International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 6 Nov - Dec 2025, pp: 1049-1066 www.ijprajournal.com ISSN: 2456-4494

Emerging Trend of Pharmacovigilance on Neurodegenerative Disease

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Date of Submission: 05-12-2025 Date of Acceptance: 12-12-2025

ABSTRACT
The emerging trend of pharmacovigilance in neurodegenerative diseases emphasizesRoutine surveillanceRegarding drug security, real-time Drug reaction documentationand post-marketing surveillance of newly developed therapeutics. Recent advances, such as theseutilized in quinidinedextromethorphan for PBAand targeted antibodies targeting protein aggregates memorylossdisease, highlight the importance of ongoing safety evaluation to balance therapeutic benefits against risks. Drug safety monitoring data provide significant knowledgewithin drug interactions, prolongedadverse reaction and patient-specific responses, ultimately guiding clinicians toward safer and more effective treatments.
Neurological conditions like AD, PD,as well as ALS are long term , developing disease defined via those slow breakdown of structure and role regarding nerve cells, directing toward reasoning ,motion impairment. These conditions create a significant global health issues because of the increasing prevalence, complex pathophysiology, and limited treatment options. The management of neurodegenerative disorders often requires long-term pharmacotherapy involving multiple drugs, which increases the potential risk of ADR Therefore, PV —are branch of knowledge as well as training regarding identifying , evaluation,interpritaion along with reducing the risk of side effects and other medicament regarding issues —has become a vital component of neurological and psychiatric healthcare.
Keywords: pharmacovigilance, adverse drug reactions Pseudobulbareffects, (AD), (PD), (ALS), Dextromethorphan/quinidine (DMQ)

I. INTRODUCTION

A nerve degenerative disorder is the ailment in which a CNSunit either die else cease to function. There is presently no solution for these illnesses, which usually get worse with time. They may be brought on by environmental factors like excessive alcohol use, certain viruses, or poisons, or by hereditary factors, malignancies, strokes, or other conditions. PD as well as ADthis are two examples. Neurological disorder are a group about illnesses that mostly impact the brain's neurons. The primary fundamental unit related to neuro system, which consists of mind plus vertebral cord, are neurons. When neurons are damaged or die, the body is unable to replace them since they cannot renew or replenish themselves like other cells can. These illnesses are both incurable and incapacitating, causing nerve cells to gradually degenerate or die, resulting to problems with movement (ataxias) or cognitive function (dementias). Uncontrollable crying or laughter that is frequently excessive or unsuitable for the circumstance are signs of pseudobulbar affect (PBA). Consequently, there is difference in relation to those individual's truefeelingstate together with there external sentimental expression. Different words have been used to describe the illness, which has occasionally led to misunderstandings. These include pathological crying and laughter, emotional dysregulation, emotional obligation, over sensitivity, uncontrollable emotional expression, plus automatic emotional expressive disorder.

Nervous system disorder mainly frequently connected with PBA
Motor neuron disease
Movement regulation disorders
Chronic demyelinating disorder
Neuro trauma
Neurocognitive disorder
Motor neuron disease
Movement regulation disorders
Chronic demyelinating disorder
Neuro trauma
Neurocognitive disorder
Brain hemorrhage

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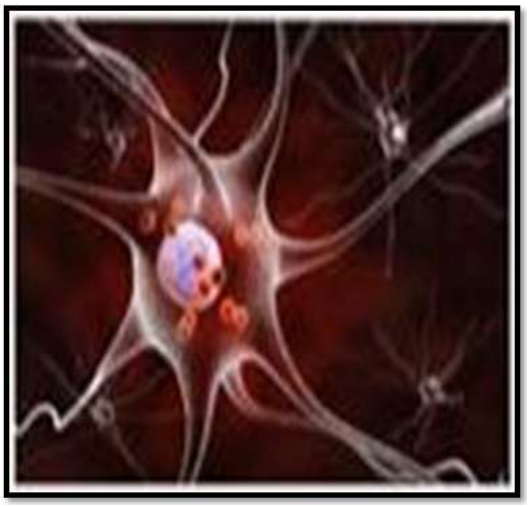

Fig No: 1 Neuronal Damage

Pseudobulbar affect (PBA) has serious consequences, including decreased social connections a plus reduce theover all wellfair. It frequently causes shame for the patient, their family, and caretakers. Those who are already coping with severe neurological conditions. [1] Are further burdened by this.

According to research by Tateno et al., patients with PBA exhibited worse social functioning and higher anxiety symptoms than those without the illness. [2] Furthermore, PBA was correlated among

the raised incidence related diagnosable mental illnesses, with between 30% and 35% of PBA patients additionally experiencing depression. [3]

PBA can also make rehabilitation more difficult. For instance, in patients with locked-in syndrome, PBA hampered attempts at communication, the use of any residual motor skills, and the evaluation and treatment of swallowing problems. Therefore, managing patients with a variety of neurological illnesses requires an awareness of PBA and an understanding of its treatment, providing physicians with a chance to produce the positive variation inside the being of these subject. [4,5]

NEURODEGENERATIVE DISORDERS

Since neurons are vital for nervous system communication, they are required to the subject mind to work manually. [6,7] Nerve cell found throughout anatomy, even though majority are produced into neural tissue. [8,9] This core composed of brain cell constituted via neural precursor cells during generation, but it's production extremely decreases into the adulthood .[10] Neurodegeneration, that progressive loss of neurons and the degradation of their structure and function, exist as a serious physical condition issue as well as key aspect of the development belong to many thinking organ illnesses, despite the fact that neurons are not eternal. [11'12]

Synaptic dysfunction, disruptions in nerve cell system, plus spinocerebellar buildup in aberrantly changed amino acid chain located in cerebrum are the hallmarks of neuro degeneration. [13,14,15] Neurodegenerative disorders (NDs) [16,17]Are illnesses that exhibit neuro degeneration ALS, PD, AD, infectious protein disease, Anterior horn cell disease, Hereditary neurodegenerative disorder, Muscle weakness genetic disorderas well asataxia atypical instances of NDs. [18,19]

The progressive neutral loss, Aβmonomersgroup and create small polymer belongs to different shapes, which sets the stage for cognitive loss. [20]Eventuallymisfold to create Aβ plaques.Tau aggregates generated as a outcome of an inflammatory response brought on via the development of these plaques. [21,22]The conversion of healthy neurons into sick ones is facilitated by this mechanism. Further inflammatory reactions follow the damage to more neurons, which leads to greater cell loss, brain malfunction, and cognitive decline. [23,24]

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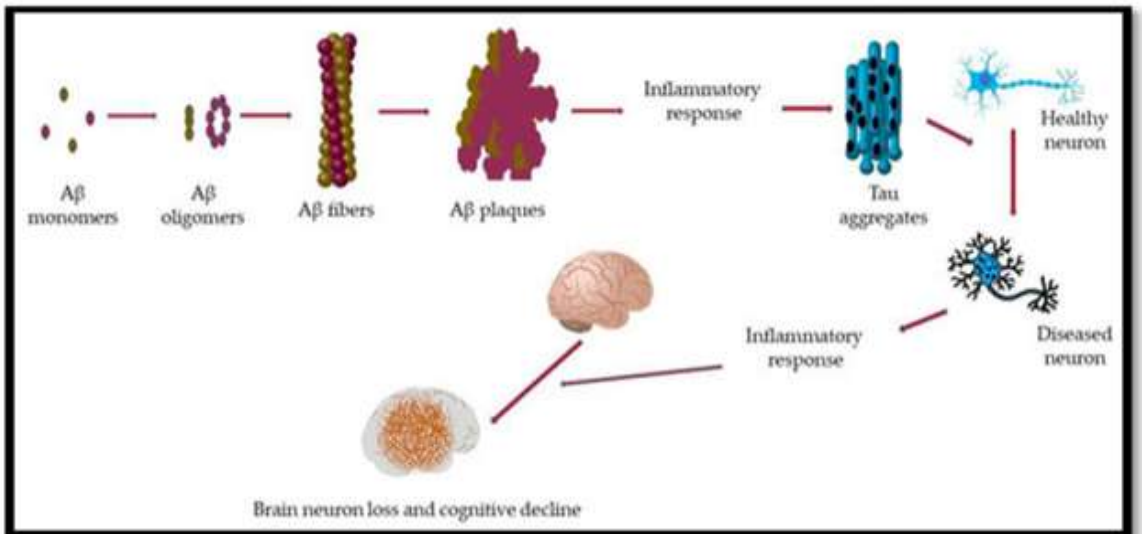

Fig No: 2 Neurodegeneration

Neurodegenerative disorders can impact a wide range of human capacities because the brain regulates numerous physical functions. These include more complicated tasks same as urinary organ plus intestine control and psychological abilities, as well as more basic ones similar speaking , motion,steadiness,as well as Postural control. [25,26] While some therapies aim to improve symptoms, reduce discomfort, and restore movement and balance, the majority of NDs develop without remission. Some of the most prevalent neurodegenerative illnesses shall be broadly covered inside the following parts. [27]

Symptoms

Neurodegenerative diseases commonly present with an variety of cognitive, motor, habitual,sensational, autonomic plus speech-associated symptoms. Patients may experience progressive memory loss, confusion, difficulty in learning new information, impaired judgment, reduced concentration, language problems, and dementia.movement related signs poor coordination, balance problems, shuffling gait, frequent falls, muscle weakness, spasticity, involuntary movements, fasciculations, and eventual paralysis in some disorders. Behavioral and psychiatric manifestations such as depression, anxiety, mood swings, apathy, agitation, hallucinations, delusions, and socially inappropriate behavior are also common. Sensory disturbances may include loss of smell, vision problems, numbness, tingling, neuropathic pain, and temperature sensitivity. Speech and swallowing problems like slurred or slow speech, reduced voice volume, difficulty swallowing, choking episodes,

and drooling are frequently seen. Autonomic dysfunction may cause constipation, urinary urgency or incontinence, orthostatic hypotension, sexual dysfunction, sweating abnormalities, and poor sleep regulation. Together, these symptoms vary between disorders namely AD, PD, amyotrophic lateral sclerosis,plus others but generally reflect the progressive decline in neuronal structure and function.[28]

Alzheimer disease (AD)

Current studies with in originof disease related to ADshows that tau as well as Aβ aggregated amino acid chain is important contributors tothe sickness progression.[29] AD has been found to be characterized by generation of amyloid-Beta protein diposites into mind as well as NFT composed of over phosphorilated tau. [30,31] The hippocampus circuitry are the management derived from neurodegenerative disorders is the Alzheimer's disease.[32]

Declarative episodic memory and other hippocampal and medial temporal lobe-dependent processes are also commonly impacted. [33] Deficits into the administrative role , like issues with chossingplus problem-solving, also usually appear early in the illness.[34]

Parkinson's Disease (PD)

Tremors, tight muscles, trouble walkin or problem withinequilibrium as well asorganization are all symptoms of Arkinson's disease (PD), a degenerative neurological condition. [35,36] Life spanare very necessary danger element in PD,

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however both hereditary and environmental variables have a role. It is also thought that other element, like this smoking,more amountcaffeine use, and affect the chance to getting PD. [37,38] levelshould the exact system is still unidentified. [39, 40]

Disease mechanism in PDcontains the expansion ofneuron artery and the atrophy of the prefrontallobe. The reduction of coloration within the LC as well as SNpc are the most noticeable alteration in the PD brain, though, and it outcomes out of dead of DA neurons that contain neuronal pigment. [41] The disease's characteristic motor symptoms are brought on by this cell death, which interferes within dopamine pathwayto the stratium. [42]

Amyotrophic lateral sclerosis(ALS)

ALS disease, mostly referred asa neuro degenerative disorder, are the increasing condition which damages brain as well as spinal cord neuron, resulting in paralysis and muscle weakness. [43,44] Motor neurons in ALS slowly degenerate and eventually die. [45] Blocking messages from reaching and leaving the brain. Although over 30 genes have been connected to ALS, over 70% of conditions arelead due to genetic variation in four main DNA segment : C9orf72TARDBP SOD1, plus FUS. [46]Those genes generate proteins arecontribute to a important function into glial cell action, mitochondrial function, DNA repair, and preserving cellular equilibrium. [47] The reduction of motor nerve in ALS are trusted become exacerbated by dysfunction in these mechanisms. [48]

Protein aggregation buildup in neurons is a major pathogenic characteristic of ALS. AltreductiAlthoremaamino acid chain including SOD and NF protein are formation of the accumulation, TARDNAdisordersprotein (TARDBP) is the most frequently observed protein in these aggregates. [49] Whether these protein clumps are the source of or a result of neuronal injury is yet mare central. [50]

RECENT THERAPEUTIC APPROACHES FOR MANAGEMENT OF ND

Treatmentfor NDare typically tailored to each specific diseaseIn reexamine, us discuss pharmacological methods that are recently being employed totreat Major neurodegenerative diseases (as outlined in table1)

Neurological Disorder	Drug Class	Mechanism	Drugs
Alzheimer disease	Amyloid-directed antibody	Target sand clears amyloid-beta plaques	Aducanumab
	Cholin esteras e Inhibitors	Prevent the breakdown of acetylcholine	Donepezil, rivastigmine, galantamine
	Glutamate regulators	Block N-methyl-D-aspartate (NMDA) receptor to improve glutamatergic signal processing	Memantine
Parkinson disease	Dopamine supplements	Restore dopamine levels	Levodopa
	Decarboxylas e inhibitors	Prevent the breakdown of levodopa in the body	Carbidopa
	Dopamine agonist	Mimic the effects of dopamine	Apomorphine hydrochloride, pergolide, pramipexole dihydrochlori de, ropinirole hydrochloride,rotigotine
Amyotrophic Lateral Sclerosis	Glutamate-receptor antagonist	Blocks glutamate receptors to reduce excitotoxicity	Riluzole
	Free-radical scavanger	Neutralizes free radicals to reduce oxidative damage	Edaravone

Table No: 1 Present-day treatment strategies for managing neurodegenerative disorder

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Pharmacolgical strategies for AD

Main goal of pharmacological strategies for AD management is to target several pathways that contribute to the disease's progression. 3 medicament category that the united state food and drug administration has currently approved into the theropy form Alzheimer Disease are listed under.

Antibody Targeting Amyloid-Beta (Aβ) Plaques

In June 2021, the FDA authorized Aducanumab (Aduhelm), the first disease-modifying medication for Alzheimer's disease (AD) [51]. Every four weeks, it is given by intravenous (IV) infusion over the course of about an hour. An IgG1 monoclonal antibody called aducanumab selectively targets and aids in the removal of extracellular amyloid-beta (Aβ) plaques in the brain. Although the medication was given conditional approval, clinical studies have revealed that although it lowers the Aβ plaque load, there isn't any conclusive proof that this lowers the patients' cognitive function. It is anticipated that ongoing clinical trials will yield more conclusive information regarding aducanumab's potential to improve cognitive function. [52]

However, because aducanumab is the first treatment to specifically address the underlying pathology of AD, its approval has excited patients and advocacy groups, raising hopes for the development of comparable medicines soon. Several bioactive compounds, including secretase inhibitors and therapeutic antibodies, have been investigated in several clinical trials; however, many of these have been discontinued.

AAB-003, MEDI1814, RO7126209, and SAR228810 are among the Aβ-targeting antibodies that have finished Phase I trials. Additionally, Aducanumab, which has finished Phase III studies, targets Aβ aggregation directly. Similarly, gosuranemab is in Phase II, whereas antibodies that target tau or TREM2, such as BIIB076, bepranemab, and JNJ-63733657, have completed Phase I trials. Consequently, the FDA may soon approve more antibody-based treatments for the treatment of AD. [53]

Cholinesterase Inhibitors :

The most commonly recommended drugs forAD at moment areacetylcholine esterase blocker. Galantamine, rivastigmine as well as donepezil are three primary cholinesterase inhibitors used in clinical practice. ACH releasing neurons are impaired in Alzheimer disease, and there is a decrease inamounts belong to ACH into Cerebral cortical areas related tomind. Acetylcholine levels in dementia patients can be raised to aid delay cognitive deterioration, according to research. Patients benefit from cholinesterase inhibitors because they decrease acetylcholine breakdown and increase cholinergic activity in the brain. [54]

Minor to intermediate Alzheimer disease donepezil are frequently recommended. It comes in oral tablet form in dosages of 5 or 10 mg per day. Intermediate to serious instances, higher amount of donepezil have lately been sanctioned,alternatively alone or combined with memantine,ACH inhibitor utilized with respect to minor to intermediate AD as well asdistinctive to its transdermal patch formulation, inhibiting both acetylcholinesterase and butyrylcholinesterase enzymes. Galantamine, an acetylcholinesterase inhibitor, is sanctioned to minor to intermediate AD, with prescribed dosage 16–24 mg per day. Galantamine not only inhibits cholinesterase but also allosterically modifies nicotinic cholinergic receptors. [55]

Agents regulating glutamate activity:

such brain's main glutamateis the primary excitatory neurotransmitter. Neurodegeneration and nerve damage result from glutamate's excessive stimulation of postsynaptic glutametergic NMDA receptors. [56] However, there have been signigficant negative effects linked to completely inhabiting glutamatergic receptors. Memantine offers therapeutic advantages by permitting regulated NMDA receptor activation and guarding against the negative consequences of excessive receptor stimulation. [57]

Therapeutic Approaches for PD:

Regenerating the reduced dopamine amount in the brain'ssubstantia nigral region is the primary treatment approach in PD. To achieve this, several strategies havde occurred devised. The most typical course of treatment combines carbidopa and levodopa. [58] A dopamine precursor called levodopa aids in regaining motor function that has been impaired as a result of dopamine insufficiency. To stop levodopa from breaking down withinb the peripheral body system before it reaches the central organcarbidogopa is administeremoreover, the enzyme catechol-O-methyl transferase (COMT), which would otherwise methylate and degrade levodopa, is blocked by entacapone and tolcapone, decreasing the drug's efficacy. [59,60]

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Dopamine agonists, which mirror the actions of dopamine and are also utilized in managing PD, include hydrochloride form of apomorphine (HCL), pergolide medication, and .Monoamine preserving agent, a different type of medications, such as rasagiline and selegiline, function by preventing the brain's dopamine from being broken down, maintaining its levels andto preserve its levels and prevent further depletion. [61]

Therapeutic approaches for ALS :

Frontotemporal degeneration action abnormalities, and along with a cognitive impairment is hallmarks of motor neuron disease, .during the first five years symptoms aappear the most of motor neuron disease patients pass away due to pulmonary failure. [62] Currently, riluzole medication and edaravone are the only pair of ALS medicationa authorized by the FDA. According to therapeutic studies, riluzole can prolong ALS patients' survival by three to four month as apposed to a placebo.This disease's course has been demonstrated to be slowed by edaravone, adominative stress suppressor hat where licensed in 2017 as an parentral infusion at a dose of 60 mg/day. Further more treatments, ALS individual undergo symptomatic care to promotebetterlifequality. However, there aren't any proven disease-modifying treatments for ALS at the moment. [63

PATHOPHYSIOLOGY OF PSEUDOBULBAR

The pathophysiology of Pseudobulbar Affect (PBA) In neurodegenerative diseases involves disruption of the brain circuits that regulate emotional expression. Normally, the corticobulbar pathways from the prefrontal cortex send controlled signals to the brainstem to match emotional expression with actual feeling. [64] In neurologicaldisorder like AD, PD ,ALS, together with Multiple Sclerosis (MS), these pathways become damaged due to neuronal loss, demyelination, or impaired neurotransmitter regulation. This disconnect causes a failure of voluntary control over emotional expression, leading to sudden, inappropriate, and exaggerated episodes of laughing or crying. [65] A key component is the disinhibition of the brainstem "emotional expression centers," especially the pontine nuclei, which release emotional responses without proper cortical filtering. Neurotransmitter imbalance—particularly involving serotonin, norepinephrine, and glutamate—further contributes to emotional instability. As a result, the brain misinterprets or amplifies emotional signals, producing expressions that are away the ratio towards those persons actual emotion, which is the hallmark of PBA. [66]

Pseudobulbar Affect (PBA) is a complicated and poorly understood pathophysiology. Damage to the cortico-ponto-cerebellar network, which controls the motor control of emotional expression, is thought to be the cause. [67] Research show that those placeof the neural damage is more significant relative to the underlying illness process itself, and PBA is frequently observed in a range of neurological diseases. According to Wilson's 1923 theory, PBA was caused by motor cortex injuries that interfered with voluntary inhibition to the brainste. [68] It was believed that because the circuits governing these reactions were disinhibited, this loss of inhibition led to involuntary emotional expressions like sobbing and laughter. [69] But according to more recent hypotheses, PBA is caused by disruption in a larger cortico-ponto-cerebellar network that includes descending routes to the brainstem, cerebellum, and basis pontis, and motor, limbic system ,along with corelated cortical region. [70] In healthy circumstances, the cerebellum assists in regulating emotional expression to make sure it fits the emotional situation. When this network is disrupted, people may express emotions in ways that are overly dramatic or unsuitable for the circumstance .[71] Lesion investigations and neuroimaging give proof that this circuitry is involved in PBA.A comparative study of individuals includingor excluding pseudobulbaraffect, for instance, discovered those people with pseudobulbar affect. [72] Had alterations in their white matter tracts in regions such as the middle cerebellar peduncle, transverse pontine fibers, and frontotemporal cortex. These changes implied that these areas had lost their integrity. The involvement of disturbed fronto-cerebellar circuits in PBA is further supported by decreased fractional anisotropy in the left motor cortex. [73]

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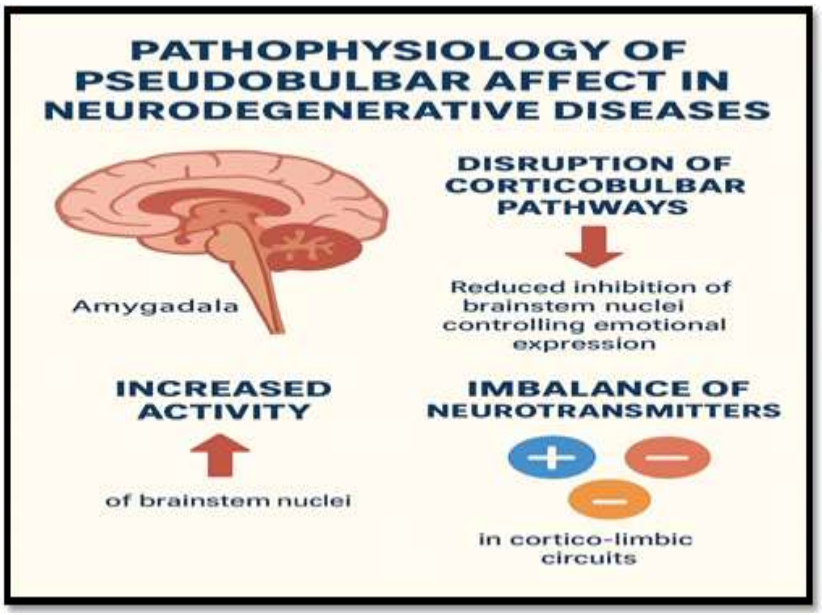

Fig No: 3 Pathophysiology of Pseudobulbar

The significance of these regions in PBA is further supported by other publications that demonstrate that damage to particular regions, such as the thalamus, basis pontis, or cerebellum, is sufficient to produce symptoms of the disorder. [74] The greater occurrence of PBA in atypical parkinsonian disease for example neurodegenerative multisystem disorder as well as degenarative movement disorders is consistent with this suggested me subjective. Damage to the brainstem and cerebellum, for instance, can compromise the cerebellum's capacity to regulate unconscious eiagnosis of pseudobulbar affect (PBA) is primarily clinical and relies on a systematic combination of history-taking, observation, standardized screening, neurological assessment, targeted investigations, and exclusion of primary psychiatric or metabolic causes; clinicians should first elicit a detailed history from the patient and caregiver documenting the phenomenology of episodes. [75]

PSEUDOBULBAR AFFECT IN PARKINSONS DISEASES

Subject having the range belonging nervous system disorder, along with PD, may experience PBA. It is defined by unexpected, unmanageable bursts including laughter and tears, which are believed to happen when the neurological disorder interferes with brain regions that regulate emotions.

Causes of Pseudobulbar

Emotional responses in PBA patients are involuntary and frequently do not correspond with their true feelings. These tantrums can be severe, happen multiple times a day, and sometimes take place at inappropriate times. PBA may occur in persons together with PDonce having benefits associated levodopa treatment start towards off. It can also be brought on through invasive neuromodulation thertherapas well asa operative method that can lessen PD-related motor symptoms by implanting a device that sends electrical pulses to the brain. Apart from Parkinson's disease, PBA to be related along with other neurological conditions include brain tumors. Memoryloss disease, stroke ,neuroinfammatory disease, brain trauma ,motor neuron disease.

It can affect the quality life ofA person's social interactions can be significantly impacted by PBA. PBA-related emotional outbursts can cause someone to cry while they're truly feeling happy olaugh amid ser emotions ious situations.

Although these episodes are typically short-lived, they can occur often, hindering effective Communication. The sudden and inappropriate emotional reactions can make social situationsChallenging and embarrassing for individuals with PBA. As a result, some maywithdraw fromSocial activities and experience feelings of isolation. [76]

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MD Disordooers

PBA is a separate ailment even though it can be confused with bipolar disorder or depression. Nonetheless, research indicates that people with PBA frequently have greater prevalences of anxiety and other mental health issues. Between 30% and 35% of PBA patients also experience depression. Sobbing bouts are a common side effect of sadness, although they usually last considerably less time with PBA than with depression, which can cause sobbing to linger for weeks or even months. [77]

Diagnosis

Diagnosis of pseudobulbar affect (PBA) is primarily clinical and relies on a systematic combination of history-taking, observation, standardized screening, neurological assessment, targeted investigations, and exclusion of primary psychiatric or metabolic causes; clinicians should first elicit a detailed history from the patient and caregiver documenting the phenomenology of episodes—their sudden onset, brief stereotyped duration (usually seconds to minutes), high frequency, involuntary nature, and disproportion or incongruence with the patient's subjective mood—as well as triggers (if any), temporal pattern, functional impact, and any antecedent neurological event or progressive neurological disease. Physical as well as neurological examination focuses on signs of the underlying disorder and corticobulbar involvement (bulbar weakness, dysarthria, dysphagia, upper motor neuron signs, reflex changes) while mental-state examination evaluates baseline mood and screens for depression, bipolar disorder, psychosis, or anxiety disorders that can mimic or coexist with PBA; because affective disorders typically present with sustained mood change and congruent emotional expression, distinguishing features include the brevity, stereotypy, and mood–expression discordance seen in PBA. Standardized instruments—most commonly the CNS-responsibility scale (seven element self assessment where higher scores suggest PBA, with commonly used cutoffs differing by population) and those Pathological Laughing and Crying Scaleto brain attack populations—are valuable for screening and symptom quantification but do not replace clinical judgment. [78]

Neuroimaging (MRI preferred; CT if MRI unavailable) is used to identify structural lesions affecting corticobulbar or frontotemporal circuits that support the diagnosis by demonstrating a plausible neurological substrate; laboratory tests (thyroid function, B12, electrolytes, glucose, and others as indicated) exclude metabolic contributors to emotional lability, and neuropsychological testing can help separate PBA from dementia-related affective changes or depression when diagnostic uncertainty persists. When initial assessment is equivocal, serial observation, collateral history, and multidisciplinary review (neurology, psychiatry, neuropsychology, speech/swallow therapists) improve diagnostic accuracy; ultimately, a confident diagnosis of PBA hinges on demonstrating involuntary, brief, and mood-incongruent emotional outbursts in the context of neurological disease, with other psychiatric, medication-induced, or medical causes reasonably excluded, because correct identification directs appropriate symptom-targeted therapy and avoids unnecessary antidepressant or antipsychotic treatments. [79]

Pharmacological Treatment of Neurodegenerative Diseases

Pharmacological treatment of neurodegenerative diseases focuses on correcting neurotransmitter imbalances, slowing neuronal degeneration, reducing symptoms, and improving daily functioning.

AD , that major drugs include acetylcholinesterase blockers (Rivastigmine ,Donepezil, , Galantamine), which avoid collapse the ACH and improve memory, along with NMDA receptor antagonists like Memantine, which reduce excitotoxicity caused by excessive glutamate signaling and help stabilize cognition.

In Parkinson's disease, pharmacological therapy aims to restore dopamine levels using Carbidopa, Levodopa dopamine agonists like Pramipexole and Ropinirole, MAO-B bolckers such as Rasagiline as well as

Selegiline, and COMT inhibitors (Entacapone), which enhance dopamine availability and reduce motor symptoms like tremor, rigidity, and bradykinesia.

ForALS, the medications Riluzole (decrease glutamate adverse effects) and Edaravone (powerful antioxidant reducing oxidative stress) help slow disease progression

An FDA-approved medication called Nuedexta®, which combines quinidine sulfate and dextromethorphan is intended to lessen the emotional outbursts linked to pseudobulbar affect (PBA). Clinical investigations have demonstrated that this treatment, which combines two

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medications into a single pill, effectively reduces PBA episodes. The longer a patient takes the medicine, the more symptoms they usually suffer. After the first week of treatment, episodes typically decrease by 44%, and after 12 weeks, they decrease by 82%. Diarrhea, lightheadedness, coughing, vomiting, weakness, ankle or foot edema, UTIs, flu-like symptoms, and gas are among the most frequent adverse effects of Nuedexta. [80]

Non-Pharmacological Treatment of Neurodegenerative Diseases

Non-pharmacological therapy plays a crucial role in slowing functional decline, improving brain plasticity, strengthening motor and cognitive abilities, and supporting emotional well-being.

Cognitive rehabilitation and memory training (puzzles, structured recall, orientation therapy, computerized brain exercises) help maintain mental abilities in Alzheimer's and other dementias by stimulating neural circuits and improving executive functions.

Physical therapy (gait training, strength exercises, balance training, stretching) is essential for PD , ALS, and progressive genetic neurodegenerative disease because the prevents muscle stiffness, reduces fall risk, and maintains mobility for as long as possible.

Speech and swallow therapy help patients with bulbar symptoms, dysphagia, and communication difficulties by improving articulation, safe swallowing techniques, and preventing aspiration

Occupational therapy teaches patients energy conservation, home safety adaptation, fine-motor skill training, and operate belonging to adaptive equipment maintain independence inside everyday tasks .

Lifestyle interventions such as Mediterranean diet, antioxidants-rich foods, omega-3 fatty acids, regular aerobic exercise, and adequate hydration support mitochondrial health and reduce inflammation, which helps slow disease progression.

Psychological and behavioral therapy is extremely important, as many neurodegenerative diseases produce depression, anxiety, irritability, and personality changes; counseling, mindfulness, meditation, and caregiver support reduce stress and improve coping ability.

Environmental modification, such as removing hazards, labeling items for memory support, improving lighting, and simplifying home layouts, increases patient safety.

Social engagement activities like group games, music therapy, dance therapy, and community interaction help stimulate emotional circuits and improve mood.

Assistive technologies—wheelchairs, walkers, communication devices, memory aids, and sensor-based monitoring systems—help maintain independence and safety.

Advanced non-drug options involving deep brain stimulation to PD , which improves motor symptoms; transcranial magnetic stimulation (TMS) for cognitive and mood enhancement;andrespiratory therapy for ALS to support breathing. Together, these non-pharmacological strategies complement medications to slow decline, enhance function, reduce caregiver burden, and significantly improve the patient's quality of life. [81]

EVALUATION OF PSEUDOBULBAR

Unfortunately, none of the scales that are available to measure Pseudobulbar Affect (PBA) symptoms have been properly validated for use with individuals who have parkinsonian illnesses. Furthermore, it has been demonstrated that these scales' results do not consistently match those of more formal diagnostic interviews, indicating that they might not accurately measure PBA in this population. Their applicability is further limited by their reliance on self-reported data, especially in people suffering from Parkinson's disease dementia who might not be able to give a precise history. Another major drawback is that these scales have not been validated in various cultural situations outside of North America.Despite these drawbacks, it is crucial to consider these scales, as they are routinely applied in research analysisthe frequency belong to pseudobulbar affect within parkinsonian illnesses. A self-reported instrument for measuring PBA, the "Center for Neurological-Study Lability Scale (CNS-LS)" to be primary established within ALS patients in the US and Canada before being extended to MS patients.

There are seven items on the scale, which are separated into two subscales: one that measures labile laughter (four items) and another that measures labile tearfulness (three items). It is unclear if these CNS -Lateral Scale is appropriate to evaluating pseudobulbar affect signs within parkinsonian patients because contain only have been verified inside Amyotrophic Lateral Sclerosis or multiple sclerosis groups.Indeed, one study discovered that the specificity of detecting PBA withinindividual along with PD to be only 51%

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when a CNS-LS cutoff score of 11 or above was used. Additionally, there isdisagreement over the ideal cutoff score for defining PBA; studies have used values between 11 and 21. An 18-item survey called the "Pathological Laughing and Crying Scale (PLACS)" was created to gauge theseverity of PBA. A cutoffscore of 13 was shown to have high sensitivity (0.88) and specificity (0.96) for diagnosing PBA in stroke patients in the United States. [82]

PREVALENCE OF PSEUDOBULBAR

Country	Parkinsonian Disorders(PD)Pseudobulbar	Alzheimer's dementia(AD) Pseudobulbar	Motorneurondisease (ALS) Pseudobulbar
Global/pooled estimates	~16.5%(meta-analysis study ranges 1-31% to 1-43%in different review)	~9-39%(reported ranges);some dementia cohorts show higher up to ~50%in specific samples)	~27%(pooled across ALS studies,study ranges ~11-71%) ~1/3 at diagnosis in some population series.
United States	Reported clinical/study ranges commonly ~3-26%(dome clinical sample &screening studies reports ~26%)	Studies/reporting ranges within dementia cohorts ~9-39%(depending on dementia subtype &assessment).	ALS cohorts /registries reports ~20-35%(varies by study;pooled ~27%)
United kingdom/europe (general	Reported ranges ~1-31 across PDcohorts ,meta-analysis place pooled estimates mid -teens	Dementia cohorts in Europe show variable PB prevalence (often 10s of %) depending on subtype (vascular dementia often higher)	European ALS studies included in pooled analysis show ~11-71%range;pooled ~27%
India	Limited/sparse direct data reviews note few India specific prevalence studies. PD PBA estimates for India are not well-reported global ranges (1-31%)pooled ~16.5%)are typically used as reference	Very limited India -specific data small or case reports exist;global dementia PBA ranges (939 %or higher in some cohorts)are referenced for Indian reviews	Very limited India ALS PBA data regional clinical reports only global pooled ALS PBA (~27%)is the best available estimate until more India cohort data published.
Turkey	Single-country reports and review show PDPBA ranges (examples up to ~31%in some studies)country studies report wide variability	Country/dementia studies report variable PBA(some Turkish dementia cohorts show elevated rates).	ALS studies from multiple countries included in pooled analysis;country-level ALS PBA varies but falls within pooled ranges.
Italy/otherwestern Europe	PD cohorts reports a wide range (single studies 1-31%)meta-analytic pooled estimates fall in the mid -teens	Dementia cohorts show variable PBA prevalence some clinical samples reports very high rates depending on subtype.	Country studies included in pooled ALS analysis;individual studies vary but fit the pooled ALS estimates (~27%)

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Brazil	Few country-specific PD PBA prevalence studies some regional reports consistent with global ranges (single-study variability)	Dementia cohorts in latin america show variable PBA prevalence limited high-quality country estimates	A multi study pooled analysis including Brazil reported ALS PBA pooled estimates (~27.4%).

Table No: 2 PBA influence incidence evaluate in Individual together with Parkinsonian disorders

That frequency belonging to PBA varies estimatover countries and nervous system's diseases due to differences in patient populations, diagnostic criteria, screening tools, and healthcare reporting systems. Globally, pooled data indicate that PBA occurs in approximately 16.5% belonging to patienthaving Parkinson's disease , although individual studies report a wide range from 1% to over 30%, depending on this utilize belonging to the tools similar to neurological lesions scale and this disease stage at assessment. In Alzheimer's disease and other dementias, PBA prevalence also varies significantly, typically ranging between 9% and 39%, with higher rates in subtypes involving frontal lobe impairment such as dementiadue to vascular cause and frontal and temporal lobe dementia. In ALS, PBA is most prevalent, with pooled global estimates around 27%, and some studies reporting even higher rates, particularly in bulbar-onset ALS where emotional regulation pathways are more severely affected. In the United States and Western Europe, prevalence data are more robust, with PD showing 3–26%, dementia cohorts typically falling within 9–40%, and ALS consistently around 20–35%, supported by strong clinical reporting infrastructure and large neurological databases.

Countries such as the United Kingdom, Italy, Germany, Brazil, and Turkey demonstrate similar patterns, though individual studies display methodological variability. In contrast, India lacks large-scale epidemiological studies on PBA across PD, dementia, and ALS, resulting in reliance on global pooled estimates; however, small clinic-based observations suggest that prevalence patterns are likely similar, though underreported due to limited awareness, diagnostic tool usage, and neurological specialty access. Taken together, the table highlights that PBA must be recognized as a significant and underdiagnosed neuropsychiatric complication worldwide, with ALS showing the highest burden, dementia demonstrating broad variability due to disease heterogeneity, and PD presenting moderate but clinically important rates. The differences across countries predominantly reflect disparities in research capacity rather than true epidemiological differences, emphasizing the need for standardized screening and better regional data, especially in low- and middle-income countries such as India. [83]

TREATMENT OF PBA IN NEURODEGENERATIVE DISORDERS

PBA is still not well recognized or diagnosed in clinical practice, regardless its comparatively incrased occurance upon the individuals within the nerve disorders . None of these patients who reported symptoms of involuntary sobbing or laughing to their doctors were diagnosed with PBA, according to a comprehensive epidemiological study that included over 8,500 patients who were examined for the condition using current diagnostic techniques. In actuality, the majority of these patients were diagnosed with depression, with only 41% receiving a diagnosis. For some patients, this misdiagnosis frequently results in inadequate treatment. The next section discusses the various PBA treatmentoption.

SSRIS,TCAs AND SNRIS:Serotonergic agent such TCA, SSRIs, and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) own historically remained utilized as unproved use therapies related to PBA. Many case studies, non blinded trials, or retrospective comparative studies that demonstrate the quick alleviation of PBA symptoms with various treatments provide evidence in favor of the usage of these drugs. Nevertheless, the majority of these investigations have been carried out on patients who have stroke, ALS, or multiple sclerosis. Patients case studies including Parkinson's disease individual together with pseudobulbar affect brought on by thalamicsurgery, as well as individuals with MSA-C, provide the majority of recored supportinsuwithin the utilize in antidepressants in individuals regarding parkinsonian diseases. Theutilized owned by depression medication in to manage PBA within people among parkinsonia is not well supported by clinical trial data.

Antidepressants may help treat both pseudobulbar or concurrent depression within

International Journal of Pharmaceutical Research and Applications
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individual in Parkinson's disease, as many of them also suffer from depression. But according to a number of research, PBA is more common among antidepressant-using individuals with movement problems than in nnon-antidepressant-using individual.These is various method into view within connections. Single theory is that antidepressants could inadvertently exacerbate or cause PBA symptoms to arise. On the other hand, individuals with PBA can be more susceptible to concurrent depression, to that those to be started therapy together with antidepressants. It's also possible that some patients received antidepressant treatment especially for PBA because the studies did not state whether the medications were administered for depression or PBA. To elucidate this link, more investigation is required. [84]

Tricyclic Antidepressants(TCAs):

Amitriptylin:Mechanism of Action:Strong serotonin reuptake inhibitor (SRI)Moderate norepinephrine reuptake inhibitor (NRI)Blocks:Muscarinicreceptors (anticholinergic effect)Histamine H1 receptors (sedation)Alpha-1 receptors (hypotension)

Role in Neurodegenerative Diseases: Used for neuropathic pain (diabetic neuropathy, Parkinson's neuropathy)Helps sleep disturbances in Alzheimer's and Parkinson'sReduces crying episodes in Pseudobulbar Affect (off-label)Reduces irritability & agitation in Alzheimer's (with caution due to anticholinergic effects)

Nortriptyline:Mechanism of ActionSelective norepinephrine reuptake inhibitionMild serotonin reuptake inhibitionLess anticholinergic and sedating than amitriptyline

Role in Neurodegenerative Diseases: Preferred in elderly patients (Alzheimer's, Parkinson's) due to fewer side effectsUseful for:Mild to moderate depressionNeuropathic painPBA (off-label)Safer than amitriptyline

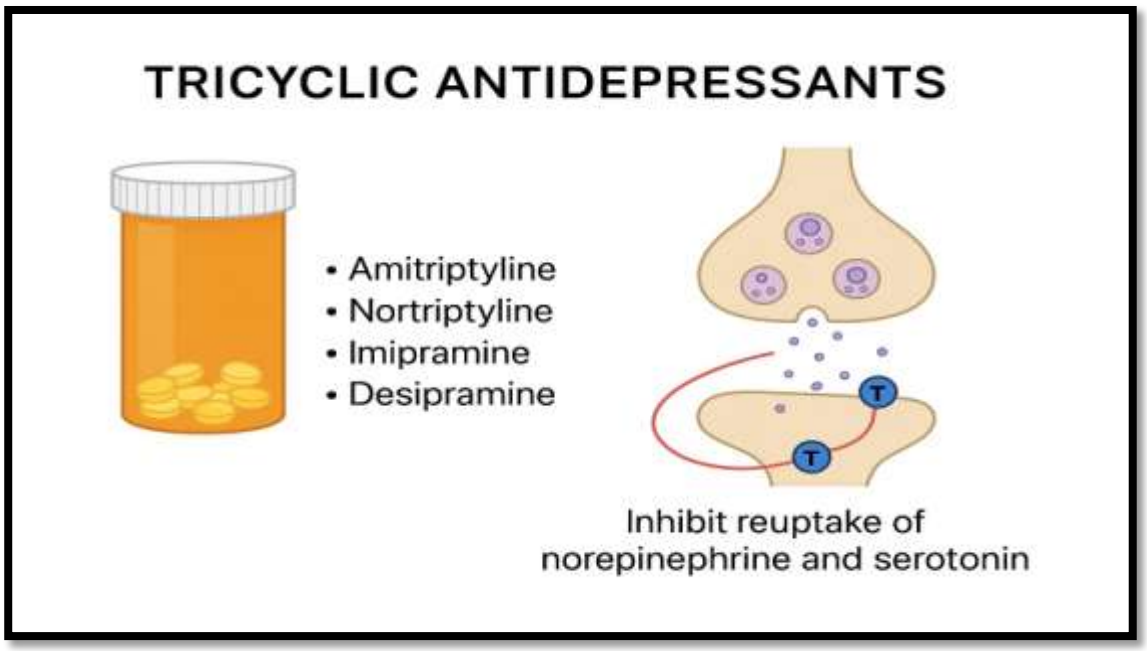

Fig No: 4 MOA of Tricyclic Antidepressants

Selective 5ht Blockers

Fluoxetine:MechanismStrong5 HT transporter inhibitorMild anti-inflammatory effectsEnhances neuroplasticity

Mechanism among Nervdegenerative Diseases:Reduces depression in progressive memory loss Diseases,dopamine deficiency disorder, ALSHelps Pseudobulbar Affect (PBA)Improves motor recovery after stroke (well-studied)May reduce amyloid toxicity in Alzheimer's

Sertraline:MechanismPotent SERT blockadeMild dopamine reuptake inhibition → helpful in Parkinson's diseaseStrong anxiolytic effective Role in Neurodegenerative Diseases:First-line in Parkinson's for depression and anxietyHelps irritability, agitation, mood swings in Alzheimer'sUseful in PBA (crying episodes)Preferred in elderly due to good safety

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Selective Norepinephrine Reuptake Inhibitor(SNRIs)
Duloxetine:MechanismInhibits selectiveserotoninreuptak transporter+ norephinephrin transporter Enhances serotonin + norepinephrine in CNSPotentiates descending pain inhibitory pathways in spinal cordRole in Neurodegenerative DiseasesTreats neuropathic pain in Parkinson's disease, diabetic neuropathy, and multiple sclerosisImproves depression and anxiety in AD/PDMay reduce central pain sensitization common in neurodegeneration
Venlafaxine:MechanismLow dose → inhibits serotonin reuptakeHigher dose → inhibits norepinephrine reuptakeVery high dose → mild dopaminergic effect
Role in Neurodegenerative Diseases: Used for major depression associated with AD, PDHelps agitation/anxiety in Alzheimer'sMay reduce pain syndromes in PD and neuropathy

Dextromethorphan/quinidine(DMQ)

The only food and drug administrative sanction therapy in order topseudobulbar affect , was created especially to treat this illness. Dextromethorphan exit although towards work via glutamate antagonist activity in N-Methyl Deaspartateand sigma -1 target site , while its precise mode of action is still unknown. It is believed that its therapeutic effects arise from modifying neurotransmission within the cortico-pontocerebellar circuits, which are involved in the pathophysiology of PBA. It binds most strongly in the brainstem and cerebellum. The main active ingredient is dextromethorphan, but quinidine is added towards prevent that Cytochrome P -450 biocatalyst Cytochrome P-D6 from swiftly metabolizing it. Quinidine raises the plasma levels of dextromethorphan by blocking this enzyme, making smaller dosages of the medication effective.

Medical studies involving DMQ, similar to those involving SSRIs and TCAs, have primarily focused on the drug's efficacy and tolerability in managing conditions such as ALS, MS, AD, cerebrovascular injury, and traumatic brain injury. Investigators found that individuals with MS and ALS suffering from PBA who received DMQ at regimens of 20/10 mg or 30/10 mg administered twice per day exhibited a marked reduction in the occurrence and intensity of PBA attacks across a 12-week duration in the STAR investigation (Safety, Tolerability, and Effectiveness Outcomes of AVP-923 in PBA), a randomized, placebo-regulated experiment.Moreover, the non-blinded PRISM II study, incorporating participants with traumatic brain injury, cognitive decline, and cerebrovascular events, demonstrated that DMQ at 20/10 mg administered twice daily substantially reduced PBA manifestations.

The majority of side effects, including headache, vertigo , nausea, fatigue, and diarrhea, at which low to intermediate according to both studies, which also revealed that DMQ was well tolerated across these situations. A 52-week regimen at a dose of 30/30 mg dextromethorhane quinine two times a day was found to be safe in an non blinded, multisite study evaluating the security regarding individual dextromethorphan and quinine among patients having varity in nerve disorders, such as the little number belonging to individualstogether with Parkinson'sdisease(number of individuals = 11) or irregular insonism (number ofindividuals= 7). Among patients with parkinsonian syndrome, the most frequent adverse symptoms were fatigue (4.3%), headache (21.7%), dizziness (21.7%), nausea (4.3%), and dry mouth (8.7%). These side effects were modest to moderate, same like in previous research. However, as of right now, no research has explicitly assessed how well DMQ works to treat PBA in parkinsonian illnesses.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 6 Nov - Dec 2025, pp: 1049-1066 www.ijprajournal.com ISSN: 2456-4494

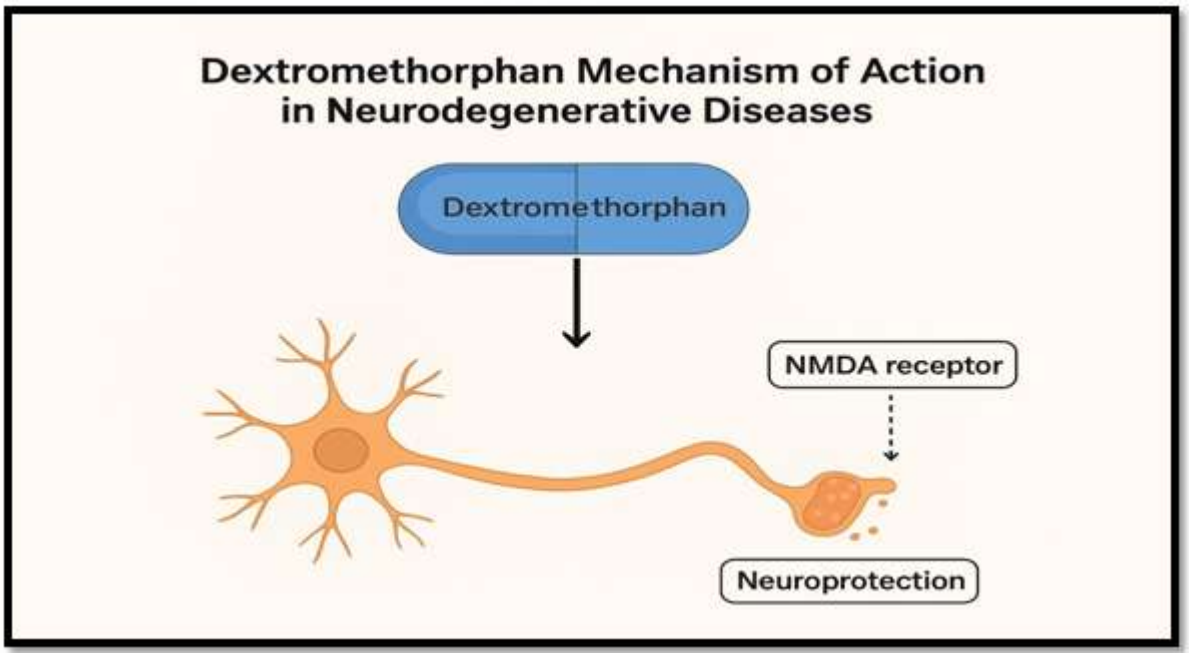

Fig No: 5 MOA of DMQ

Benefits of Pharmacovigilance in Neurodegenerative Diseases

Improved drug safety
Reduced ADR-related hospitalizations
Better quality of life
Early detection of harmful effects
Support for regulatory decisions
Improved prescribing practices
Better patient compliance and Enhanced understanding of long-term effects. [85]

II. CONCLUSION

PBA acts as complex neuropsychiatrne disorder on frequently observed inside the patients having neurodegenerative and parkinsonian disorders but often remains underdiagnosed. There is significant variation in prevalence reports, highlighting the urgent need for standardized and culturally validated diagnostic tools. Although treatments such as SSRIs, TCAs, and the FDA-approved dextromethorphan/quinidine (DMQ) combination have shown promise in other neurological conditions like ALS and multiple sclerosis, their efficacy in parkinsonian disorders remains inadequately studied. Strengthening pharmacovigilance systems and conducting targeted clinical research are essential to ensure early recognition, accurate diagnosis, and optimized therapeutic management of PBA. Enhanced awareness and evidence-based interventions can significantly enhance subject wellbeingas well as minimize the psychosocial stress associated with neurodegenerative diseases.

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