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ROLE OF VITAMIN-D IN NEUROLOGICAL & PSYCHIATRIC ILLNESS

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Certificate

This to certify that Manisha Rathore student of Post Graduate Diploma in Pharmaceutical Management (PGDPM) from Institute of Health Management Research, Jaipur, Batch 4th has successfully undergone her summer training in Sun Pharmaceuticals Ltd., Mumbai and has done projects on:

- Role of vitamin-D in neurological & psychiatric illness

The candidate has successfully carried out the mentioned study assigned during her summer training from 15 April 2013 – 20 June 2013 and her approach towards the study was sincere, scientific and analytical.

We wish her success in all her future endeavors.

20/9/13

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CERTIFICATE

This is to certify that the dissertation submitted in partial fulfillment for the award of IHMR college is a result of the bonafide research work carried out by Ms. Manisha Rathore under my supervision and guidance. No part of this report has been submitted for award of any degree, diploma, fellowship or other similar title or prizes.

Guide: Mr Vineet Jain
Company: Sun Pharmaceutical Industries Ltd.
Place: Mumbai

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EXECUTIVE SUMMARY

❖ OBJECTIVE

To understand doctor's perception about role of Vitamin D in neurological and psychiatric illness

❖ SUB OBJECTIVES

1. To understand patient profile, indications, dosage & duration of treatment of Vitamin D in neurological and psychiatric illness
2. Need GAP Analysis to find out GAP between available treatment options
3. To study and analyze current competitor's market

❖ MEDICAL RATIONALE

Potential Role	Mechanism of action	Potential Therapeutic Application
Neuroprotective	***Reduction of nitric oxide synthesis, induction of Neurotrophins, direct antioxidant like effects***	**Parkinson's Disease, Alzheimer Disease**
Neuro-immunomodulating	***Immunosuppressant effects*** like systemic and local increase in expression of cytokine, altered macrophage and sensitization to apoptotic signals	**Autoimmune disorders like multiple sclerosis**
Antiepileptic	***Reduces seizure threshold in hippocampus***	**Epilepsy**
Developmental	Due to ***antiproliferative activity***, it regulates brain development, differentiation and apoptosis	**Minimizing risk factors of developmental brain disorders**

❖ MARKET RATIONALE

- Vitamin market is **2838.57 crore (Grw: 16%)**
  Plain Vitamin D market value is **146.09 crore (Grw: 158%)**

- ***Top selling brands in Vit-D market are***

Brands	Company	Market Value(in crore)	Market share (%)
Calcirol	Cadila	30.1	20.6
Uprise-D3	Alkem	15.4	10.6
D-Rise	USV	12.3	8.5
Tayo-60K	Eris Life Sciences	9.6	6.6

(Source-ORG data Feb'13)

- As per CMARC Feb'13, **CNS segment is untapped** market in vitamin D market

❖ RESEARCH METHODOLOGY

- Sample size-95
- Data collection-Primary and Secondary
- Specialties covered-Neurologist, Psychiatrist and Physician
- Areas covered-Mumbai i.e Western (54%), Central(26%),South (11%) and Harbour (9%)

❖ CONCLUSION

- Majority of doctors see ***less than 10%*** patients with Vitamin-D deficiency in a week
- ***Neurologists are well aware*** about the role of Vitamin D in neurological & psychiatric illness. Some of ***psychiatrists and majority of physicians not much aware of the role***
- Major ***psychiatric indications*** wherein Vitamin D is prescribed-
    - Depression, anxiety, dementia
- Major ***neurological indication*** wherein Vitamin D is prescribed-
    - Neuropathy, myopathy and multiple sclerosis
- ***Current preferred dosage form-Granules & duration of treatment-4 to 6 weeks***
- But granules are to be taken with milk, so a bit cumbersome. Injections are quite painful, preferred in extremely resistant cases

❖ RECOMMENDATION

- ***Segmentation*** should be done in specialties like ***neurologist, psychiatrist and physician. Because***

  Vitamin D market-***fragmented market***, CNS segment is untapped. So a great potential lies ahead
- ***Primitive pricing*** should be done
- ***Promotion : Awareness*** needs ***to be created*** especially amongst ***psychiatrist and physician*** by
- Means of ***Continuing medical education***
- ***Clinical evidences*** supporting role of Vitamin D in psychiatric disorders
- Also ***doctors*** need to be ***educated*** to go for ***early diagnosis of Vitamin D status***
- ***Competitive Positioning:***
- Better formulation through better technological advantage over others in crowded Vit-D market
- Build the market through awareness and activities
- First year we should look at educating doctors on Vit-D rather than conversion
- Create our own competitive advantage which others would find difficult to follow

INTRODUCTION

Vitamin D (cholecalciferol) is a fat-soluble seco-steroid synthesized in skin (as hormone) or ingested with food (as Vitamin). Itself biologically inactive, Vitamin D undergoes bioactivation by double hydroxylation in liver and kidney, leading to formation of 1,25-dihydroxyvitamin D(1,25-D, calcitriol, soltriol) – the main biologically active form of Vitamin D.

Ten years ago it was suggested that Vitamin D was the 'forgotten Neurosteroid'. Over the past 10–15 years, studies in which the diet or Vitamin D signaling has been manipulated in experimental animals have provided convincing evidence that this Vitamin, more accurately referred to as hormone, is required for normal brain homeostasis and development.

Biological role-

- Regulation of mineral homeostasis, tissue proliferation, differentiation and apoptosis, as well as the cardiovascular and immune systems
- Acts as a neurosteroid, as the vitamin D receptors (VDR) and enzymes of bioactivation/metabolism are found in brain neurons, glial cells, brain macrophages, spinal cord and the peripheral nervous system

FORMS OF VITAMIN D

Vitamin D comes in many forms but the two major physiologically relevant ones are

1. **Vitamin D_2 (ergocalciferol)-** It originates from the yeast and plant sterol, ergosterol
2. **Vitamin D_3 (cholecalciferol)-** It originates from 7-dehydrocholesterol, a precursor of cholesterol, when synthesized in the skin

Vitamin D intake from food and nutrient supplements is expressed in either international units (IU) or micrograms (μg).

The biological activity of 1 μg of vitamin D is 40 IU.

SOURCES OF VITAMIN D

❖ SUNLIGHT

1. The major source of Vitamin D for humans is the exposure of the skin to sunlight.
2. The optimal wavelength of light for production being 290-315nm UVB.

However, a variety of factors limit the cutaneous production of Vitamin D as mentioned below-

- **Excessive exposure to sunlight** causes a photodegradation of previtamin D_3 and Vitamin D_3 to ensure that Vitamin D_3 intoxication cannot occur

- **An increase in skin melanin pigmentation or the topical application of a sunscreen** will absorb solar ultraviolet B photons and thereby significantly reduce the production of Vitamin D_3 in the skin
- **Latitude, time of day and season of the year** have a dramatic influence on the cutaneous production of Vitamin D_3. Above and below latitudes of approximately 40° N and 40° S, respectively, Vitamin D_3 synthesis in the skin is absent during most of the three to four winter months

❖ FOOD SOURCES

1. Very few are naturally rich in Vitamin D.
2. Wild caught salmon, cod liver oil, oily fish, mushrooms, milk and some other dairy products and some orange juices and cereals contain Vitamin D.
3. Almost all of the human intake of Vitamin D from foods comes from fortified milk products and other fortified foods such as breakfast cereals.
4. The Vitamin D content of unfortified foods is generally low, with the exception of fish, many of which contain 5 to 15 µg (200 to 600 IU)/100 g.

❖ DIETARY SUPPLEMENTS

In supplements and fortified foods, Vitamin D is available in two forms-

1. Vitamin D_2 (ergocalciferol)
2. Vitamin D_3 (cholecalciferol)

Vitamin D_3 is approximately 87% more potent than vitamin D_2 in raising serum 25(OH)D concentrations and maintaining those levels for a longer time and its metabolites have superior affinity for vitamin D-binding proteins in plasma.

RECOMMENDED DIETARY ALLOWANCE

Recommended Dietary Allowance Of Vitamin D				
Age	**Male**	**Female**	**Pregnancy**	**Lactation**
0-12 months	400 IU	400 IU		
1-13 years	600 IU	600 IU		
14-18 years	600 IU	600 IU	600 IU	600 IU
19-50 years	600 IU	600 IU	600 IU	600 IU
51-70 years	600 IU	600 IU		
›70 years	800 IU	800 IU		

(Source-National Institute Of Health)

VITAMIN D DEFICIENCY

Vitamin D deficiency occurs when people do not have an appropriate dietary intake or exposure to UVB rays. ***It is universally accepted that the circulating level of 25-hydroxyvitamin D should be used as an indicator of Vitamin D status due to its ease of measurement, long half-life in circulation (approximately 2 or 3 weeks) and the correlation of its level with clinical disease states*** . The following categories for blood levels of 25(OH) D have been proposed:

Optimal	**greater than 75 nmol/l**
Sufficient	**50-75 nmol/l**
Insufficient	**25-50 nmol/l**
Deficient	**less than 25 nmol/l**

CAUSES OF VITAMIN D DEFICIENCY

There are many causes of Vitamin D deficiency. Generally, they can be divided into two groups: UVB-related deficiency and medical/physical condition-related deficiency.

1. **UVB-related deficiency**

- **The elderly-** The elderly due to the decreased presence of skin 7-dehydrocholesterol which is the precursor for UVB mediated synthesis of Vitamin D are particularly at risk of Vitamin D deficiency. Moreover, reduced mobility or institutionalization that discourages sun exposure, reduced renal production of 1,25-dihydroxyvitamin D as well as decreased intake of fortified foods pose great difficulties in Vitamin D formation in body.
- **Dark skin-** People with dark skin have great amounts of melanin in their epidermis. Melanin competes with 7-dehydrocholesterol for absorption of UVB photons. Therefore, people of dark skin are less efficient in producing vitamin D than whites. It is reported that a person with skin type 5/6 (dark skin) requires 10-50 times the exposure to sunlight to produce the same amount of vitamin D as does a white person with skin type 2/3.
- **Season, latitude and the time of day -**It has been established that the ozone layer can absorb UVB radiation above 290 nm which is responsible for generating previtamin D_3. Zenith angle, defined as the angle of the sunlight reaching the Earth's surface, decides the thickness of ozone layer which sunlight needs to penetrate. The thicker the ozone layer is, the fewer amounts of UVB photons can reach the earth, thus few previtaminD_3 can be produced. Zenith angle is dependent on factors such as time of day, season of the year, and latitude.

- **Sunscreen users** - Sunscreens can efficiently absorb UVB radiation. This dramatically prevents the interaction of UVB with 7-dehydrocholesterol, the process of previtaminD_3 generation. It has been shown that when used properly, a sunscreen with a sun protection factor of 8 reduces the production of previtamin D_3 by 95% and 99% by a sun protection factor of 15.

2. Medical/physical condition-related deficiency

- **Fat malabsorption-** As a fat-soluble Vitamin, Vitamin D requires the presence of dietary fat in the gut for absorption. Certain pathological conditions, such as Crohn's disease, cystic fibrosis (CF), celiac disease, surgical removal of part of the stomach or intestines are associated with fat malabsorption and thus may lead to Vitamin D deficiency. For example, CF patients suffer from pancreatic exocrine insufficiency. This results in malabsorption of fat-soluble vitamins, including Vitamin D. CF patients, depending on the degree of exocrine insufficiency, absorb approximately 50% less Vitamin D than normal.

- **Anticonvulsant use-** Anticonvulsants, also called antiepileptic drugs, have been used to treat epileptic seizures and bipolar disorder. It is well recognized that long-term use of some antiepileptic drugs including phenobarbital, phenytoin and carbamazepine and the antimicrobial agent rifampicin (RIF) can result in osteomalacia. The induction of the catabolism of 1,25-dihydroxyvitamin D by these drugs is thought to contribute to their deleterious side effects.

- **Chronic kidney disease**- In order to become biological active Vitamin D, kidney plays an important role in this transforming process. Chronic kidney disease such as patients with stage 4 or 5 chronic kidney disease, as well as those requiring dialysis, leads to an inability to make sufficient 1,25-dihydroxyvitamin D which has a direct effect in inhibiting parathyroid hormones expression.Thus 1,25-dihydroxyvitamin D_3 intake is needed to maintain calcium level in blood as well as to control parathyroid hormone levels.

- **Obesity-** Obese people are prone to be Vitamin D deficient since they have lower 25-hydroxyvitamin D levels.

VITAMIN D TOXICITY

Vitamin D toxicity, also called ***hypervitaminosis D***, is a rare but potentially serious condition that occurs when excessive amounts of Vitamin D is present in body. ***Hypercalcemia is the hazard criterion for Vitamin D.***

Institute of Medicine has set the ***tolerable upper intake level (UL) for Vitamin D at 2000 IU/d, defining this as "the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population***." However, because sunshine can provide an adult with Vitamin D in an amount equivalent to daily oral consumption of 10,000 IU/d, this is intuitively a safe dose. The incremental consumption of 40 IU/day of Vitamin D_3 raises serum 25(OH)D by approximately 1 nM (0.4 ng/ml). Therefore, if sun-deprived adults are to maintain serum 25(OH)D concentrations >75 nM (30 ng/ml), they will require an intake of more than the UL for vitamin D.

The ***mechanisms*** that ***limit Vitamin D safety*** are ***the capacity of circulating Vitamin D-binding protein and the ability to suppress 25(OH)D-1-alpha-hydroxylase***.

Vitamin D causes hypercalcemia when the "free" concentration of 1,25-dihydroxyvitamin D is inappropriately high. Plasma concentrations of unmetabolized Vitamin D during the first days after an acute, large dose of Vitamin D can reach the micromolar range and cause acute symptoms.

VITAMIN D RELATED DISORDERS

In children, Vitamin D deficiency results in ***inadequate mineralization of the skeleton causing rickets,*** which is characterized by widening at the end of the long bones, rachitic rosary, deformations in the skeleton and outward or inward deformities of the lower limbs causing bowed legs and knocked knees, respectively.

In adults, Vitamin D deficiency leads to ***a mineralization defect in the skeleton causing osteomalacia.*** Vitamin D deficiency causes a decrease in ionized calcium in blood, which in turn leads to an increase in the production and secretion of PTH. PTH stimulates the mobilization of calcium from the skeleton, conserves renal loss of calcium and causes increased renal excretion of phosphorus leading to normal fasting serum calcium with a low or low-normal serum phosphorus. The elevated PTH leads to an increase in the destruction of the skeletal tissue in order to release calcium into the blood.

Other disorders include ***osteoporosis, psoriasis, prostate cancer*** etc.

VITAMIN D AND NERVOUS SYSTEM

❖ BRAIN, VITAMIN D SYNTHESIS AND DEGRADATION

It was assumed that the brain 1,25-$(OH)_2D_3$ supply was dependent on the plasma concentration of 1,25-$(OH)_2D_3$. However, recent data demonstrating the brain localization of Vitamin D_3 25-hydroxylase and 25-hydroxyvitamin D_3-1α-hydroxylase enzymes suggest that the ***central nervous system (CNS) can locally perform the bioactivation of the Vitamin D_3 prohormone*** .Also the microglial cells in culture produce 1,25-$(OH)_2D_3$ from its precursor.

The localization of the enzymes involved in the biosynthesis of 1,25-$(OH)_2D_3$ in the brain and the presence of 1,25-$(OH)_2D_3$ in the cerebrospinal fluid suggest the ***existence of a catabolic pathway for this hormone in the CNS***.

The first step of the major pathway involved in the inactivation of this hormone is achieved by Vitamin D_3 24-hydroxylase and the corresponding gene is upregulated in glial cells exposed to 1,25-$(OH)_2D_3$.Thus, together, these results suggest the existence of both the ***biosynthetic and the degradative pathways for 1,25-$(OH)_2D_3$ in the brain.***

❖ MECHANISM OF ACTION OF VITAMIN D

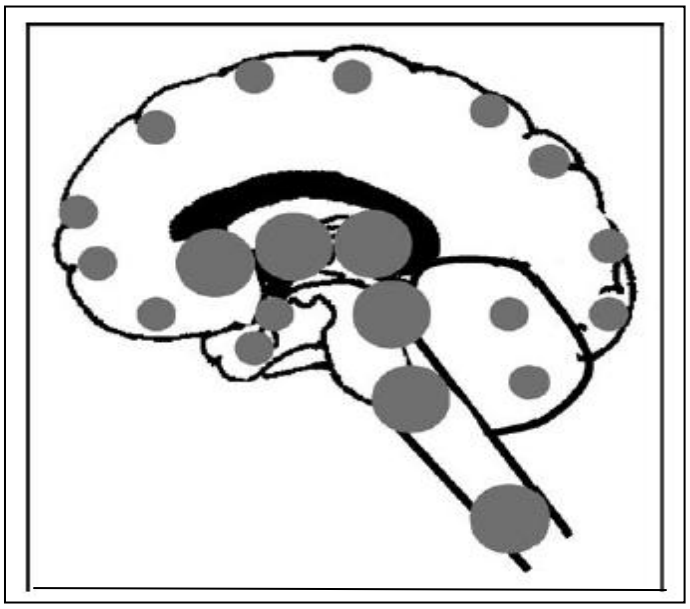
➢ THE VITAMIN D RECEPTOR (VDR)

The ***nuclear functions*** of 1,25-$(OH)_2D_3$ ***are mediated through the Vitamin D receptor*** (VDR).It has been found that ***both mRNA encoding the VDR and the protein itself are present in the nervous system.*** Thus, *VDR* gene expression has been demonstrated in neuronal and glial cells.

VDR belongs to the nuclear hormone receptor superfamily and acts as a ligand-inducible transcription factor. It regulates gene expression by binding to specific DNA-response elements of target genes after heterodimerization with the retinoid X receptor and the recruitment of several nuclear receptor coactivator proteins, including members of the steroid receptor coactivator family.

Heterodimerizations of the VDR with the nuclear receptors for all-*trans* retinoic acid and thyroid hormone or with Smad3 [a member of the SMAD protein family transducing the signal for transforming growth factor β (TGF-β)] have also been reported and suggest the existence of crosstalk between these signaling pathways. These heterodimerizations could play a role in neuroontogenesis because *VDR* expression is regulated developmentally within nervous tissues.

Central nervous system targets for vitamin D derived from animal autoradiographs and recent human data include-
neocortex,striatum,hypothalamus,hypophysis,thalamus,amygdala,hippocampus,piriform cortex,cerebellum,raphe,substania gelatinosa and spinal cord.
Size of dots corresponds to relative intensity of vitamin D binding.



➢ NON-GENOMIC ACTIONS

Non-genomic effects have also been described for steroids and thyroid hormones. These effects are probably mediated via specific membrane receptors. Hence, the rapid, non-genomic effects of 1,25-$(OH)_2D_3$ could be mediated by interaction of the hormone with a specific plasma membrane receptor.

Regulation of Ca^{2+} channels and activation of protein kinase C and mitogen-activated protein kinase pathways are some of the non-genomic signal transduction events triggered by 1,25-$(OH)_2D_3$.It has been suggested that ***1,25-$(OH)_2D_3$ could act in the brain in a similar way to neuroactive steroids by modulating neuron excitability and other electrophysiological phenomena.***

❖ NEUROPROTECTIVE EFFECTS OF VITAMIN D

➢ Neurotrophins (NGF, NT-3, NT4/5) and the neurotrophic factor GDNF

Neurotrophins are secreted proteins that support the survival and differentiation of neurons and also function in the adult brain. Of the 4 neurotrophins in mammals (NGF, BDNF, NT-3, and NT4/5), calcitriol affects the expression of 3 of them.

1. ***NGF*** is present mainly in the hippocampus and neocortex, where ***it affects neurotransmission and synaptic plasticity.***
2. Functions of the other neurotrophins linked to calcitriol ***include enhancement of synaptic transmission in the hippocampus by NT-3 and involvement in calcium signaling by NT4/5.***
3. GDNF is another type of neurotrophic factor. It is a distant member of the transforming growth factor β (TGFβ) superfamily. In the brain, ***GDNF affects the survival and differentiation of dopaminergic cells.***

Calcitriol regulates the synthesis of nerve growth factor (NGF) and various studies have demonstrated that ***1,25-$(OH)_2D_3$ can act on cells of the nervous system by modulating the production of neurotrophins.*** For instance, the synthesis of NGF, neurotrophin 3 (NT3) and glial cell line-derived neurotrophic factor (GDNF) was upregulated by calcitriol, whereas neurotrophin 4 (NT4) was downregulated.

Thus 1,25-$(OH)_2D_3$ or its synthetic analogs could be valuable in the treatment of neurodegenerative diseases.

In addition to its influence on neurotrophin synthesis, 1,25-$(OH)_2D_3$ could mediate its neuroprotective effects via the modulation of neuronal Ca^{2+} homeostasis.

➢ Calcium Binding Protein

Another way in which 1,25-$(OH)_2D_3$ might mediate its ***neuroprotective effect is to induce the synthesis of Ca^{2+}-binding proteins,*** such as parvalbumin.

Many calcium-binding proteins are present throughout the body and in the CNS. Three have been shown to be modulated by Vitamin D in brain tissues or cells—***calbindin-D28K, parvalbumin and calretinin***. All three of these calcium-binding proteins are widely distributed in both the adult and fetal brain.

In the adult brain, each of these protein is uniquely distributed and they also exhibit temporal patterns during development and aging . They fill the cytoplasm of neuronal processes, are commonly used as neuronal markers and are present in some areas of the brain at very high concentrations. For example calbindin-D28k comprises some 15% of the total protein in adult Purkinje cells in the cerebellum.

1. All three proteins are believed to ***serve a neuroprotective role as calcium buffers***, but they are also involved in critical brain functions.
2. In addition to its calcium-buffering properties, calbindin-D28k undergoes a conformational change on binding Ca^{2+} and functions as a Ca^{2+} sensor. It is required for normal signaling of synaptically evoked calcium transients and is involved in synaptic plasticity, long-term potentiation (LTP) and memory formation and possibly in the regulation of exocytosis (synaptic secretion of neurotransmitters)
3. In the brain, ***calmodulin is involved in neurotransmitter activity***, ***NMDA-induced synaptic plasticity and short-term plasticity*** (transient alteration of the efficiency of synaptic transmission between neurons). Calcium/calmodulin-dependent protein kinase II ***(CAM kinase II)*** is highly concentrated in neurons and is believed to play a ***central role*** in a variety of brain functions, including ***learning and memory***; it has been suggested that CAM kinase II is the molecular basis of long-term synaptic memory.

➢ Nitric Oxide Synthase (iNOS)

$1,25\text{-}(OH)_2D_3$ has also been reported to ***inhibit the synthesis of inducible nitric oxide synthase (iNOS),*** an enzyme induced in CNS neurons and non-neuronal cells during various insults or diseases such as ischemia, Alzheimer's disease, Parkinson's disease, AIDS, infections, multiple sclerosis.

iNOS produces ***nitric oxide***, one of the biological effects of which is to ***damage both neurons and oligodendrocytes when it is produced at high levels .***

➢ Gamma-Glutamyl Transpeptidase

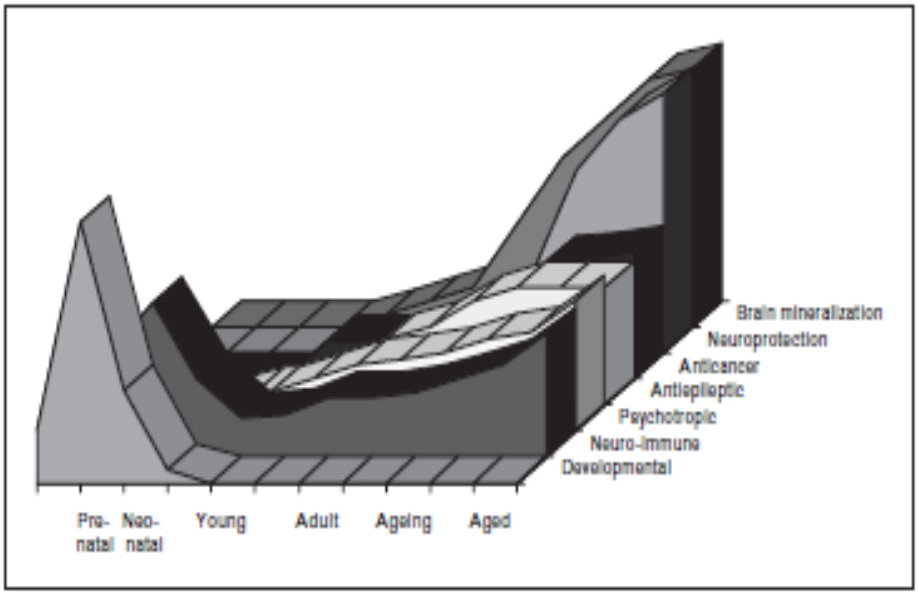
Brain gamma-glutamyl transpeptidase (***gamma-GT) is increased after Vit-D administration*** and this positive effect was noted in pericytes and parenchymal astrocytes. Gamma-GT is thought to participate in the scavenging of reactive oxygen species and ***Vit-D could be an effector controlling detoxification processes in the brain.*** Astrocytes play a pivotal role in CNS detoxification pathways, where glutathione is involved in the elimination of oxygen- and nitrogen-reactive species such as nitric oxide.

Gamma-GT, an enzyme of central significance in glutathione metabolism, is regulated *in vivo* in astrocytes by Vit-D_3. It appears that both gamma-GT gene expression and specific activity, induced by lipopolysaccharide, are potentiated by Vit-D_3.

Vit-D_3 enhance intracellular glutathione pools and significantly reduce nitrite production induced by lipopolysaccharide.

Thus ***gamma-GT, glutathione, and vit-D_3 play a fundamental role in astrocyte detoxification pathways, which, at least in part, explain neuroprotective effects.***

Relative importance of Vitamin-D related mechanism for brain functioning at different stages of life



CLINICAL STUDIES DATA

STUDY (REF)	METHODOLOGY	OBSERVATIONS
SEASONAL AFFECTIVE DISORDER Gloth et al. 1999(3)	Randomized controlled trial was conducted in 15 subjects with SAD.8 subjects received 100000 IU vitamin D and 7 subjects received phototherapy.	All subjects receiving vitamin D improved in all outcome measures. The phototherapy group showed no significant change in depression scale measures. Vitamin D status improved 74% in vitamin D group and 36% in phototherapy group.
EPILEPSY Hollo et al. 2012(24)	13 consecutive epilepsy patients were recruited from 2 epilepsy outpatient clinics. Seizure numbers were compared during a 90 day period before and after treatment onset.	Seizure numbers significantly decreased upon vitamin D supplementation. Median seizure reduction was 40 %.
PARKINSON'S DISEASE Knekt et al. 2010(67)	A cohort study of 3173 men and women ages 50 to 79 years and free of Parkinson's disease at baseline.	Individuals with higher serum vitamin D concentrations showed a reduced risk of Parkinson disease. The relative risk between the highest and lowest quartiles was 0.33 (95% confidence interval, 0.14-0.80) after adjustment for sex, age, marital status, education, alcohol consumption, leisure-time physical activity, smoking, body mass index, and month of blood draw.
Suzuki et al 2013(67)	Patients with PD (n = 114) were randomly assigned to receive vitamin D_3 supplements (n = 56; 1200 IU/d) or a placebo (n = 58) for 12 months in a double-blind setting. Outcomes were clinical changes from baseline and the %tage of patients who showed no worsening of the modified Hoehn and Yahr (HY) stage and Unified Parkinson's Disease Rating Scale (UPDRS).	In this randomized, double-blind, placebo-controlled trial, daily supplementation with 1200 IU vitamin D_3 for 12 months significantly prevented the deterioration of PD as measured with the HY stage, UPDRS part II and total, and some domains of the PDQ39, with no apparent increase in risk of hypercalcemia or adverse events during the study period.

COGNITION Llewellyn et al. 2010(20)	Prospective evaluation of 858 adults (≥65years) participating in the INCHIANTI study between 1998 and 2006 with follow up assessments every 3 years.	Low vitamin D concentration (‹25nmol/l) was significantly associated with decline in cognitive function compared with subjects with sufficient conc. (≥75nmol/l).
Annweiler et al. 2010(45)	Cross sectional study of 752 women (≥75 years) in the Epidemiologie de Losteoporose (EPIDOS) cohort.	Compared with women with serum 25(OH)D conc.≥10ng/ml (n=623), women with 25(OH)D deficiency(n=129) had lower mean SPMSQ score and more often had an SPMSQ score‹8.Serum deficiency was associated with cognitive impairment.
Wilkins et al. 2006(18)	Cross sectional study of 40 adults with mild AD and 40 non-demented,from a study of memory and aging.	Vitamin D deficiency was associated with low mood and with impairment on 2 of 4 measures of cognitive performance (short blessed test and clinical dementia rating scale).
DEPRESSION Witte et al. 2008(65)	Population based cohort study of 1282 community residents (aged 65-95 years) depression was measured using self report and diagnostic interview.	Levels of 25(OH)D were 14% lower in 169 persons with minor depression and 14% lower in 26 persons with major depressive disorder compared with levels in 1087 control individuals.Levels of PTH were 5% and 33% higher,respectively.Depression severity was associated with decreased serum 25(OH)D levels and increased serum PTH levels (*P*=.008).
Anglin et al. 2013(202)	1 case control study, 10 cross sectional studies and 3 cohort studies with a total of 31424 participants were analyzed.	Lower vitamin D levels were found in people with depression compared with controls and there was an increased odds ratio of depression for the lowest v. highest vitamin D categories in the cross - sectional studies. (OR=1.31,95%CI 1.0-1.71)

R. Jorde et al. 2008(264)	Cross-sectional study and randomized double blind controlled trial of 20,000 or 40,000 IU vitamin D per week versus placebo for 1 year. A total of 441 subjects (body mass index 28–47 kg m^{-2})159 men and 282 women (aged 21–70 years) were recruited.	Subjects with serum 25(OH)D levels<40 nmol/ L scored significantly higher (more depressive traits) than those with serum 25(OH)D levels ≥40 nmol/ L on the BDI total. In the two groups given vitamin D, but not in the placebo group, there was a significant improvement in BDI scores after 1 year. There was a significant decrease in serum parathyroid hormone in the two vitamin D groups without a concomitant increase in serum calcium.
Yuri et al. 2010(95)	A population based cohort study (INCHIANTI study) of 531 women and 423 men (aged≥65 years). Depressive symptoms were assessed at baseline and at 3 and 6 year follow-ups using the Center for Epidemiological Studies-Depression Scale (CES-D).	Those with 25(OH)D less than 50nM at baseline(compared with those with higher levels) experienced significantly higher scores on measures of depression at 3 and 6 year follow up.
ALZHEIMER'S DISEASE Beauchet et al. 2012(67)	A cohort study of 498 community-dwelling women(mean 79.8±3.8 years)free of vitamin D who were divide into 3 groups according to onset of dementia within 7 years(i.e.no dementia, alzheimer's disease or other dementias).Baseline vitamin d dietary intakes were estimated from self-administered food frequency questionnaire.	Women who developed AD(n=70)had lower baseline vitamin D intakes(mean 50.3±19.3 µg/wk)than non demented(*n* = 361; mean intake = 59.0 ± 29.9 µg/wk, *p* = .027) or those who developed other dementias (*n* = 67; mean intake = 63.6 ± 38.1 µg/wk, *p* = .010).It was found that vitamin D dietary intake was associated with a lower risk of AD.

MULTIPLE SCLEROSIS Burton JM et al. 2008(14)	25 people were given oral vitamin D_3.	After 12 months, a 41% reduction in the number of relapses and a significant improvement in EDSS was reported for the 25 people receiving vitamin D_3 compared to the 24 who were untreated.
Smolders J et al. 2008(16)	267 people were tested for vitamin D level and its association was determined in MS patients	A study of samples from 267 people found that higher levels of vitamin D were associated with a lower relapse rate. Low levels were associated with higher disability scores. People with progressive forms of MS had lower levels than those with relapsing remitting MS.
Wingerchuck DM et al. 2005(76)	15 people were given vitamin D and their relapse rate was checked	15 people with MS who received 100 IU/d for 48 weeks experienced a 50% reduction in relapses.

MEDICAL RATIONALE

It can be play a role in neurological & psychiatric disorders by acting in the below mentioned ways-

Potential Role	Mechanism of action	Potential Therapeutic Application
Developmental	Due to ***antiproliferative activity***, it regulates brain development, differentiation and apoptosis.	**Minimizing risk factors of developmental brain disorders**
Neuroprotective	Reduction of calcium toxicity, ***modulation of glutathione metabolism***, direct antioxidant like effects, ***reduction of nitric oxide synthesis, induction of neurotrophins***	**Parkinson's Disease, Alzheimer Disease**
Neuro-immunomodulating	***Immunosuppressant effects*** like systemic and local increase in expression of cytokine, altered macrophage,dendritic and T-cell functions and sensitization to apoptotic signals	**Autoimmune disorders like multiple sclerosis**
Antiepileptic	***Reduces seizure threshold in hippocampus***	**Epilepsy**
Anticalcification	***Relieves intracranial calcification*** (affecting basal ganglia, cerebral cortex and cerebellum)	**Treat/prevent brain calcification in elderly**

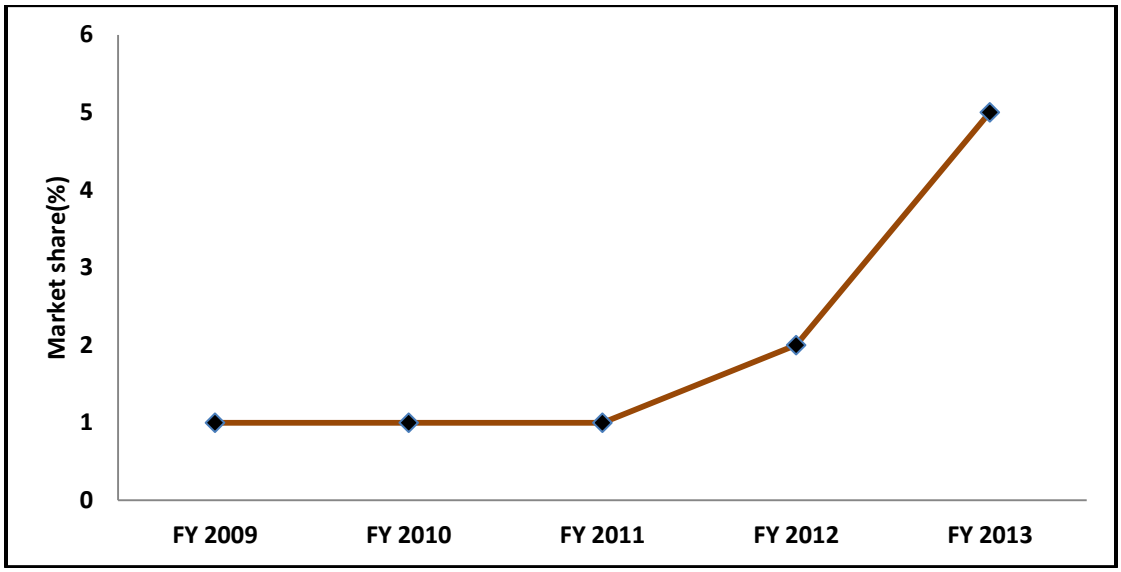
MARKET ANALYSIS

Top Selling Brands In Market

BRAND	COMPANY	DOSAGE FORMS	MARKET SHARE (%)
Calcirol	Cadila Pharma	Granule, capsule	20.6
Uprise-D3	Alkem	Soft gel capsule,injection, syrup	10.6
D-Rise	UV	Granule, soft gel capsule	8.5
Tayo 60	Eris Life Science	Chewable tablet	6.6
Mashyne	USV	Granule, drops	5.3
D-360	Elder Pharma	Sachet, capsule	4.7
Vitanova	Zuventus Pharma	Granule, soft gel capsule, injection	4.6
Arachitol	Solvay Pharma	Injection	4.5

(Source-ORG Data Feb'13)

➢ Market Share: Plain Vit- D In Overall Vitamins Market

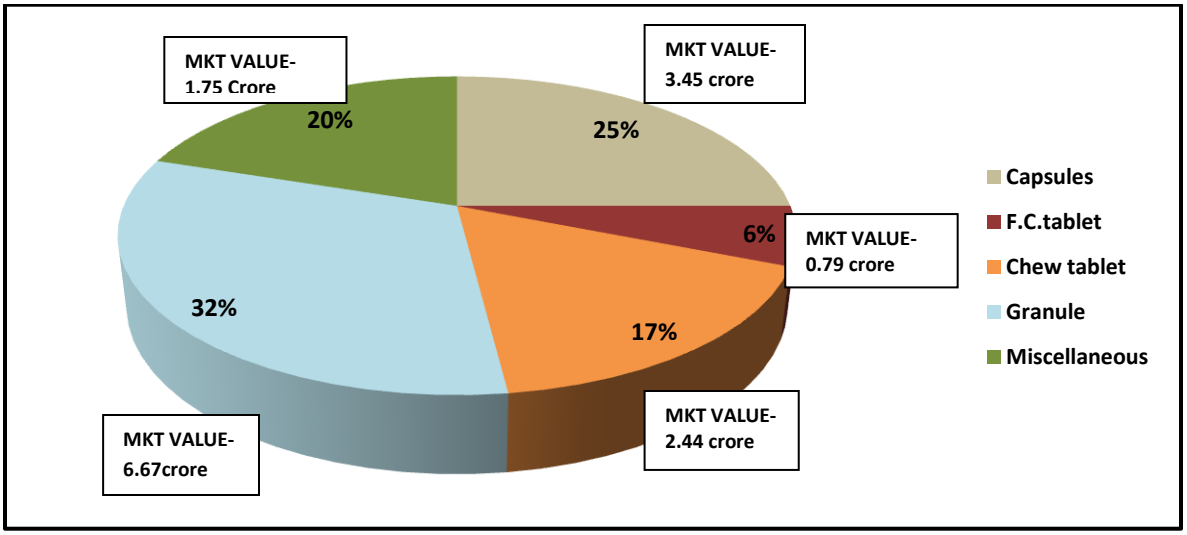


(Source-ORG Data Feb'13)

INTERPRETATION

- The market share of Vitamin D has increased from 1% in 2009 to 5% in 2013

➢ SKU WISE VIT-D MARKET ANALYSIS



(Source-ORG Data Feb'13)

INTERPRETATION-

- A large share of market is occupied by granules followed by capsules
- In case of tablets ,chewable form solely occupies a major share
- Other dosage forms are also present in market like syrups, suspension and mouth spray

RESEARCH OBJECTIVE

OBJECTIVE

To understand doctor's perception about role of vitamin D in neurological & psychiatric illness

SUB OBJECTIVES

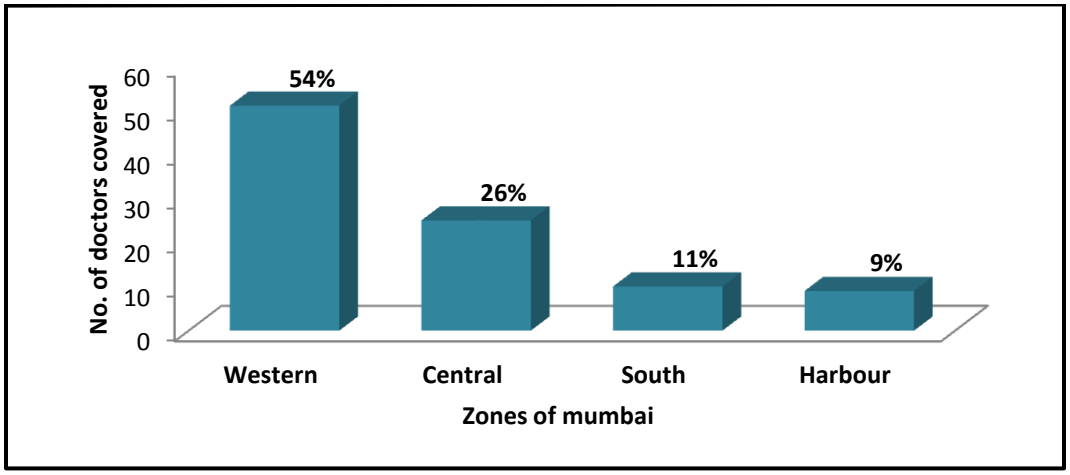
1. To understand patient profile, indications, dosage & duration of treatment of Vitamin D supplements in neurological and psychiatric illness
2. Need GAP Analysis to find out GAP between available treatment options
3. To study and analyze current competitor's market

RESEARCH METHODOLOGY

SR NO.	PARAMETERS	DESCRIPTION
1.	Research type	Qualitative and Quantitative
2.	Data collection	Primary and secondary
3.	Measurement Technique	Structured questionnaire
4.	Sample selection	Area wise and speciality wise
5.	Sample size	95
6.	Sample unit	Neurologist, Psychiatrist and Physician
7.	Sampling technique	Convenience sampling
8.	Analysis technique	Using Microsoft Excel

➢ AREAS COVERED FOR PRIMARY DATA COLLECTION-

Different zones of Mumbai were covered-



ANALYSIS OF COLLECTED DATA

SPECIALITIES COVERED-

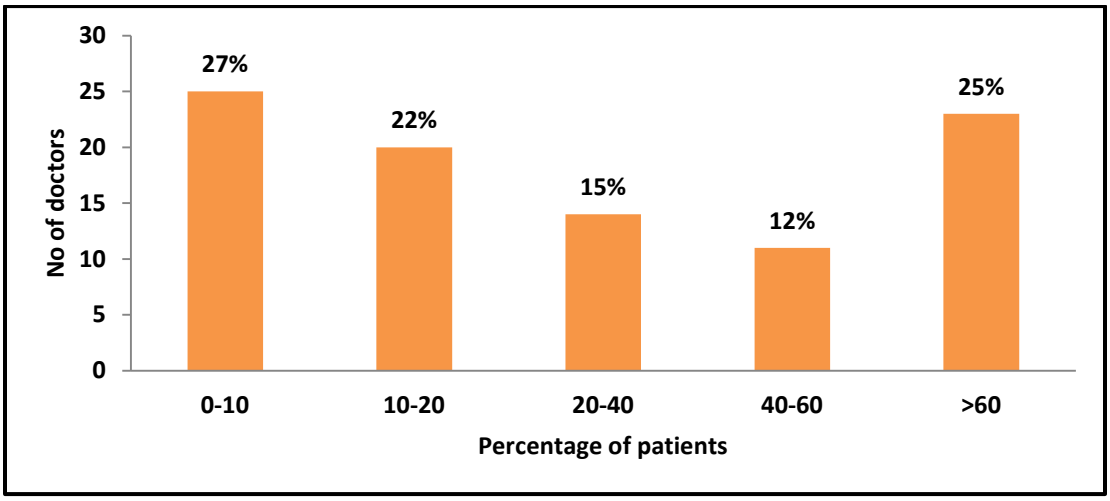
Neurologists-23

Psychiatrist-54

Physician -18

1. **In your clinical practice, how much percentage of patients do you see with vitamin D deficiency in a week?**

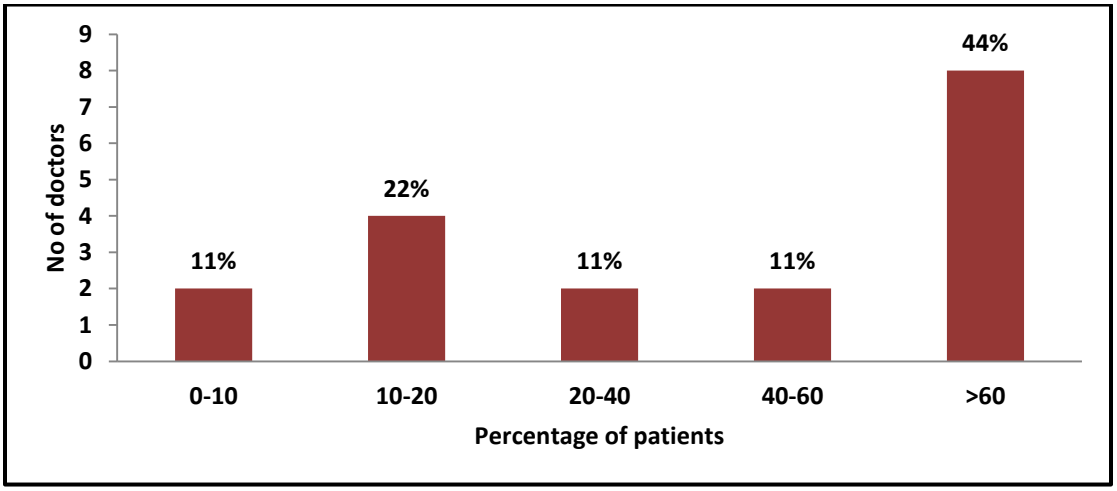
❖ **OVERALL RESPONSE OF DOCTORS**



INTERPRETATION

- Majority of doctors see less than 10 % of Vitamin D deficient patients per week
- This can be accounted because of lack of awareness for Vitamin D deficiency

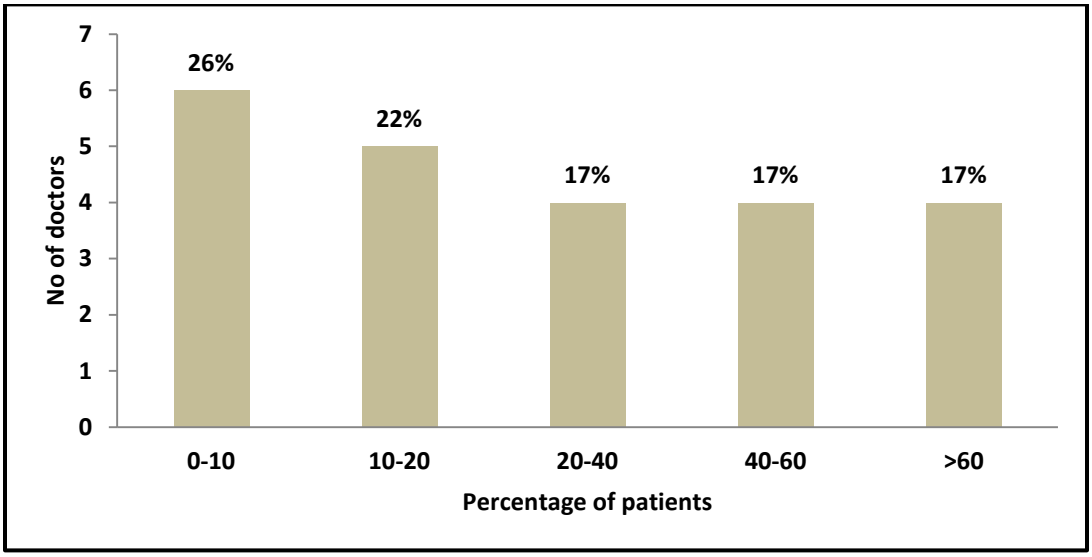
❖ **RESPONSE OF PHYSICIAN**



INTERPRETATION

- More than 60% of Vitamin D deficient patients are seen by majority of doctors
- Reasons for high percent is more awareness generated towards treating cardiovascular and diabetes through Vit-D supplementation

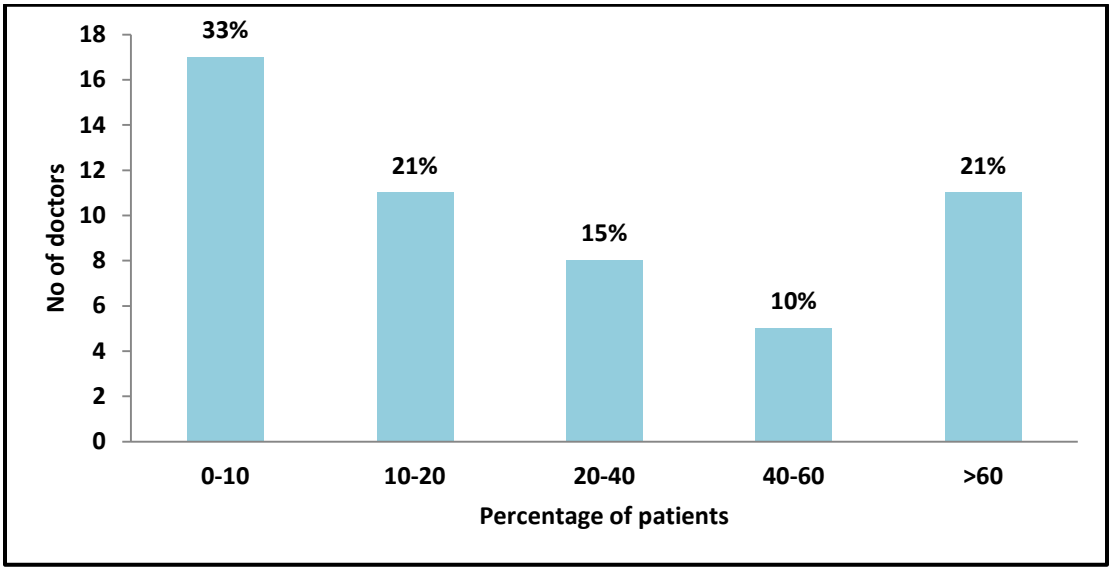
❖ Response of Neurologist



INTERPRETATION

- 26% of doctors see Vitamin D deficiency in 0-10% of patients per week
- Reason being the neurologists test the Vit- D levels in patients only under severe disease state and elderly population

❖ Response of Psychiatrist

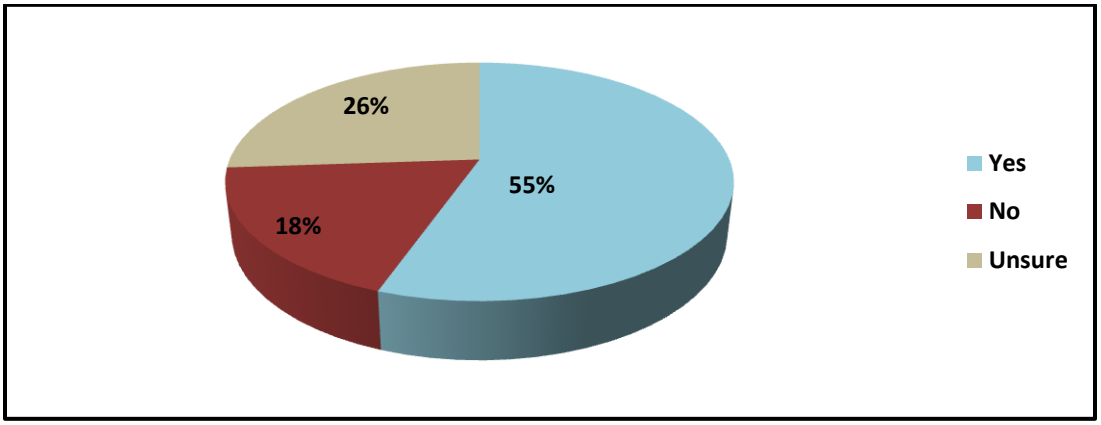


INTERPRETATION

- Majority of doctors see less than 10 % of Vitamin D deficient patients per week
- Reasons are low awareness level and psychiatric conditions manifesting from Vit-D deficiency in patient group

2. Is vitamin D deficiency associated with neurological and psychiatric illness?

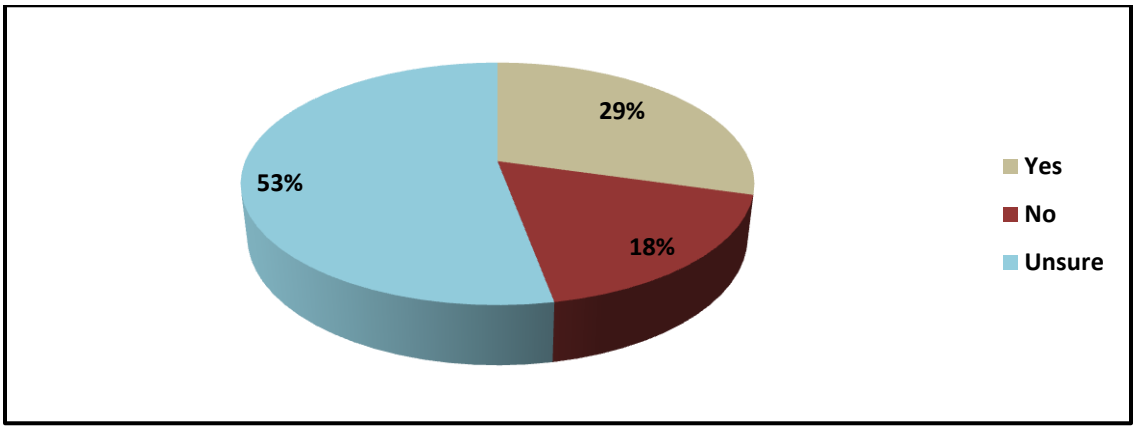
❖ **Overall Response**



INTERPRETATION

- Majority of doctors (51%) say that Vitamin D deficiency is related or can be one of the contributing factors in some of the neurological & psychiatric illness.
- On the other hand, a few doctors (19%) say that there exists no association between Vitamin D deficiency and neurological & psychiatric illness
- Therefore more than 45% of doctors are not much concerned towards Vit- D role in mental illness

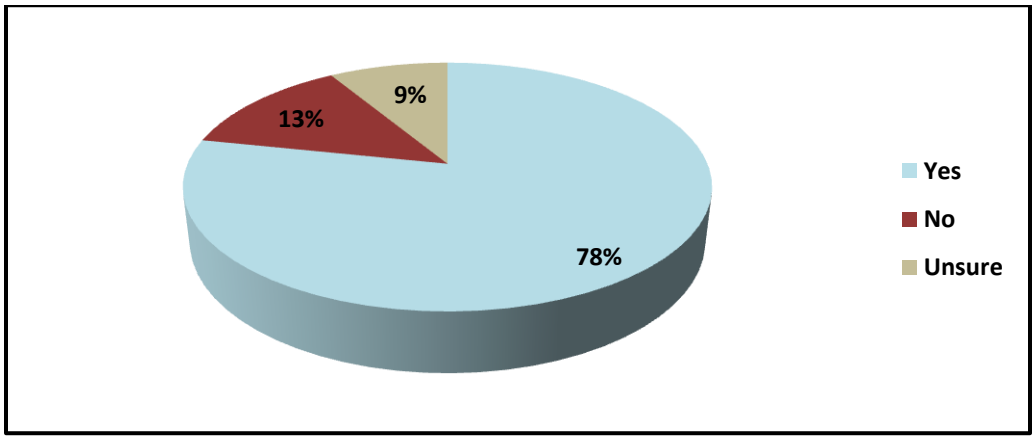
❖ **Response of Physician**



INTERPRETATION

- 53% of physicians are still unsure whether any kind of association exists between Vitamin D and neurological & psychiatric illness or not
- Reasons are they are more into direct symptomatic improving drugs rather than treating the underlying metabolic disorders

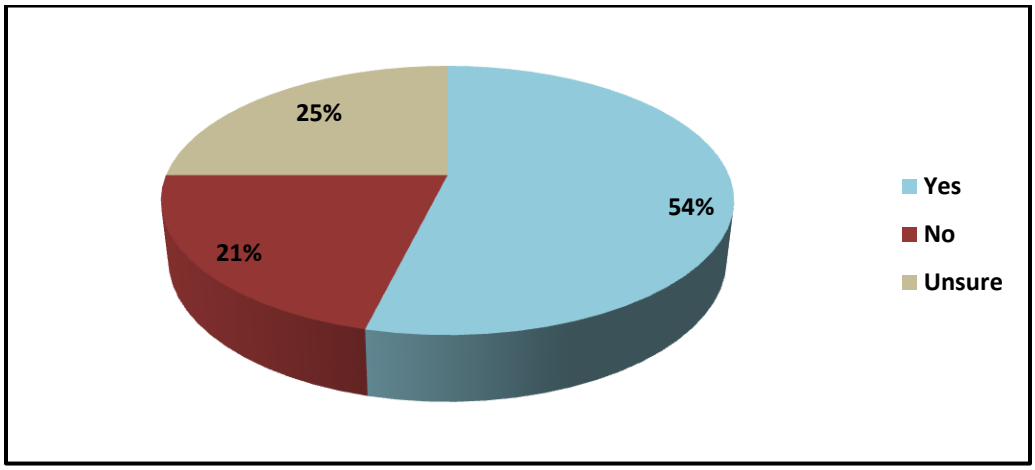
❖ Response of Neurologist



INTERPRETATION

- 78% of neurologists are in favour of the notion that their exists an association between Vitamin D and neurological illness
- This is heartening as there is scope and opportunity to build the future market with first mover advantage

❖ Response of Psychiatrist



INTERPRETATION

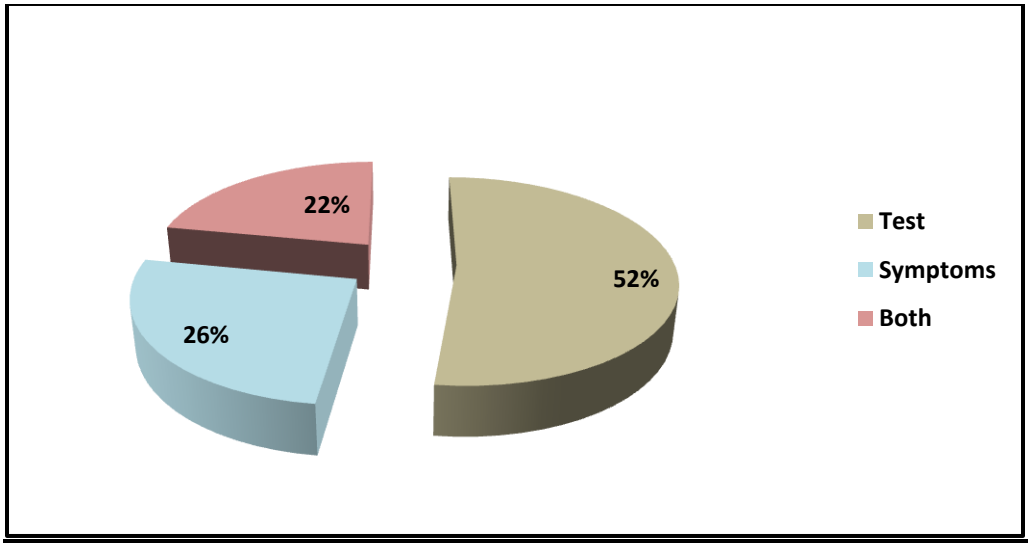
- 54% of doctors say that Vitamin D deficiency is associated with neurological &/or psychiatric illness
- This is good for building a new market in psychiatry where every patient gets treated with Vit-D deficiency and improving the treatment outcomes

3. **What are your views about the role of vitamin D in neurological and psychiatric illness?**

ROLE OF VITAMIN D

- Neuroprotective
- Involved in neuromuscular transmission and affects neuronal excitability
- Involved in cognitive function
- Immunomodulator
- Supplemental
- Slows down the progression of other diseases
- Alters brain chemistry
- Supportive role in relieving body symptoms
- No causal relationship
- Useful in co-morbid condition

4. **How do you diagnose the status of vitamin D in your patients?**



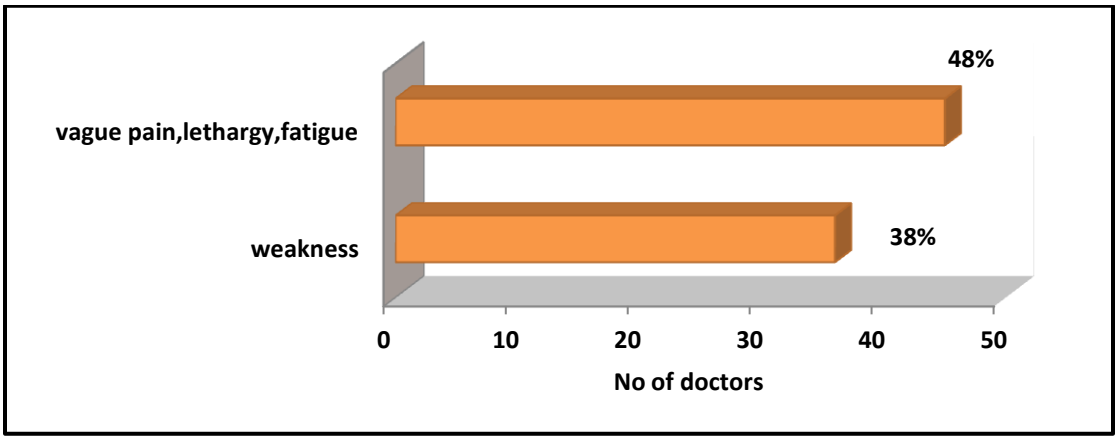
INTERPRETATION

- Maximum no of doctors (52%) diagnose the Vit- D levels in their patients through tests
- 26% of doctors determine it empirically
- 22% of doctors use both tests and symptoms to diagnose the Vit- D status

- There is greater need to have proper evaluation of Vit-D status to delay the disease progression

Please mention the symptoms seen-

❖ **Overall Response**

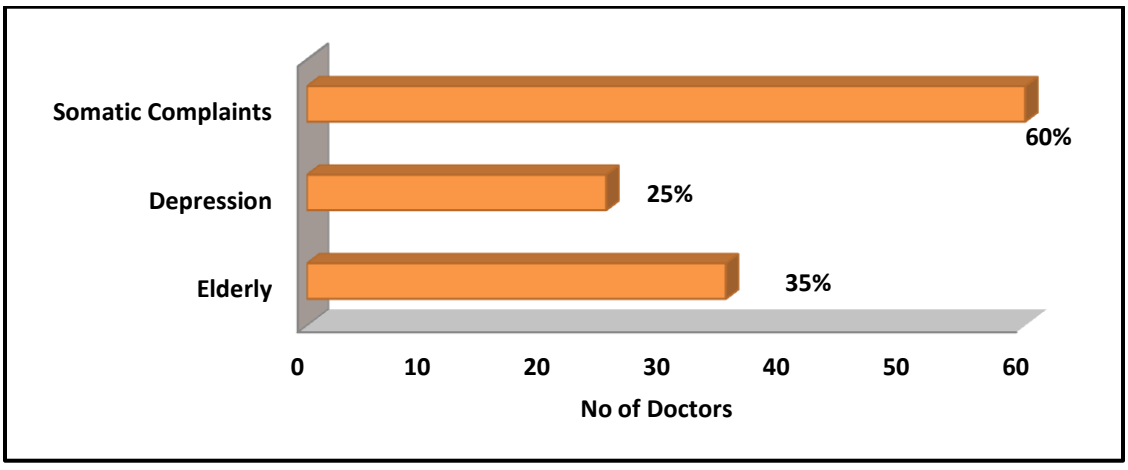


INTERPRETATION

- Majority of Vit-D deficient patients complain of vague pain, lethargy and fatigue
- These symptoms tend to aggravate in Multiple Sclerosis, Depression, Parkinson's and Myopathy and Schizophrenia

5. In which conditions do you recommend vitamin D level testing?

❖ **Overall Response**



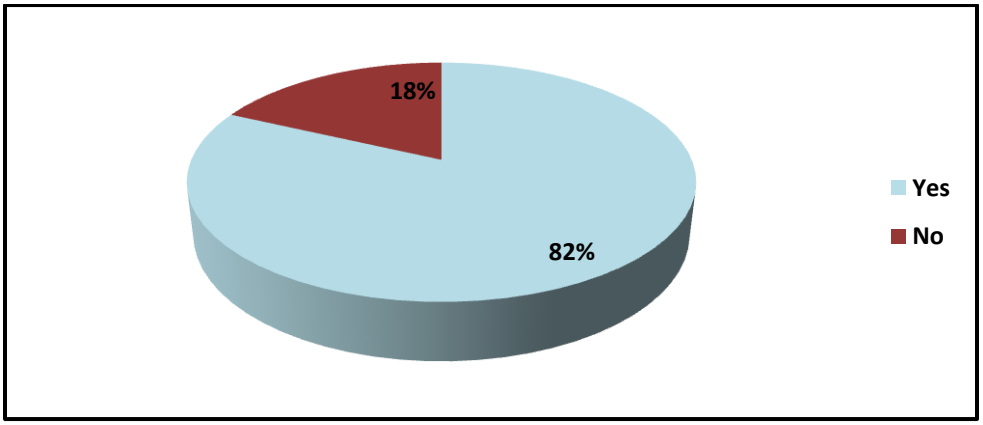
INTERPRETATION

- Majority of doctors test the Vitamin D levels of their patients when patients complain about bodyache, backache, extreme pain etc.

- It is too early to comment as many doctors are using Vit- D supplement as a fad or in cases where the patients are resistant to current treatment
- We have to build Vit-D as a serious treatment option in neurological & psychiatric illness

6. In your clinical practice, have you prescribed vitamin D in neurological &/or psychiatric disorders?

❖ **Overall Response**



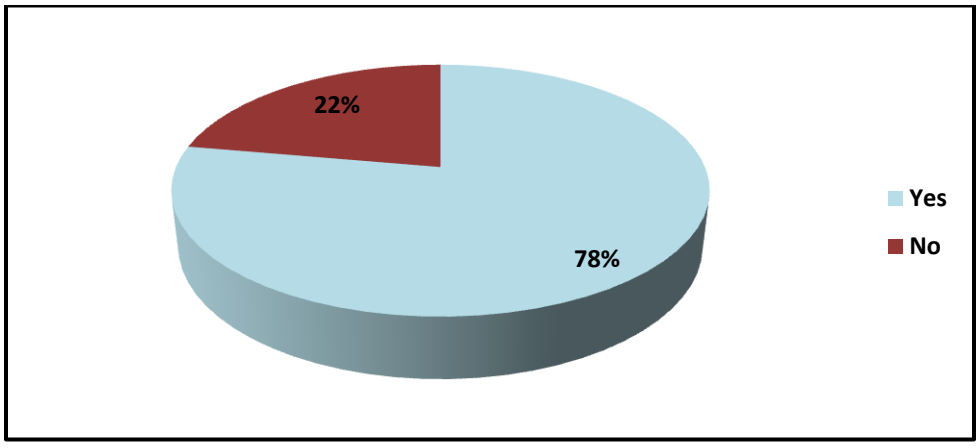
INTERPRETATION

- 77% of doctors have prescribed Vitamin D in neurological & psychiatric illness
- 17% of doctors have not yet prescribed it.

The most common reasons for non-experience are-

- No strong clinical evidence in this context
- Affordability

❖ **Response of Physician**



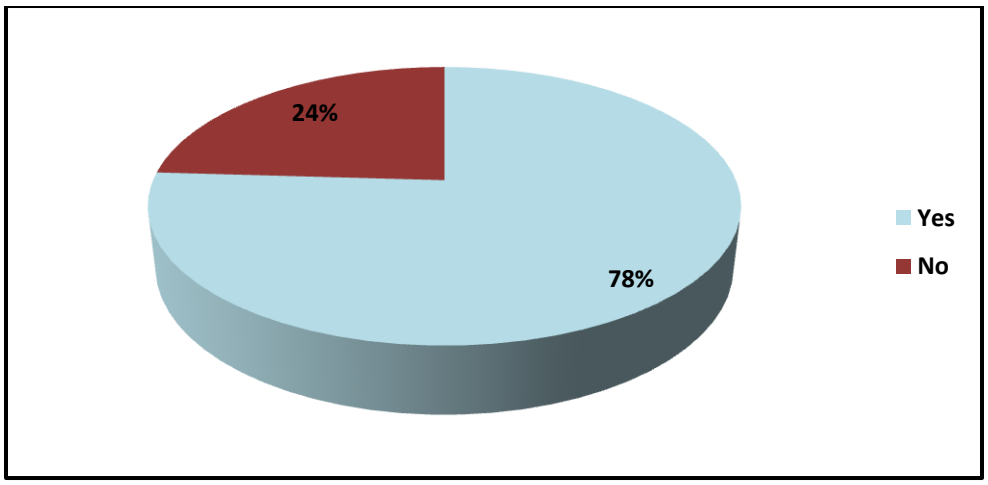
INTERPRETATION

- 78% of doctors have prescribed Vitamin D in neurological & psychiatric illness whereas 22% of doctors have not yet prescribed it
- They find better rationale for using Vit-D in their practice

❖ **Response of Neurologist**

- All the doctors prescribe Vitamin D in neurological illness specially neuropathy, myopathy and multiple sclerosis

❖ **Response of Psychiatrist**

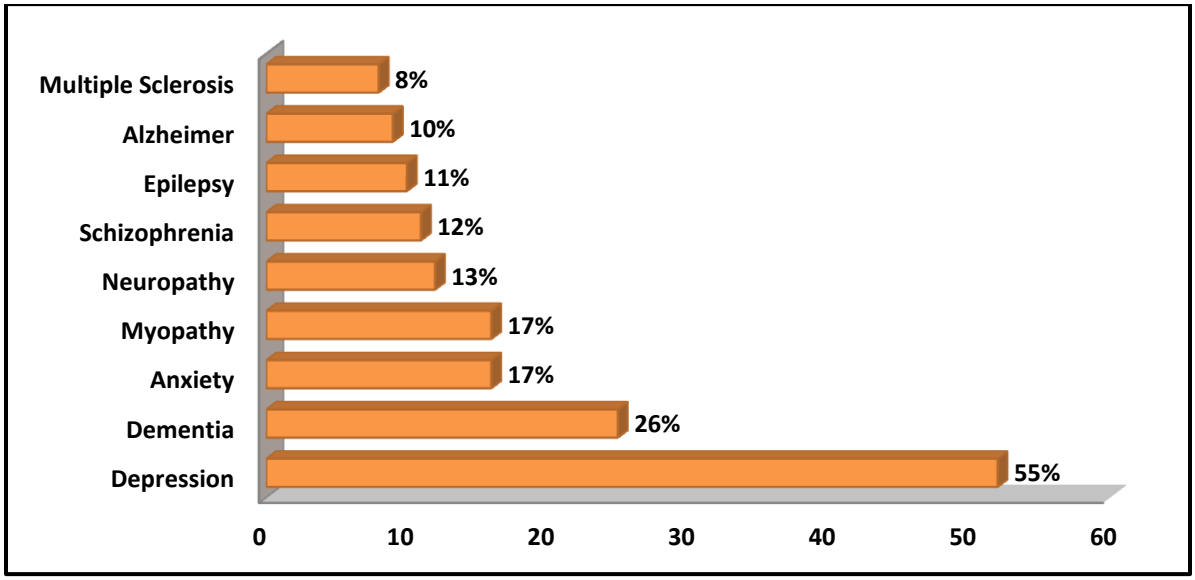


INTERPRETATION

- 78% of doctors prescribe Vitamin D in neurological & psychiatric illness whereas 24% do not prescribe.
- The no of prescriptions are less in comparison to the new cases they see every day

7. In which specific neurological &/or psychiatric indications have you prescribed vitamin D?

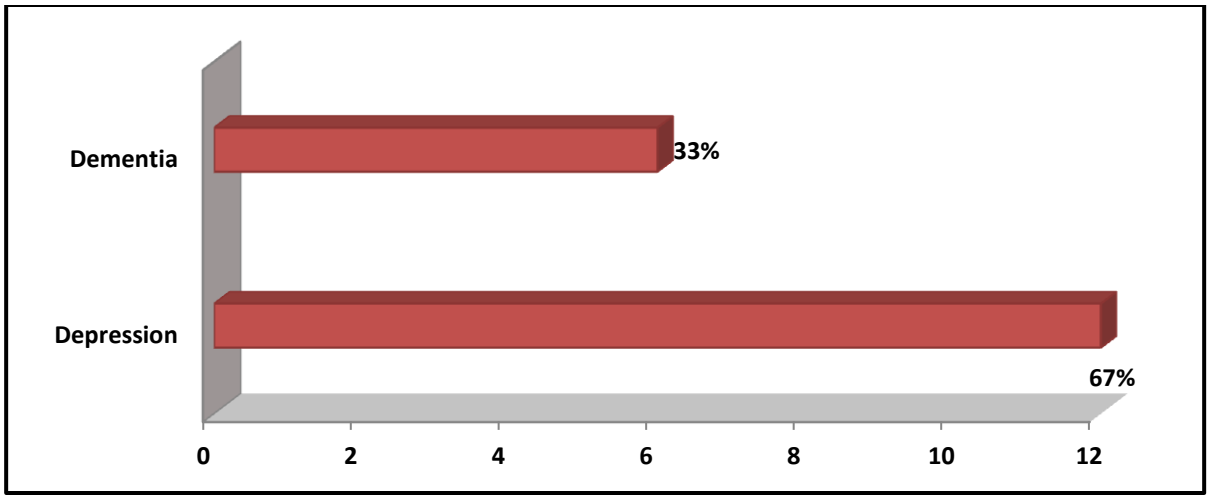
❖ **Overall Response**



INTERPRETATION

- Depression is the most common psychiatric indication, wherein the doctors have prescribed Vitamin D, followed by Dementia
- Myopathy is most common neurological indication, followed by neuropathy

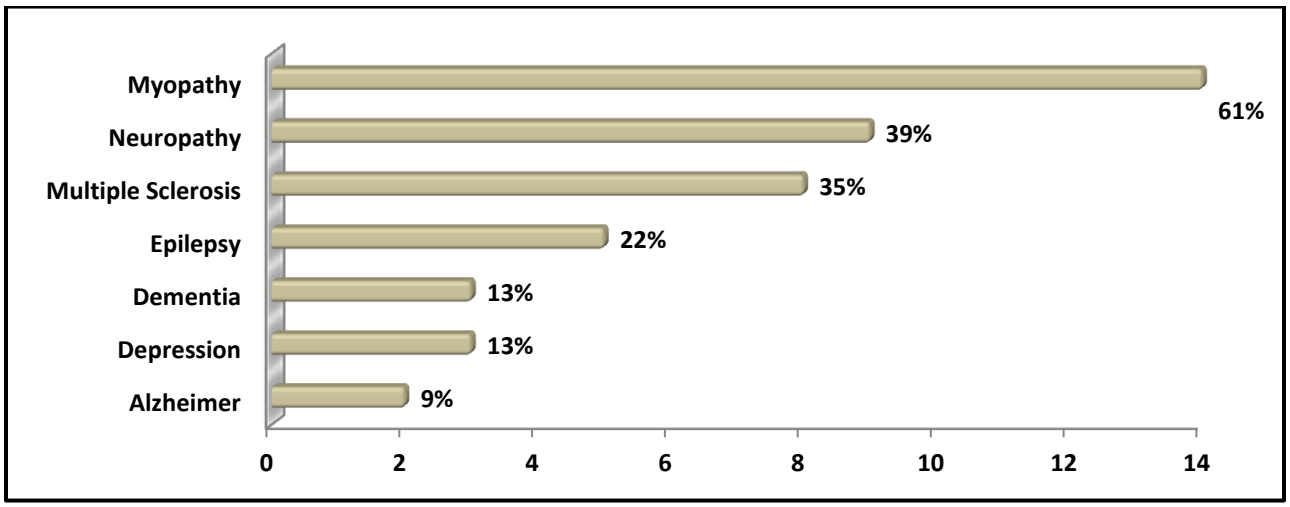
❖ **Response of Physician**



INTERPRETATION

- Depression is most common psychiatric indication where Vit-D is used by physicians

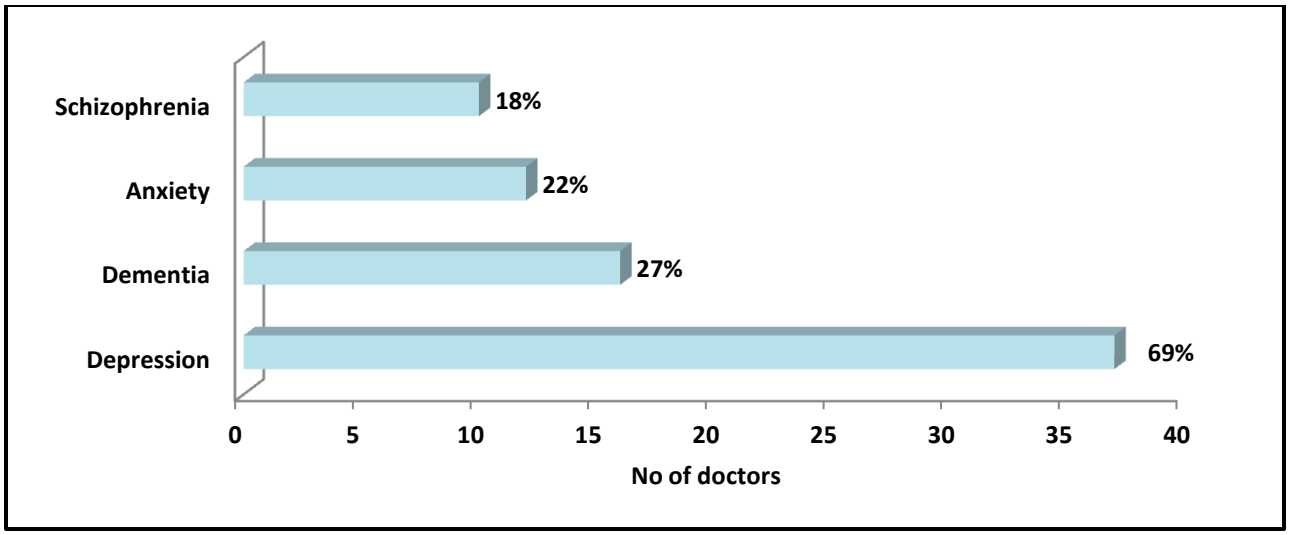
❖ **Response of Neurologist**



INTERPRETATION

- Majority of doctors prescribe Vitamin D in myopathy, followed by neuropathy and multiple sclerosis

❖ **Response of Psychiatrist**

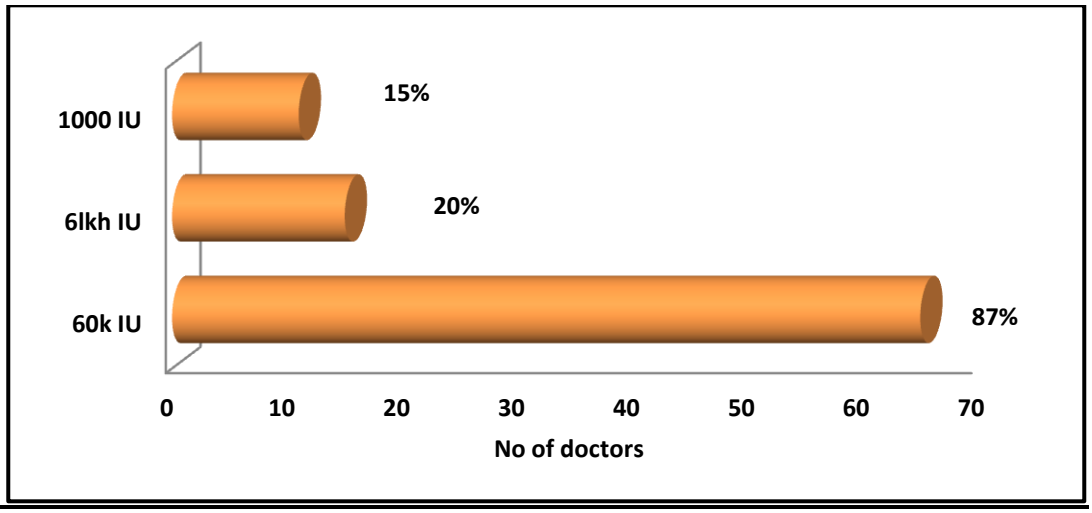


INTERPRETATION

- Depression is the major indication wherein doctors prescribe Vitamin D followed by dementia
- Other psychiatric indications include anxiety and schizophrenia

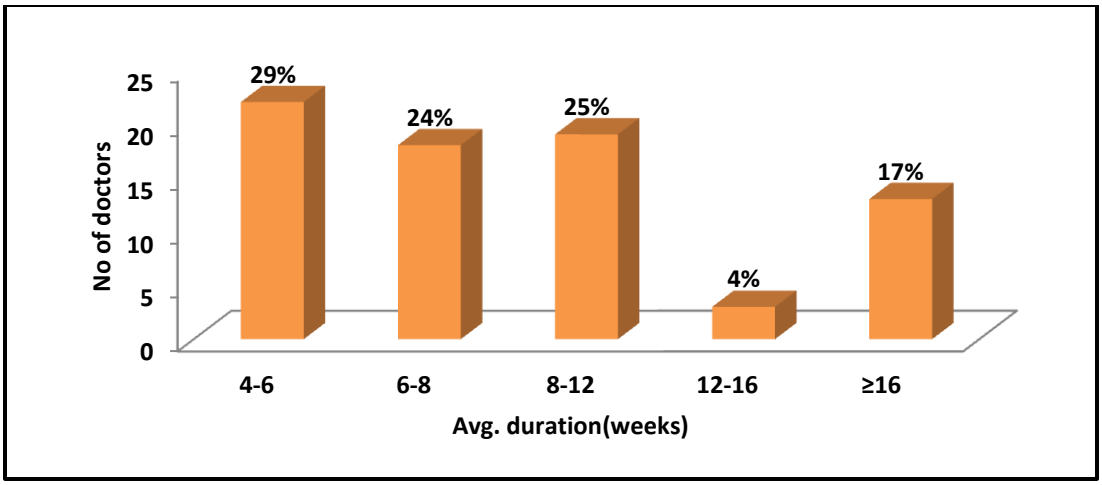
8. What is your preferred dosing and treatment duration of vitamin D therapy in above mentioned indications?

- **Overall Response**



INTERPRETATION

- 60K IU is the most preferred weekly dose
- Some doctors also prefer 60 lkh IU of Vitamin D administered through i.m route



INTERPRETATION

- 4-6 weeks is the most preferred duration of treatment for Vitamin D therapy
- Only a marginal difference exists between the doctors that prescribe Vitamin D for 6-8 weeks and 8-12 weeks
- Low doses are generally given for longer duration

9. What are the signs of improvement seen in patients after treatment with vitamin D?

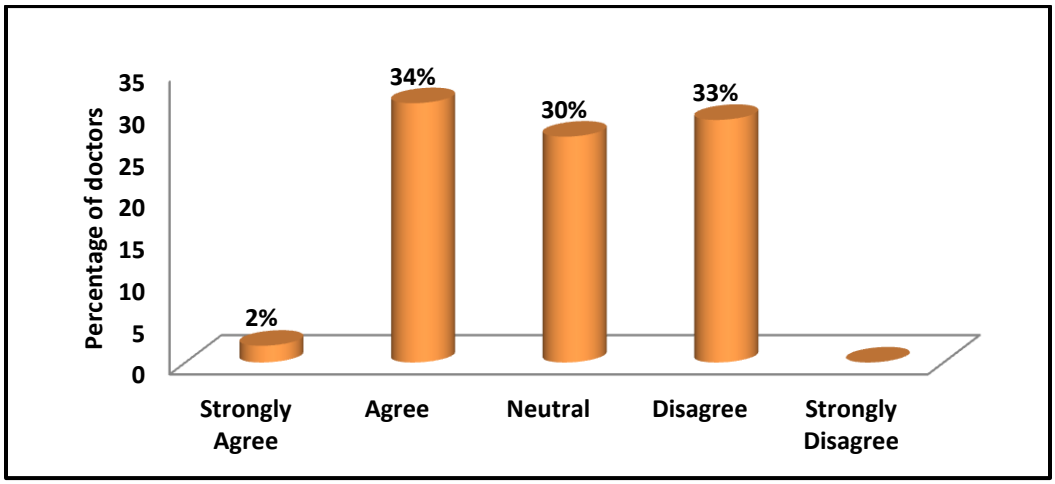
- Majority of doctors say that the physical well being of patient is improved after supplementation with Vitamin D
- Pain, fatigue decreases with Vitamin D therapy.
- Vitamin D brings about an overall improvement in patient condition
- Memory ,concentration and cognition improvement
- Better mood and alertness are seen as some other signs of better response

10. What place does vitamin D hold in treatment of neurological & psychiatric illness?

- Majority of doctors say that Vitamin D is used as a supplement in neurological &/or psychiatric illness
- Perceived as augmentative drug therapy to improve the efficacy of first line treatment

11. People with vitamin D deficiency are at high risk for disorders like Parkinson's, Alzheimer, Depression and Epilepsy.

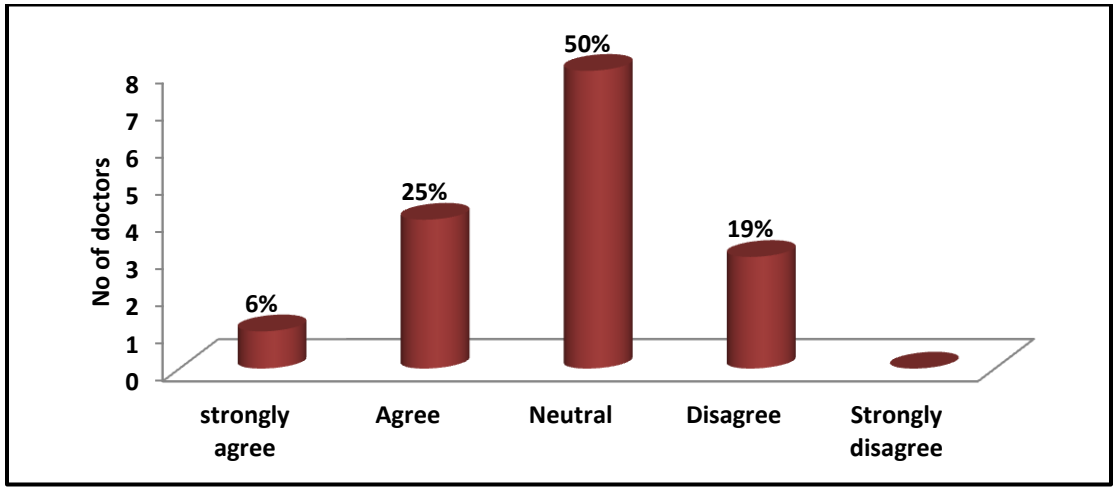
❖ **Overall Response**



INTERPRETATION

- An extreme response was seen from the doctors in context with the statement that people with Vitamin D deficiency are at high risk for disorders like Parkinson's, Alzheimer, Depression and Epilepsy.
- Vitamin D plays an important role in neurological & psychiatric illness, so the deficiency needs to be addressed

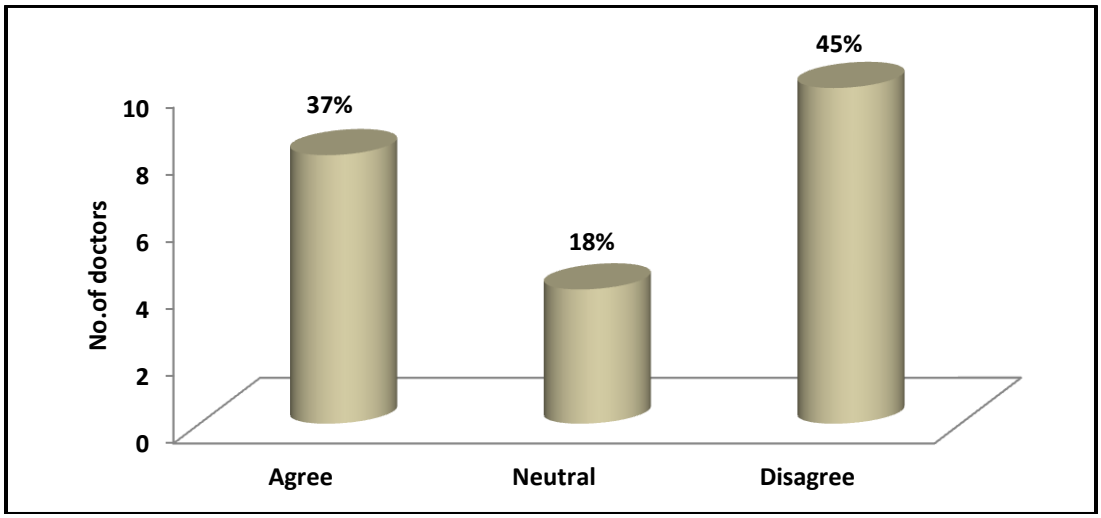
❖ **Response of Physician**



INTERPRETATION

- Physicians are not much aware regarding the role of Vitamin D in neurological & psychiatric illness
- They gave a generalized opinion about role of Vitamin D as they are not much aware

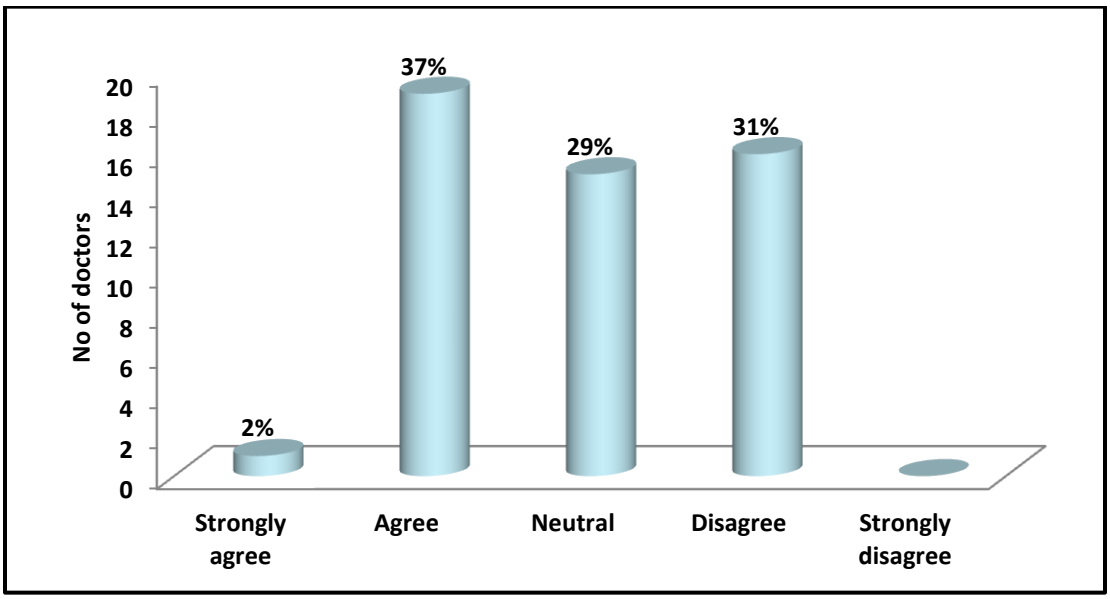
- **Response of Neurologist**



INTERPRETATION

- One-third of doctors agree to this point

- **Response of Psychiatrist**

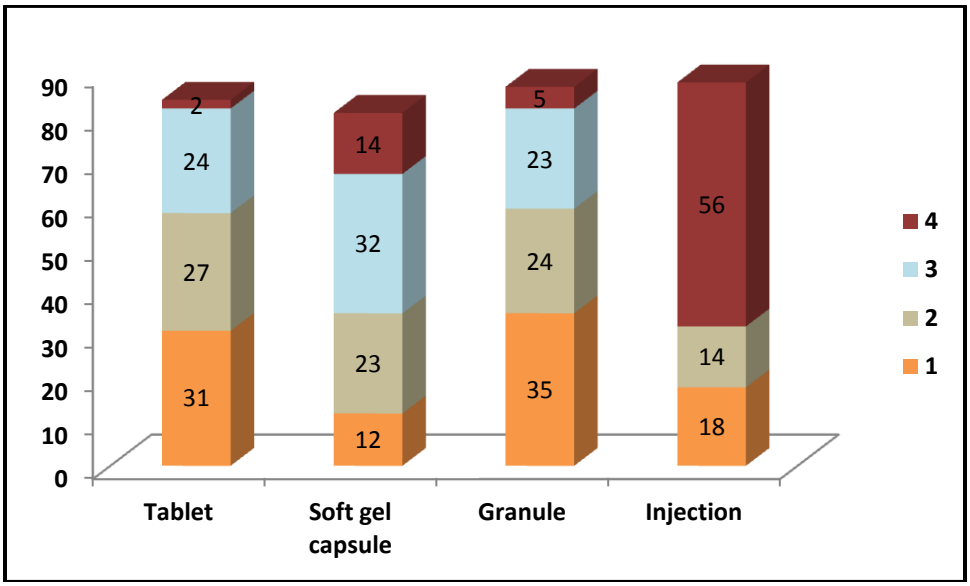


INTERPRETATION

- Majority of doctors agree that people with low Vitamin D levels are at high risk for developing psychiatric illness

12. Rank the following dosage forms on basis of your preferred treatment choice for vitamin D deficiency (1-highly preferred, 4-least preferred)

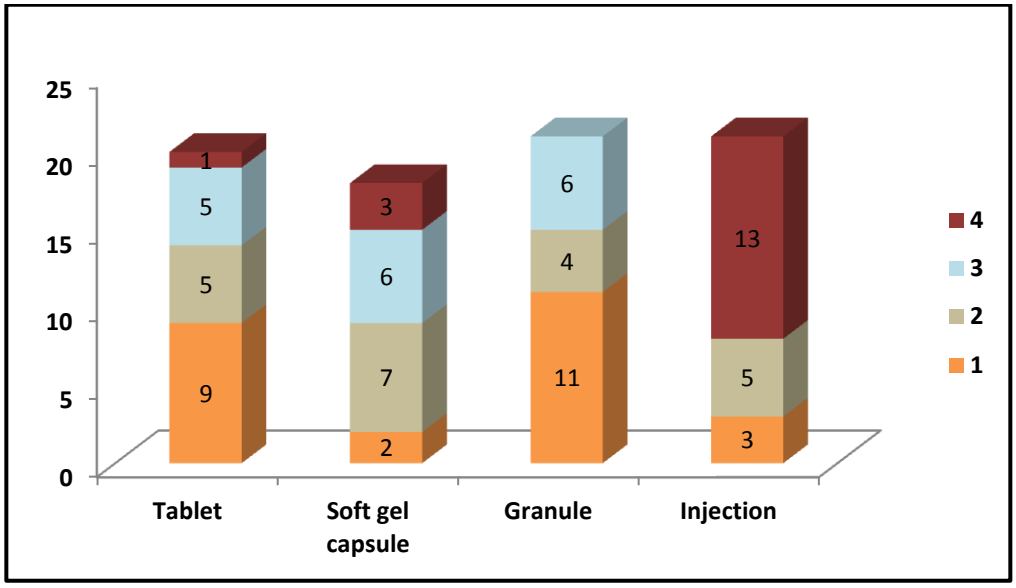
❖ **Overall Response**



INTERPRETATION

- Granules is the most preferred treatment choice for Vitamin D deficiency for majority of doctors. Advantages being
  - Patient compliance and easy to swallow
  - However it needs to be taken along with milk, which some doctors find difficult to explain
- Tablets are 2nd most preferred dosage form.
  - Patient compliance is one of the contributing factors for preference
- Soft Gel capsules are 3rdpreferred option
- Injection are the least preferred ones. Since they are quite painful, so patients avoid taking it.So used sparingly in highly treatment resistant cases

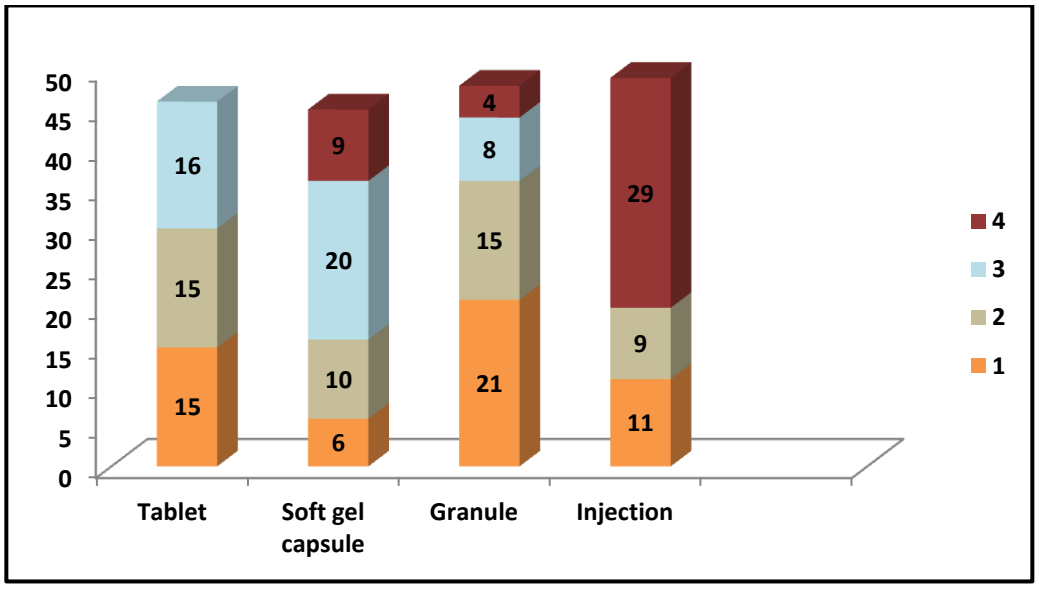
❖ **Response of Neurologist**



INTERPRETATION

- Granule is the preferred choice of dosage form
- Tablets are 2nd most preferred dosage form

❖ **Response of Psychiatrist**

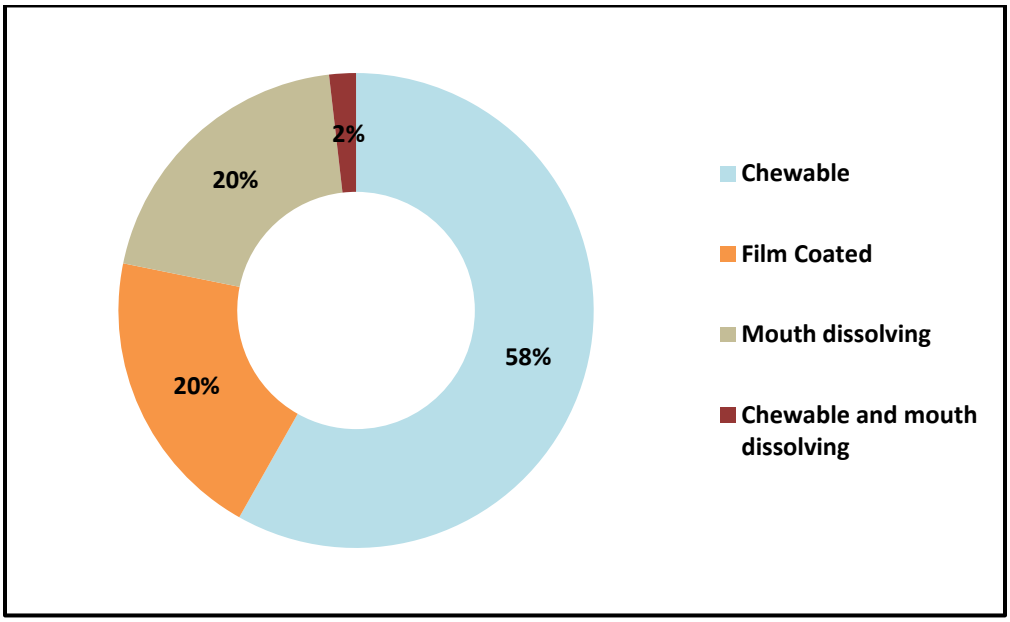


INTERPRETATION

- Granule is the most preferred dosage form
- It is followed by tablet

13. In case of tablets, what is your preferred choice?

❖ **Overall Response**

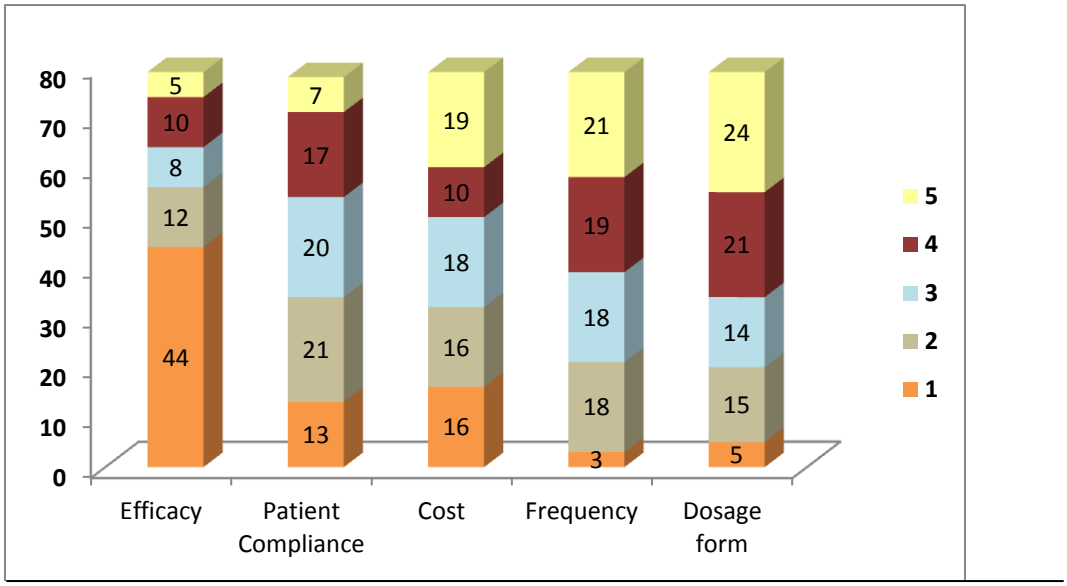


INTERPRETATION

➢ Chewable Tablet is a highly preferred choice of doctors for the treatment of Vitamin D deficiency where mouth dissolving has an edge

14. Rank the following parameters according to their importance, while choosing a particular vitamin D formulation (1-most important, 5-least important)

❖ **Overall Response**



INTERPRETATION

- A large percentage of doctors say that efficacy is an extremely important parameter that should be considered while choosing Vitamin D
- Next is patient compliance .Therefore formulation matters
- Cost factor also needs to be taken into consideration since Vitamin D is mostly given as a supplement .So that the overall treatment is not expensive to patient

RECOMMENDATIONS

❖ MARKET SEGMENTATION

➢ IDENTIFICATION OF MARKET SEGMENT

1. Secondary research
   The clinical studies suggested that vitamin D can be associated in some of the neurological & psychiatric illness. Also supplementation with vitamin D was found to be beneficial in indications like depression, seasonal affective disorder, epilepsy and multiple sclerosis.
2. The opinion of potential customers (i.e. neurologists, psychiatrist and physicians) was taken in context with the clinical findings by means of surveys.
3. In the CNS segment, vitamin D market is an untapped market. So a good opportunity lies ahead.

➢ PROFILE OF RESULTING SEGMENTS

Therefore vitamin D can be segmented in 3 different segments-

- ✓ Neurologists
- ✓ Psychiatrist
- ✓ Physician

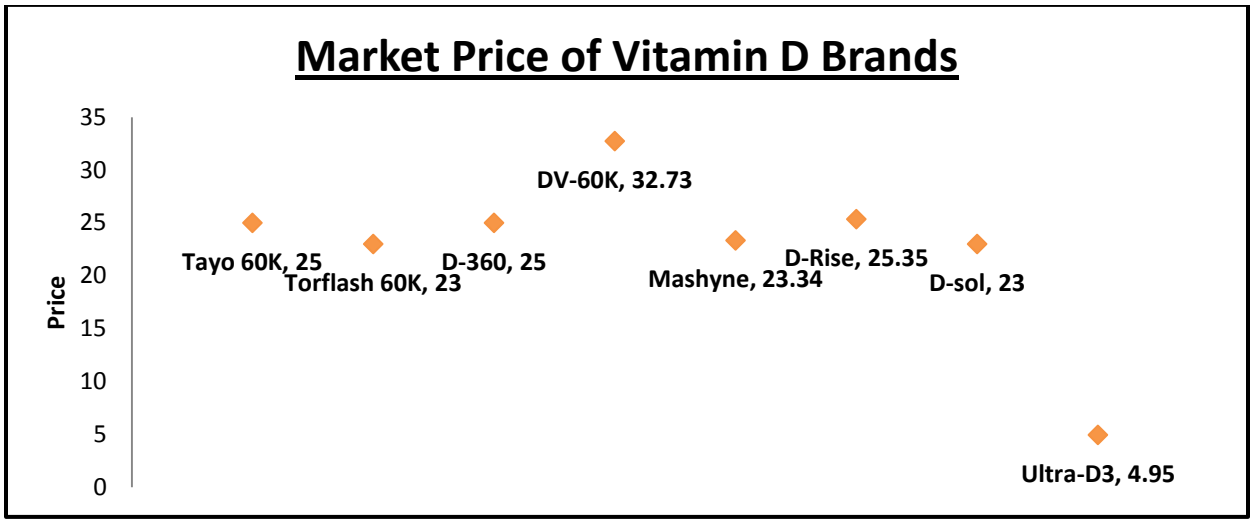
❖ MARKET TARGETING-

The below mentioned indications should be targeted specialty wise.

NEUROLOGIST	PSYCHIATRIST	PHYSICIAN
• Neuropathy • Myopathy • Multiple Sclerosis	• Depression • Dementia • Anxiety	• Depression • Dementia • Myopathy

❖ MARKET MIX FOR TARGET SEGMENT

- **Product**- Plain vitamin D
- **Price**-Primitive pricing should be done



We have to build our own brand perception window with better formulation and premium pricing which translates better perceived value by doctors and patients

➢ Promotion

Neurologist

1. Opportunity for Vitamin D with neurologist is very high as majority of the doctors were aware about its role in neurological disorder.

2. Clinical evidence needs to be distributed among neurologist to convince them regarding the usage of Vitamin D.

Psychiatrist

According to findings, some of the doctors were not aware about role of vitamin D in psychiatric disorders. To overcome this problem-

- Continuing medical education programs should be conducted
- Clinical evidence regarding role of Vitamin D in psychiatric disorders should be distributed.

Physician

1. In case of physicians, an aggressive promotion needs to be done since the level of awareness regarding the role of Vitamin D in neurological & psychiatric illness is very low. Most of them prescribe Vitamin D in cardiovascular and other general indications.

2. A booklet of research articles should be distributed in order to create awareness.

3. Also since they prescribe Vitamin D in different indications, an overall benefit of Vitamin D in different indications can be promoted rather than focusing only on its role in neurological and psychiatric disorder.

4.Large interactive programs to discuss on Vit-D role in neurological and psychiatric disorders.

5.Build KOL club who can built positive perception of Vit-d usage and share their own experience through clinical cases.

❖ COMPETITIVE POSITIONING

1. Better formulation through better technological advancement over others in crowded Vit-D market.
2. Build the market through awareness and various activities.
3. For the first year we should look at educating doctors on Vitamin D rather than conversion.
4. Create our own competitive advantage which others would find difficult to follow.

QUESTIONNAIRE

Doctor's name -_____ **Specialty -**_____

Place - _____

Dear Doctor,

I, **Manisha Rathore,** student from **IIHMR,** Jaipur am doing a survey on **"*Role Of Vitamin D In Neurological & Psychiatric Illness*"** as part of my market research project. Your opinion will be valuable for the completion of this project.

1. In your clinical practice, how much percentage of patients do you see with vitamin D deficiency in a week?

☐ 0-10 ☐ 10-20 ☐ 20-40 ☐ 40-60 ☐ >60

2. Is vitamin D deficiency associated with neurological and psychiatric illness?

☐ Yes ☐ No

3. What are your views about the role of vitamin D in neurological and psychiatric illness?

_____

4. How do you diagnose the status of vitamin D in your patients?

☐ Test ☐ Symptoms

Please mention the symptoms seen-_____

5. In which conditions do you recommend vitamin D level testing?

_____

6. In your clinical practice, have you prescribed vitamin D in neurological &/or psychiatric disorders?

☐ Yes ☐ No

If No, then what are the reasons for non-experience _____

7. In which specific neurological &/or psychiatric indications have you prescribed vitamin D?

1._____ 3._____ 5._____

2._____ 4._____ 6._____

8. What is your preferred dosing and treatment duration of vitamin D therapy in above mentioned indications?

Sr no	1.	2.	3.	4.
Dosage				
Avg Duration				

9. What are the signs of improvement seen in patients after treatment with vitamin D?

10. What place does vitamin D hold in treatment of neurological &/or psychotic illness?

☐ Refractory ☐ Supplement

11. People with vitamin D deficiency are at high risk for disorders like Parkinson's, Alzheimer, Depression and Epilepsy (Please tick the preference)

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

12. Rank the following dosage forms on basis of your preferred treatment choice for vitamin D deficiency (1-highly preferred, 4-least preferred)

Dosage form	Ranking	Reasons for preference
Tablet		
Soft gel capsule		
Granules		
Injection		

13. In case of tablets, what is your preferred choice?

☐ Chewable ☐ Film-coated ☐ Mouth dissolving

14. Rank the following parameters according to their importance, while choosing a particular vitamin D formulation (1-most important, 5-least important)

Parameter	Ranking
Efficacy	
Frequency	
Dosage form	
Cost	
Patient compliance	

15. Are you satisfied with the current formulations of vitamin D, regarding absorption and patient compliance?

☐ Yes ☐ No

If No, then please mention the unfulfilled needs_____

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