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Recent Therapeutics Approaches in the Treatment of Epilepsy

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Nikhil S. Ekhande[1*]; Mayuri H. Padwal[1]; Darshana A. Motwani[1]; Bhavana B. Choudhary[1]

1. Student, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, Dr. D.Y. Patil Educational Complex, Sector No. 29, Pradhikaran, Akurdi, Pune, Maharashtra, India 411044.

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ABSTRACT

Purpose of this Research Article is to know about the new treatment of epilepsy. The hallmarks of epilepsy include an enduring (i.e. persistent) propensity to cause seizures, unprovoked by any immediate injury to the central nervous system, as well as the neurobiologic, cognitive, psychological, and social effects of seizure recurrences. In this article epilepsy's introduction, epidemiology, etiology, types of epilepsy pathophysiology, old treatment & their pharmacological action, drug target, SV_2A Proteins are reviewed in this article. Introduction to new drugs LCM: Lacosamide; PER: Perampanel; OXC: Oxcarbazepine; VGB: Vigabatrin; RFM: Rufinamide; LEV: Levetiracetam; LTG: Lamotrigine; TPM: Topiramate; GBP: Gabapentin are been researched and discussed along with its pharmacological action, clinical trails & adverse effect.

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INTRODUCTION:

Epilepsy is known as one of the oldest brain disorders. Epilepsy word derived from Greek word meaning," a condition of being overcome, seized, or attacked. "It was referenced more than 2,000 years ago and is mentioned in the Bible, the Koran, and ancient papyri and Vedic manuscripts [1][2]. Epilepsy was once thought to be a "demonic possession" or "scared disease" since it was thought that the "falling sickness" was brought on by an angel or demon [3]. It is one of the most prevalent major neurologic disorders, epilepsy affects up to 1% of the population, placing it second only to stroke in terms of prevalence. Epilepsy affects over 50 million people worldwide, 90% of whom are from developing nations [4]. A person with epilepsy experiences frequent seizures (convulsions) throughout time. Seizures are bursts of abnormal brain activity that alter behaviour or attention [5]. A chronic neurologic illness known as epileptic disorder is characterised by repeated epileptic seizures. Epilepsies are those conditions which includes chronic recurrent epileptic seizures that can be considered epileptic disorders. An epileptic seizure is manifestation(s) of epileptic (excessive and/or hypersynchronous), usually self-limited activity of neurons in the brain [6]. Phenytoin (PHT), phenobarbital (PB), carbamazepine (CBZ), valproic acid (VPA), zonisamide (ZNS), and clobazam are the most frequently used first-generation AEDs (CLB). ZNS is a medication that is categorised as second-generation in North America and Europe. Eslicarbazepine acetate and lacosamide (LCM), two recently delivered drugs, are included in the third generation of medication.

AEDs from the post-second generation are also referred to as new AEDs. In Japan, the oral distribution of gabapentin (GBP), topiramate (TPM), lamotrigine (LTG), levetiracetam (LEV), and rufinamide (RFN) as add-on therapy was authorised in 2006. The Japanese Ministry of Health, Labour, and Welfare is considering approving vigabatrin (VGB), oxcarbazepine (OXC), perampanel (PER), and LCM.

Epidemiology:

One of the most prevalent severe neurological disorders is epilepsy [7]. Worldwide, epilepsy affects people of all ages and genders. Men have a somewhat higher incidence and prevalence of epilepsy than women [8]. The disparity may be accounted for by the various prevalence of the most frequent risk factors and the concealment of the condition in women for sociocultural reasons in some places [9].

The incidence of epilepsy is higher in the youngest and oldest age groups [8], with estimates of 86 per 100,000 per year in a well-defined population in infancy, a trend toward decline to about 23-31 per 100,000 in people aged 30- 59 years, and a subsequent increase up to 180 per 100,000 in the over 85 age group [10]. Both in children and adults, focal seizures are more common than generalised seizures. The prevalence of these clinical conditions will decline as the preventable causes of epileptic seizures, which primarily include prenatal and perinatal injuries, CNS infections and infestations, traumatic brain injury, and stroke [11], are better controlled, but aging-related diseases, particularly CNS tumours and dementias like Alzheimer's disease and other forms of dementia, will rise.Epilepsy patients have a higher mortality risk than the general population [12].

The standard mortality ratio in the HIC ranges from 1.6 to 3.0. [12].The comparable ratio for LMIC is 19.8 (95% CI 9.7-45.1) [13]. Epilepsy continues to be a significant cause of disability and mortality despite a decline in the disease burden. If used in epidemiological research, the new definition of epilepsy which now includes a sizable percentage of instances of single unprovoked seizures,will have an impact on future rates of incidence, prevalence, and mortality of epilepsy.

Etiology:

The cause of epilepsy is completely unknown. Episodes of aberrant brain electrical activity are what cause these seizures. Epileptogenesis is the process through which epilepsy emerges in a brain that is otherwise healthy. The causes of epilepsy include head trauma, brain tumours, birth abnormalities, stroke, meningitis, encephalitis, and occasionally even changed levels of substances like salt or blood sugar [14]. For instance, not everyone who has a severe head injury, which is a known trigger for seizures, will go on to acquire epilepsy [15]. Although putative seizure triggers appear to vary in strength, a known epileptic diagnosis tends to mask the distinctions. Seizures in reflex epilepises could also be triggered by sensory, motor or cognitive stimuli, such as bright lights, music, alcohol, febrile illness, heat stress etc. [16].

However, to summarize in all there are various epilepsy causes that are prevalent in various age groups, including:

1. In the neonatal period and early infancy, the most prevalent causes are metabolic disease, congenital CNS anomalies, trauma, hypoxic-ischemic encephalopathy, and CNS infections.

2. The most frequent febrile seizures in late infancy and early childhood may be brought on by CNS infections and trauma.

3. Clearly defined epilepsy syndromes are typically seen in children.

4. The causes are more likely to be secondary to any CNS lesion in adolescence and adulthood.

5. The most frequent cause of dementia in older people is cerebrovascular illness; additional reasons include CNS tumours, head trauma [17].

Types of epilepsies:

Epilepsies are to be divided into three levels, according to the ILAE (International League Against Epilepsy).

Seizure kinds, epilepsy types, and epileptic syndromes are grouped under these headings.

The ILAE emphasises that the new classification system for seizures is founded on clinical rather than pathological factors. The classification system separates seizures into focal and generalised onsets. Focal retained or impaired awareness seizures are subtypes of focal onset seizures.A focal seizure that begins as a fear feeling and progresses to focal clonic activity is still referred to as a focal emotional seizure. Focal seizures that afterwards generalise are now referred to as focal to bilateral tonic-clonic seizures. The terms "secondarily generalisation" and "secondary generalisation" are dropped in favour of only referring to seizures with generalised onset as "generalised." Additionally, there are a number of descriptive words for both motor and non motor generalised onset seizures. They involve absence with eyelid myoclonia, myoclonic absence, myoclo-nicetoniceclonic, myocloniceatonic, and epileptic spasms.

Now discussed classification was about seizures types, further according to epilepsy types it is classified into four main types:

- Focal
- Generalized
- Combined generalized and focal
- Unknown.

The sort of seizure that occurs during an epilepsy is used to categorise it. A generalised epilepsy is an epilepsy with a generalised seizure, whereas a focal epilepsy is an epilepsy with a focused seizure. An epilepsy with both focal and generalised seizures is referred to as a combination generalised and focal epilepsy. The term "unknown" epilepsy refers to epilepsy in which the onset type of the seizures is unknown or in which the clinician has not yet gathered enough clinical data to be certain of the epilepsy classification. The diagnosis of epilepsy syndrome represents the third level of the new classification. A grouping of distinct characteristics, including clinical presentation, particularly the age of onset and natural history, seizure patterns, EEG, and neuroimaging abnormalities, is known as an epileptic syndrome. Epilepsy syndrome diagnosis is crucial since it affects prognosis and treatment. Lennox-Gastaut Syndrome, West Syndrome, Dravet Syndrome, etc. are recognised epilepsy syndromes [18].

Pathophysiology:

Paroxysmal manifestations of the cerebral cortex are seizures. When the excitatory and inhibitory forces within the network of cortical neurons suddenly become unbalanced, seizures follow. A cell membrane that is unstable, or one that is close to or around an unstable cell membrane, is where the basic physiology of a seizure episode is found. Any cortical or subcortical location in the grey matter is where the seizure starts. At first, only a few neurons fire improperly. A focal seizure is caused by the breakdown of inhibitory synaptic current, normal membrane conductance, and excess excitability spreading locally or more broadly to cause a generalised seizure. This onset spreads through physiological pathways to affect nearby and far off locations. A seizure may be brought on by Abnormalities in potassium conductance, voltage activated ion channel defects, or deficiencies in the membrane ATPases involved in ion transport. The excitability and propagation of neuronal activity are enhanced by some neurotransmitters, such as glutamate, aspartate, acetyl choline, norepinephrine, histamine, corticotropin releasing factor, purines, peptides, cytokines, and steroid hormones, whereas GABA and dopamine inhibit neuronal activity and propagation. The demand for blood flow to the brain increases during a seizure in order to remove. CO_2 and provide substrate for the metabolic activity of the neurons. As the seizure lasts longer, the brain experiences more ischemia, which may cause neuronal death and brain damage [19]. Some kinds of epilepsy may be caused by mutations in various genes. Generalized epilepsy and infantile seizure syndrome have been linked to genes that produce voltage-sensitive and ligand activated ion channel protein subunits [20]. One proposed

mechanism for some types of inherited epilepsy is mutation of the genes that code for sodium channel proteins; these defective sodium channels remain open for long periods of time and cause the neurons to be overly excitable as a result; glutamate, an excitatory neurotransmitter, may be released in large amounts from the neurons; this, in turn, may trigger excessive calcium (Ca ++) release in the post synaptic cells, which may be neuron, by binding with the nearby glutamanergic [21].

Treatment

Pharmacological Action:

Eliminating the underlying cause, such as addressing an underlying infection or metabolic disorder, is the primary method of treating induced seizures [22]. Two unprovoked seizures that are more than 24 hours apart constitute epilepsy, which is normally treated with medication to stop subsequent seizures. Numerous antiepileptic drugs have been produced and utilised since the first anticonvulsant bromide was introduced in 1857. Currently, 29 different antiepileptic drugs are offered in the US. Some of these drugs, such as carbamazepine and oxcarbazepine, are more effective at treating focal onset seizures than primary generalised seizures. These drugs also include benzodiazepines, lamotrigine, levetiracetam, topiramate, valproic acid, and zonisamide. In different types of epilepsy and epileptic syndromes, only a small number of drugs have level A evidence, whereas the majority of medications have lower-level evidence. Levetiracetam, zonisamide, carbamazepine, and phenytoin all showed level A evidence in the recent review of antiepileptic drug efficacy and effectiveness as initial monotherapy conducted by the international league against epilepsy, but only oxcarbazepine was shown to have level A evidence in children with partial onset seizures. In children with absence seizures, valproic acid and ethosuximide also show level A efficacy and effectiveness. Despite the fact that many treatments have level C and D evidence, other forms of primary generalised epilepsy lack unambiguous level A proof [23]. In order to select an effective medicine while minimising side effects, neurologists choose pharmaceuticals to treat seizures after taking evidence of effectiveness/ efficacy, seizure classification, potential adverse effects, concomitant conditions, age, and gender into account [22] [23] [24]. In contrast to lamotrigine and levetiracetam, varproic acid has been demonstrated to dramatically increase the risk of serious foetal deformity in women of reproductive age. Antiepileptic drug use over an extended period of time can weaken bones. Certain drugs that stimulate the production of

hepatic enzymes have a propensity to cause additional drug interactions and may be problematic in other co-morbid illnesses that call for anticoagulation, anti-tumoral, or Anti-HIV medication. The mood can be impacted by some antiepileptic medications. Compared to lamotrigine and valproic acid, levetiracetam is more likely to cause some irritation, depression, and other mood disturbances, some drugs, including topiramate and valproic acid, are effective at treating migraine headaches [22] [23] [24]. One third of epilepsy patients still experience medically refractory seizures despite being treated with one of 29 different antiepileptic drugs [25].

Drugs used for treatment of Epilepsy

Clobazam	Carbamazepine	Clonazepam
Acetazolamide	Valproic Acid	Vigabatrin
Clorazepate	Diazepam	Eslicarbazepine
Ezogabine	Ethosuximide	Fosphenytoin
Felbamate	Lamotrigine	Levetiracetam
Lorazpeam	Lacosamide	Phenobarbital
Phenytoin	Pregabalin	Primidine
Gabapentin	Topiramate	Rufinamid
Tiagabine	Oxcarbazepine	Retigabine
Zonisamide	Perampanel	

Non pharmacological:

A failure of adequate trials of two tolerated and carefully selected antiepileptic medication schedules with adequate doses is referred to as medically intractable or refractory epilepsy [26]. For people with uncontrollable epilepsy, other non-pharmacological treatment options are epilepsy surgery, neurostimulation therapy, and dietary therapies such the ketogenic diet can all be taken into account. Surgery for epilepsy may involve hemispherectomy, repeated subpial transections, anterior corpus callosotomy, or focused respective surgery. The responsive neurostimulator (RNS), vagal nerve stimulation (VNS), and other experimental neurostimulation therapies are also used. Patients with medically uncontrollable seizures who are candidates for epilepsy surgery typically have a recognizable seizure focal. This allows for resection. Patients with focal onset epilepsy have an effective and secure alternative treatment option in epilepsy surgery epilepsy [27] [28] [29]. Significant side effects after

epilepsy surgery are ,Long-term permanent deficits occur less frequently—less than 2% of the time—and subdural electrode evaluations are far less common—less than 7% [29] [30]. In order to confirm the diagnosis and kind of focal onset epilepsy, identify the seizure type and seizure onset zone, and ascertain the debilitating effects of ictal behaviour, an epilepsy surgery evaluation often begins with long-term video-EEG monitoring [28] [31]. To further understand the brain, several neuro-radiological imaging techniques are used to decide whether the epileptogenic lesion is structural or functional. Numerous researches have demonstrated that there are different outcomes for epilepsy surgery depending on the cause of the epilepsy and where it is located [29] [32] [33] [34].

Summary of Non-pharmacological Epilepsy Treatment

Surgeries for Epilepsy	Diet counselling	Neurostimulation
1)Hemispherectomy 2)Focal Resection 3)Multiple Subpial Transection 4)Corpus Callosotomy	1)Adkins Diet 2)Modified Adkins Diet Others with low glycemic index 3)Ketogenic Diet	1)Responsive Neurostimulation Investigational therapy 2)Transcranial Magnetic Stimulation 3)Deep Brain Stimulation 4)Electroconvulsive Therapy 5)Vagal Nerve Stimulation

Drug Target:

The research for better antiepileptic medications can now take advantage of recent developments in the physiology of ion channels and other potential molecular targets, as well as fresh data on the genetics of idiopathic epilepsies (AEDs). Marketed AEDs primarily affect GABA-mediated inhibition or voltage-gated cation channels (the subunits of voltage-gated Na+ channels as well as T-type voltage-gated Ca2+ channels). The SV2A synaptic vesicle protein and 2-voltage-gated Ca2+ channel subunits have recently been identified as potential targets. Numerous genes related with various epilepsy syndromes have been found

through genetic studies of familial idiopathic epilepsies, including genes producing Na+ channels and GABAA receptors, which are well-known targets for AEDs. Other potential AED targets include various voltage-gated Ca2+ channel subunits and auxiliary proteins, A- or M-type voltage-gated K+ channels, and ionotropic glutamate receptors, according to a method based on genes related with epilepsy in animal models and people. Technological improvements in ion channel research, such as molecular cloning of channel subunit proteins and studies in epilepsy models, point to additional targets, such as G-protein-coupled receptors, such as GABAB and metabotropic glutamate receptors; hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channel subunits, which are responsible for hyperpolarization-activated current I h; connexions which start up the gap junction. More precise targeting may be made possible by new data from the structural characterisation of ion channels and improved understanding of ion channel function. Examples of desirable targets include the GABAA receptor isoforms in charge of tonic (extrasynaptic) currents or the Na+ channels underlying persistent Na+ currents. There are numerous prospects to develop better epilepsy treatments thanks to our expanding understanding of the pathophysiology of epilepsy and the structural and functional characterisation of the molecular targets [35].

SV2A Proteins:

A membrane protein known as synaptic vesicle protein 2A (SV2A), which is only expressed in synaptic vesicles, is now thought to play a role in the pathophysiology of epileptic diseases. This is due to three factors:

1) Severe seizures are seen in Sv2a-knockout mice;

2) Levetiracetam and its analogues have a specific binding site on SV2A;

3) SV2A expression varies in response to different epileptic situations in both animals (such as kindling) and people (e.g., intractable temporal lobe epilepsy and focal cortical dysplasia).

Furthermore, it has been established that SV2A malfunction has a causal role in epilepsy by causing intractable epilepsy, involuntary movements, and developmental retardation in individuals with missense mutations in the SV2A gene. A novel rat model (Sv2aL174Q rat) with a missense mutation (Leu174Gln) in the Sv2a gene was recently generated in order to investigate the mechanism of SV2A in influencing the development of epileptogenesis. These rats were extremely vulnerable to the kindling growth brought on by repeated

pentylenetetrazole treatments or amygdala electrical stimulation. Additionally, the Sv2aL174Q mutation significantly reduced depolarization-induced GABA release in the hippocampus and amygdala but not glutamate release. All of this data suggests that the SV2A-GABAergic system is essential for controlling epileptogenesis and promotes research into new antiepileptic drugs that improve SV2A-GABA system performance [36].

Recent drugs in treatment of epilepsy

Pharmacological action:

The majority of AEDs work by blocking the Na+, Ca2+, or GABAergic channels to prevent epileptic seizures [37]. The new AEDs typically have multiple minor action sites in addition to the major action site. According to pharmacological analyses, LEV, PER, and LCM all have distinctive binding sites and profiles [38].

LEV suppressed seizures in animal models of spontaneous and induced epilepsy [4,39], but unlike other AEDs, it did not prevent acute reactive seizures brought on by the injection of pentylenetetrazol and maximal electroshock [40]. After LEV was completely washed out of the perfusion, the LEV-induced inhibition of evoked abnormal firing was prolonged in slice preparations by more than 30 minutes [41].

The most prevalent isoform of integral membrane proteins, SV2A, which is its action site, was discovered to be present in all pre-synaptic terminals of the central nervous system (CNS) [42] [43] [44]. In animal models, the distribution of SV2A appears to differ between the acute progressive and chronic states of epilepsy.

There was a lower distribution of SV2A in the cerebrum and synaptotagmin-1 in the epilepsy-related region in spontaneously epileptic rats with intractable epilepsy [45]. We also discovered similar results from immunohistochemical studies using isolated brain tissue from patients with uncontrollable epilepsy. The vesicular release during high-frequency activity was decreased by LEV. The stabilisation of cortical firing and information transfer were both impacted by the modulation of neuronal activity, a type of short-term depression [46]. On the other hand, LEV suppressed the status epilepticus when administered as an injectable solution [47], indicating that it acts on L-type Ca2+ channels and other minor action sites in abnormal epileptic neurons to produce its acute anticonvulsive effect [8,48].

The first AED to target a glutamatergic transmission receptor is PER. Fast excitatory signalling occurs within and between different parts of the brain thanks to AMPA receptors, which are primarily found on the post-synaptic membrane of excitatory synapses. Fast synaptic excitation may result from their activation [49]. Antiepileptic effects can be obtained by blocking AMPA receptors throughout the entire brain, and PER is an aryl-substituted 2-pyridone AMPA receptor antagonist whose side-effect profile has been documented in rodents and epileptic patients [50].

LCM, a chiral functionalized amino acid, reduces seizures by preferentially enhancing the slow inactivation of voltage-gated sodium channels. Its profile in seizure and epilepsy animal models is comparable to that of AEDs that block Na+, such as PHT and CBZ. Unlike these substances, LCM has no effect on voltage-gated Na+ channel fast inactivation or sustained repetitive firing on a time scale of hundreds of milliseconds. LCM binds to CRMP2.30 as well. Five intracellular phosphoproteins known as CRMPs are involved in neurotrophic signalling and neuronal outgrowth. The adult brain expresses CRMP2 the most abundantly. Although there is no proof that LCM binds to CRMP-2 directly, it might take part in an indirect functional interaction [51] [52].

Clinical Trails:

Main Action site	Drugs	Action Site			
		Na^+ Channels	Ca^+ Channels	GABAergic transmission	
Na^+ Channels	**Topiramate**	**		*	* AMPA-R
	Lamotrigine	**	* N,P type	*	
	Rufinamide	*			
	Oxcarbazepine	**			
	Lacosamide	**			
GABAergic transmission	**Vigabatrin**			**	
Ca^+ Channels	**Gabapentin**		** α2δ subunit	*	
Others	**Levetiracetam**		* T type		* Intracellular Ca^{2+} Release
	Perampanel				** AMPA- R

**: Major action site; *: minor action site; AMPA-R: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, CMRP2: collapsin response mediator protein-2R, receptor.

Adverse Effects:

Adverse Effect	LCM	PER	OXC	VGB	RFM	LEV	LTG	TPM	GBP
CNS Effect									
• Encephalopathy				+++					
• Dizziness	+++	+++	+++	++	++	++	++	+++	++
• Ataxia	++	++							
• Cognitive impairment			++					++	
• Psychotic episodes		++		+++		++		++	++
• Behavioural problems				+++	++	++		+++	
• Depression				++		+			
• Sedation								+	
• Insomnia		++							
• Somnolence		+++		++	++	++	++	+++	++
General Issue									
• Seizure Aggravation		++		+++	+				++
• Weight loss					++			++	
• Weight gain		++		++					++
• Fatigue		++			++			++	
• Rash			++				++		
• Hypersensitivity			++				++	++	

LCM: Lacosamide; PER: Perampanel; OXC: Oxcarbazepine; VGB: Vigabatrin; RFM: Rufinamide; LEV: Levetiracetam; LTG: Lamotrigine; TPM: Topiramate; GBP: Gabapentin; +++: High risk; ++: Moderate risk; +: Minimal risk

CONCLUSION:

The new drugs LCM: Lacosamide; PER: Perampanel; OXC: Oxcarbazepine; VGB: Vigabatrin; RFM: Rufinamide; LEV: Levetiracetam; LTG: Lamotrigine; TPM: Topiramate; GBP: Gabapentin are been introduced in the treatment of epilepsy Neurosurgeons must take the patient's age, gender, and the extent of the injury's residual handicap into account while

treating people with focal epilepsy brought on by brain trauma. The most crucial concern during the critical stage is seizure protection. When choosing an AED for the chronic phase, consideration must be given to a patient's distinctive comorbidities and concurrent illnesses. While using new AEDs may currently require considering cost-benefit relationships, certain characteristics of the new AEDs, such as fewer drug interactions, fewer chronic adverse events, and drug side benefits, may make the new AEDs advantageous for epileptic patients who also have comorbid conditions and disabilities brought on by brain injuries.

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	***Mr. Nikhil S. Ekhande*** *Student, Bachelor of Pharmacy* *Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, Dr. D.Y. Patil Educational Complex, Sector No. 29, Pradhikaran, Akurdi, Pune, Maharashtra, India 411044.*
	***Ms. Mayuri H. Padwal*** *Student, Bachelor of Pharmacy* *Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, Dr. D.Y. Patil Educational Complex, Sector No. 29, Pradhikaran, Akurdi, Pune, Maharashtra, India 411044.*
	***Ms. Darshana A. Motwani*** *Student, Bachelor of Pharmacy* *Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, Dr. D.Y. Patil Educational Complex, Sector No. 29, Pradhikaran, Akurdi, Pune, Maharashtra, India 411044.*
	***Ms. Bhavana B. Choudhary*** *Student, Bachelor of Pharmacy* *Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, Dr. D.Y. Patil Educational Complex, Sector No. 29, Pradhikaran, Akurdi, Pune, Maharashtra, India 411044.*