe Methylcobalamin occasionally.
2. Awareness level of high dose of methylcobalamin was adequate. Maximum numbers of doctors were aware from high dose Methylcobalamin therapy.
3. Doctors opinion were scattered on high dose. 28% doctor's had opinion that high dose of Methylcobalamin is advantageous over regular dose. 64% of doctors were unable to say anything and needed more clinical evidence. Rest 8% of respondent had opinion that there is no advantage of high dose over regular dose.
4. Maximum comments of respondents were falling under positive and neutral category. (Refer table number 1)
5. Among all respondents 56% respondent were aware of high dose of methylcobalamin but only 26% respondents were prescribing high dose.
6. Prescribers were maximum prescribing in Neuropathy.
7. All prescriber of high dose of Methylcobalamin are using injectable dosage form and 2500 mcg strength.

RECOMMENDATION

1. Companies can tap this untapped market of high dose Methylcobalamin.
2. Injectable preparation is most suitable for high dose methylcobalamin preparation.
3. Scientific Literature on high dose recommends 2500 mcg and maximum doctors were using 2500 mcg. So 2500 mcg Injectabale strength is most acceptable form according to data.
4. Maximum doctors are unaware of high dose of methylcobalamin and easy to convert in loyal customers by scientific literatures and clinical evidences based marketing.
5. My study focused on doctor's specialization in neurological diseases. But from the study and responses other doctors like physician, orthopedic can also use in their therapy.

LIMITATIONS

1. Time and Money were the major constraints in this project. Because of which sample size was also small.
2. Maximum number of literature on high dose of Methylcobalamin was available in Pub-Med (USA and Europe), other Journals' of Japan and were through paid access.
3. Study included open ended questions which are qualitative in nature rather than quantitative for that groping method was used and way of understanding may be different from individual to individual.
4. Since sample size was small, so it was not possible to make strong recommendations.

ANNEXURE

Questionnaire:-

Doctors Name.....

Qualification & Speciality.....

Clinical Experience in Year.....

City.....

Email.....

Ph.No.....

Q1. Are you Prescriber of Methylcobalamin?

- ☐ YES
- ☐ NO

Q2. What Is Your Prescribing Habit of Methylcobalamin?

- ☐ REGULARLY
- ☐ OCCASIONALLY
- ☐ DEPENDING ON THE NEED OF THE PATIENT

Q3. Are you Aware of High Dose (≥ 1500 mcg) of Methylcobalamin and its Effects?

- ☐ YES
- ☐ NO
- ☐ HEARD SOMEWHERE BUT NOT SURE ABOUT IT AND ITS USAGE

Q4. Is High Dose (≥ 1500 mcg) of Methylcobalamin Formulation Advantageous over Regular Dose Formulations? Kindly Express Your Thoughts:

- ☐ YES
- ☐ NO

- o CAN'T SAY (NEED MORE CLINICAL EVIDENCE)

- 1.....
- 2.....
- 3.....

Q5. Your Preferred Indication for High Dose of Mecobalamin.

INDICATION	SCHEDULE			
	STRENGTH	DOSAGE FORM	HOW MANY TIMES IN A DAY	DURATION
NEUROPATHY				
DIABETIC NEUROPATHY				
MALE INFERTILITY				
LOW BACK PAIN				
TRAUMATIC NERVE INJURY				
SCIATICA PAIN				
NEURALGIA				
DEMENTIA				
PARALYSIS				
BELL'S PALSY				
VERTIGO				
MULTIPLE SCLEROSIS				
ALS				
PARKINSON'S DISEASE				

Q6. Overall Comments on High Dose of Mecobalamin Therapy.

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