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ADVANCEMENTS IN THE THERAPEUTIC APPROACHES TO TREAT NEUROLOGICAL DISORDERS

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ABSTRACT

As the population ages, neurological problems, particularly neurodegenerative diseases, are becoming more common. The nervous system is a highly specialized and sophisticated network. Our nervous system organizes, explains, and links us to the world around us, from sight to scent, movement to speech. Many key activities in our bodies are controlled by them, including perception, language, memory, movement, swallowing, breathing, and even bowel and bladder function. Understanding neurological disease signs is essential for receiving the proper diagnosis and care. In this book, we have discussed 7 disorders such as multiple system atrophy, cognitive impairment, vascular dementia, traumatic brain injury, epilepsy, schizophrenia, subarachnoid and intracerebral hemorrhage. Their symptoms, pathogenesis, and therapies are discussed.

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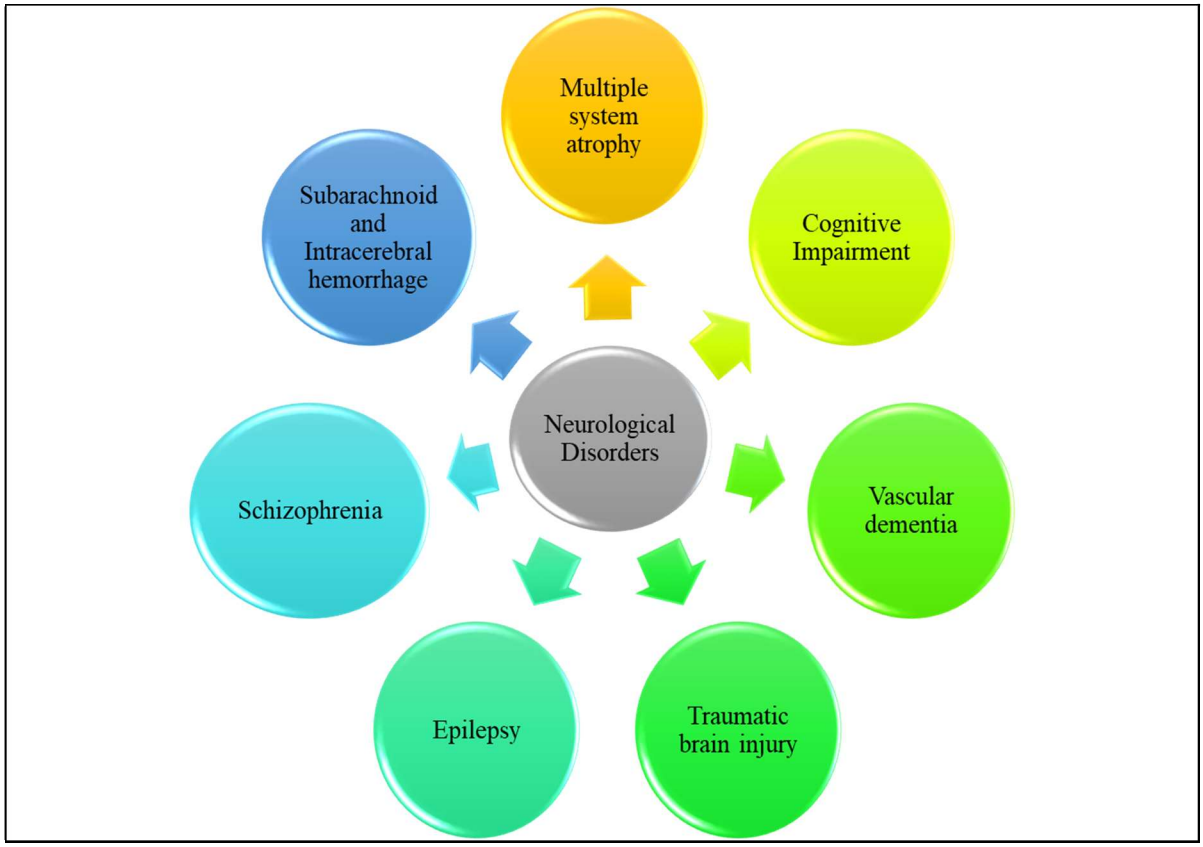

Keywords: Neurological disorders, treatments, pathogenesis, cognitive impairment

Introduction

The nervous system is a highly specialised and sophisticated network. Our nervous system organises, explains, and links us to the world around us, from sight to scent, movement to speech. Medically speaking, neurological diseases are those that impact the spinal cord, brain, and body's network of nerves. Anomalies in the spinal cord, brain, or other nerves that are structural, metabolic, or electrical can result in a wide range of symptoms. Examples of indications include paralysis, seizures, poor coordination, forgetfulness, muscle spasms, loss of sensation, pain, and altered levels of consciousness. Some of the causes of neurological issues include genetic illnesses, congenital abnormalities, infectious diseases, lifestyle health issues like malnutrition, and brain damage, nerve damage. Worldwide, hundreds of millions of people are impacted by neurological issues. Over 6.5 million persons die from strokes each year, with low- and middle-income countries accounting for more than 75% of these fatalities. More than 55 million people worldwide have epilepsy. Dementia affects 47 million individuals worldwide, with 7 million new cases diagnosed each year[1].

Numerous neurological conditions exist, many of which are rare but others of which are rather frequent. Contrarily, mental illnesses are "psychiatric illnesses" or diseases that show themselves as deviations in cognition, emotion, or behaviour and result in either pain or functional impairment. The US National Library of Medicine estimates that there are 600 neurologic diseases. Neurological difficulties include epilepsy, brain tumours, neuromuscular issues, learning difficulties, autism, ADD, and cerebral palsy,

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to name a few. Congenital disorders of the nervous system are those that develop before birth. Other issues can be brought on by tumours, degeneration, wounds, infections, and structural faults. No of the root issue, injury to the nervous system results in neurological abnormalities[2].

MULTIPLE SYSTEM ATROPHY

Multiple-system atrophy (MSA) is a deadly neurological disease that affects adults and is marked by increased parkinsonian symptoms and cerebellar and pyramidal symptoms in various combinations. The parkinsonian subtype is defined by parkinsonism as the most significant feature; the cerebellar subtype is defined by cerebellar features as the most prominent feature. MSA is an uncommon, progressing neurological disease with a prevalence of 3.4 to 4.9 cases 100,000 person/years and an estimated incidence of 0.5 to 0.6 cases 100,000 person/years[3]. Depending on the study, the average age of symptom start ranges from 54 to 63 years and the projected survival time from signs beginning is 5 to 10 years (average survival, 10 years)[4]. MSA is a varied mix of ataxia, and parkinsonism, with motor syndromes designating cerebellar subtypes (MSAC) or parkinsonian (MSA-P). Presently, existing laboratory examinations do not provide further diagnosis or prognosis accuracy beyond a comprehensive clinical evaluation. However, several fluid biomarkers and imaging data are regarded to be helpful[5]. Because of the disease's multisystem nature, it necessitates both proof and off-level multidisciplinary therapies, with the person at the core of an interdisciplinary team of good benefactors that includes doctors, occupational, physiological, neurologists, and social workers, speech therapists, nutritionists, and potential research staff. At the core of such therapy is personalized, symptomatic therapy for the patient's unique set of symptoms[6]. There are presently no authorized drugs that modify disease, despite continuous research in several mechanistically driven fields and the patient's right to participate in clinical trials. This page covers the aetiology, mechanism, management, evaluation, treatment, clinical presentation and as well as both proof-based and off-label drugs. We also talk about the importance of continued research into novel symptomatic and disease-modifying drugs for this terrible illness.

MSA is classified into two types:

- **Parkinsonian type (MSA-P)**: Symptoms related to Parkinson's disorder include resting tremors, muscle rigidity, and sluggish movements, including walking.
- **Cerebellar type (MSA-C)**: Ataxia is a condition that causes difficulty walking, keeping balance, and coordinating voluntary motions.

Symptoms of Multiple System Atrophy:

- ✓ Tremors
- ✓ Quivering voice
- ✓ Cold extremities
- ✓ Light-headedness
- ✓ Balance problems
- ✓ Difficulty writing
- ✓ Slow and unsteady walking
- ✓ Reduced or lack of sweating

Diagnosis And Clinical Presentation

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Multiple system atrophy (MSA) patients have a wide range of symptoms, including urogenital dysfunction, autonomic failure, pyramidal indications, parkinsonian characteristics, and cerebellar ataxia[7]. This CT study found a consistent spread of the disease across Europe, with alike presentations of the indications in all of the participating centres, with dysfunction of the urinary system (84%) outnumbering symptomatic orthostatic dysregulation (74%) and parkinsonism (86%) outnumbering cerebellar ataxia (65%). The second MSA consensus statement keeps the MSA-C and MSA-P diagnostic categories, which are based on the predominancy of motor presentation at the time of evaluation, as well as the designations of potential, likely and certain MSA[8]. The second MSA consensus statement keeps the MSA-C and MSA-P diagnostic categories, which are based on the principal motor presentation at the time of assessment, as well as the designations of potential, likely and definite MSA[9]. The neuropathological proof of GCIs in conjunction with olivopontocerebellar ataxia or striatonigral degeneration is used to make a definitive diagnosis[10]. The commencement of the disease is determined by the first appearance of any motor (parkinsonian disorder) or autonomic characteristics (excluding dysfunction of erectile), while preclinical neuropathology is probably to develop numerous ages before the illness. MSA is supposed to be an adult-onset, sporadic (after the age of 30 years) progressive illness characterised by parkinsonism or cerebellar impairment, as well as autonomic dysregulation symptoms. Orimo and colleagues found that separate mechanisms underpin the degradation of sympathetic nerves of the heart in Parkinson's disorder and multiple system atrophy in a recent study[11]. The detection of initial p25α aggregation in oligodendrocytes from MSA individuals has underlined the link between decreased cardiac absorption of ^{123}I-metaiodobenzylguanidine (MIBG) and oligodendroglial disease in MSA aetiology[12]. p25α, also recognized as tubulin polymerization enhancing protein, is an oligodendroglia-specific phosphoprotein with myelination-related functions. P25α is shifted into oligodendroglial accumulation in MSA patients, which is frequently co-localized with α-synuclein positive GCIs[13]. These data support the theory that MSA patients have a key oligodendrogliopathy that occurs before neuronal loss[14]. In human brains affected by MSA, aberrant build-up of fibrillar α-synuclein has been documented in nuclei (NCIs and NNIs) and neuronal cytoplasm, in addition to neurites[15]. Even though these additions have not been identified as an important neuropathological characteristic for MSA, they are likely to play a part in the course of the disease. Although these additions have not been identified as a crucial neuropathological standard for MSA, they are probably to be important in the course of the disease. NNIs appear to emerge initially in the illness progression in MSA brains' inferior olives and pontine nuclei, according to data from recent post-mortem studies[16]. In addition, neuronal p25α accumulation has been described in MSA, both alone and in conjunction with α-synuclein in some NCIs40, comparable to that observed in dementia and Parkinson's disorder with Lewy bodies. This commonality suggests that synucleinopathies cause neuronal dysfunction via common routes including cytoskeleton disruption, protein displacement, and aggregation. Two degenerative mechanisms in MSA have been hypothesized based on this evidence: Neuronal synucleinopathy with aggregation formation and GCI-linked oligodendrogliopathy with eventual neuronal degeneration (neurites, NCIs, and NNIs). Even though the molecular processes of aggregation, synuclein misfolding, and fibrillation in numerous synucleinopathies may be similar, disease-specific cascades influenced by environmental and genetic factors are probably to separate these illnesses[17]. In contrast to Parkinson's disorder, MSA has been conveyed in only a few families[18]. A

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genome-wide investigation for putative single nucleotide polymorphism links in MSA discovered an important link among these SNPs (rs11931074, rs3857059, and rs3822086) at the SNCA gene and MSA risk[19]. This genetic finding suggests that α-synuclein processing plays a key role in MSA development. Environmental elements have yet to be determined. Occupational behaviours, such as contact with metals, additives, solvents and numerous other pollutants, as well as a history of farming, have been related to an elevated risk of MSA in several controlled studies. However, these early findings were not confirmed in a recent investigation[20]. In transgenic mice with controlled overexpression of human α-synuclein under the control of specific oligodendroglial promoters, the role of oligodendroglial α-synucleinopathy as a trigger of MSA-like degeneration of neurons was examined. Axonal synuclein accumulation and axonal deterioration, dysfunction of mitochondria, an intense reaction of CNS microglia to pathogenic insults, and ambient oxidative stress were all caused by the insolubility and hyperphosphorylation of synuclein in transgenic mice Figure 1 [21]. The overexpression of α-synuclein transgenic models are a beneficial tool of experiments for studying basic processes related to GCI-like pathology in vivo; though, they have very well limits, such as the inability to multiply entire MSA degeneration and the lack of recorded MSA-like changes in CNS neurotransmission expression.[22].

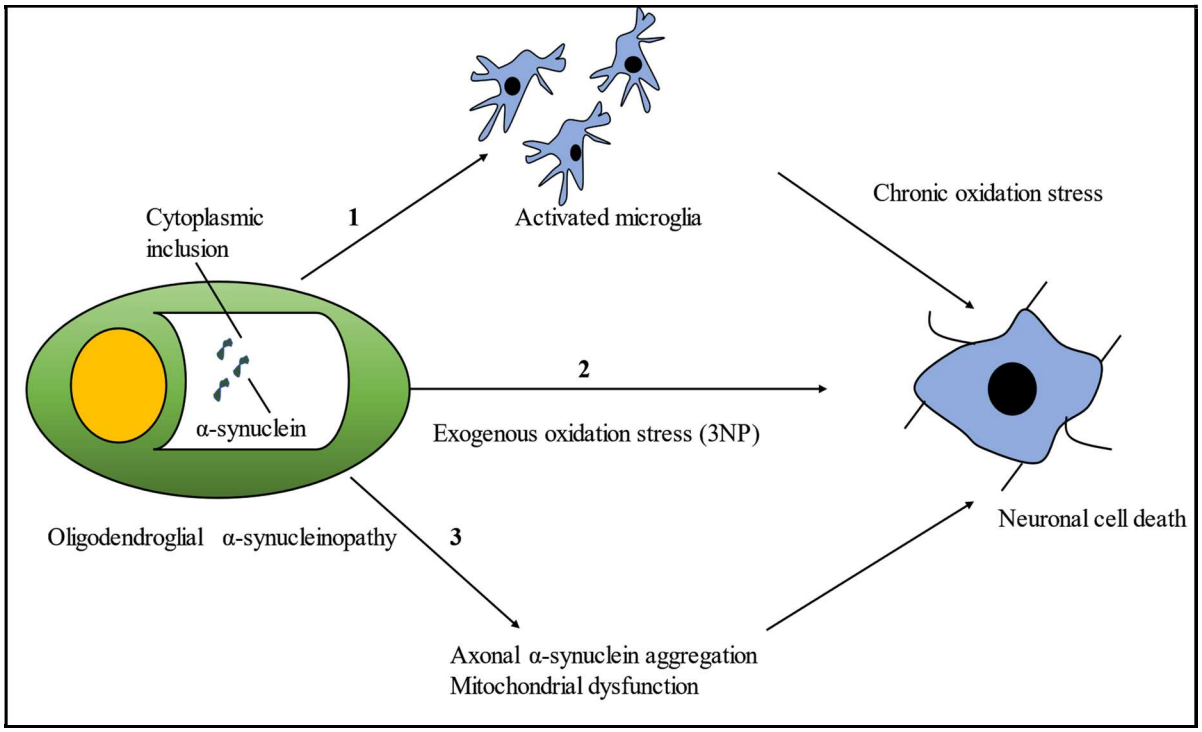

Figure 1 Pathogenic routes for multiple system atrophy (MSA) shown in models of a transgenic mouse. Based on observations from models of a transgenic mouse with synucleinopathy of oligodendroglial, three mechanisms in MSA have been identified. GCI illness may stimulate the activation of microglia, which induces prolonged oxidative stress and finally contributes to neuronal cell death (1). Otherwise, pathology of GCI may boost susceptibility to oxidative stress (exogeneous), tends to result in neuronal cell death in the olivopontocerebellar and striatonigral systems (2), or GCI pathology may cause secondary axonal-synuclein aggregation or dysfunction of mitochondrial oligodendroglial, likely to result in neuronal cell death. (3) In α-synucleinopathy of oligodendroglial, an inclusion of sickle-shaped

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cytoplasmic made up of misfolded α-synuclein is detected. In condensed chromatin, dying neurons, membrane rupture of the nucleus, and shrinkage of the cell are all observable. 3-nitropropionic acid is abbreviated as 3NP. "Glial cytoplasmic inclusion" stands for "glial cytoplasmic inclusion." MSA is an acronym for multiple system atrophy.

Symptomatic therapies

The current suggestive treatments for MSA patients will be described in this section. Table 1 provides a summary of current treatments.

Table 1 Suggestive treatments for multiple system atrophy patients

Feature	**Current First-Line Treatment**	**Alternative Treatments**
Alternative Treatments	Levodopa (1 g/day)	Paroxetine, amantadine (a positive trend in the small trial) *, DAs, (A positive trend in the small trial) *, physiotherapy
Ataxia	Physiotherapy	Gabapentin, vitamin E, amantadine, propanolol, baclofen, Clonazepam, buspirone
OH	Nonpharmacological interventions (custom-fitted elasticated socks, resting with the head of the bed raised, water consumption, short meals) Droxidopa*, midodrine*	Fludrocortisone, pyridostigmine*, desmopressin at bedtime
Neurogenic lower urinary tract dysfunction	Postvoid residual volume ≥100 mL: clean intermittent self-catheterization. Postvoid residual volume <100 mL: anticholinergic drugs for detrusor hyperactivity, (alpha-adrenergic blockers for detrusor sphincter) dyssynergia.	BoNT-A in the detrusor muscle or urethral sphincter, surgery (Sphincterotomy or sphincteric wall stenting), permanent catheterization
Constipation	Polycarbophil 70, macrogol, high liquid and fibre intake, traditional laxative treatment	Lubiprostone
Erectile dysfunction	Intracavernosal injection of	Sildenafil (not recommended

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	prostaglandin E1or papaverine	in patients with OH) *, SC apomorphine injections
Drooling	Anticholinergic drugs, inj. of BoNT-A into the salivary glands	
Breathing disorders	Positive air pressure continuously	Laryngeal surgery or BoNT treatment, adaptative servo-ventilation (life-threatening and/or daytime stridor, aberrant vocal cord, movement on laryngoscopy).
Dystonia	BoNT injection (focal dystonia)	Anticholinergics, tetrabenazine DAs, muscle relaxants, amantadine,
Camptocormia	Physiotherapy combined with a custom orthosis, wearing a backpack	BoNT inj., proterelin
RBD	Melatonin, Clonazepam	
RLS	Pregabalin, rotigotine, ropinirole and pramipexole	enacarbil, L-dopa, pramipexole, ropinirole, Gabapentin,
Depression	Psychotherapy, SSRIs	Electroconvulsive therapy, repetitive TMS

Almost of presently utilised treatments are constructed on the opinions of professionals and do not satisfy standards of scientific proof. Asterisks (*) indicate suggestions based on double-blind, randomised, placebo-controlled trials in individuals with MSA.

Autonomic failure- OH

OH, seems to affect MSA-P and -C individuals equally and is the primary criteria for clinical MSA diagnosis. Long-term therapy produces nocturnal hypertension, hypokalemia, and postural oedemas, which are thought to be associated with the sympathetic preganglionic neuronal loss in the thoracolumbar spinal cord's intermediolateral column. Pyridostigmine improved OH in a randomised, double-blind, crossover study without causing supine hypertension, most likely by stimulating sympathetic tone by exciting ganglionic neurons. Despite this, only 17 of the 58 randomised patients had multiple system atrophy, making decisions difficult to make. Figure 2 illustrates a therapy protocol[23].

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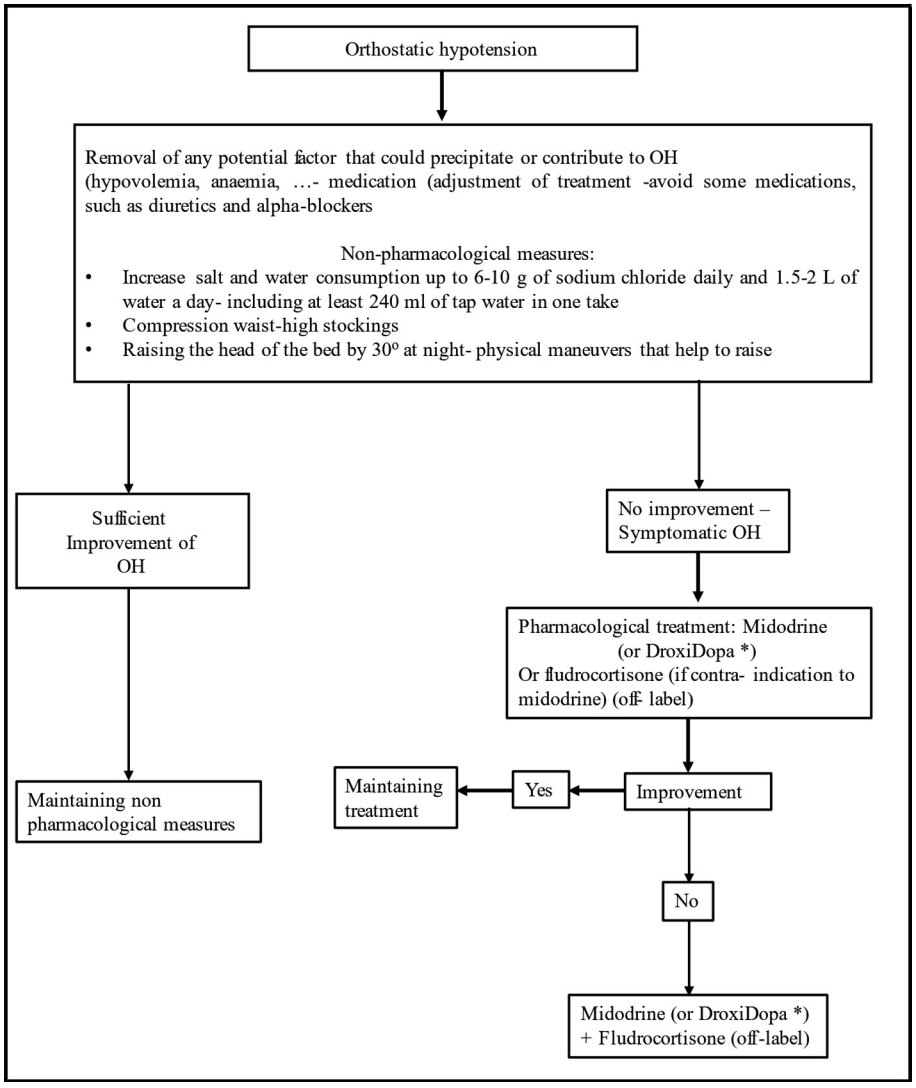

Figure 2 Multiple-system atrophy (MSA) treatment algorithm for OH. Labeled in the United States but not in Europe (FDA approval in February 2014).

Disease Modifying Strategies

Drug and other non-cell-based interventions

Neuroprotection is commonly thought of as a treatment strategy for slowing or even halting disease development by attenuating or preventing neuronal degeneration[24]. Because toxic α-Syn aggregation is so important in MSA pathogenesis, effective interventional approaches will need to stop oligomer formation and/or eliminate already produced accumulations. Unfortunately, most CT centred on aims with an ambiguous connection to principal α-Syn accumulation, and all drug or non-cell-based trials have so far been negative, due to a variety of translational challenges, including insufficient proof of goal assignation, underpowering, severe disease phases at trial entry, and an absence of valid and reliable biomarkers. (See Table 2 for a summary of preclinical and clinical multiple system atrophy studies, as well as Figure 3). The European Multiple-System Atrophy Study Group (EMSA-SG) conducted a placebo-controlled, double-blind trial to assess the effects of recombinant human growth

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hormone (r-hGH), but no noteworthy changes were detected between the placebo and r-hGH-tested groups.

Table 2 Preclinical trials in MSA models.

Intervention	Animal model	Results
Riluzole (anti-glutamatergic drug)	Sequential double-toxin, double-lesion rat model[25]	When compared to controls, the riluzole-treated group had fewer motor disturbances and a smaller striatal lesion volume.
	MPTP + 3-NP mouse model[26]	Riluzole enhanced motor scores and reduced striatal neurodegeneration.
Minocycline (tetracycline derivative)	Double-toxin, a double-lesion rat model of MSA[27]	There were no behavioural effects, no neural protection, and less activation of microglia and astrocytes.
	PLP-α-Syn model of mouse MSA[28]	Important decrease of degeneration of neurons in the SNpc and striatum
Rasagiline (irreversible MAO-B inhibitor)	PLP-α-Syn model of mouse MSA combined with 3-NP administration[29]	Behavioural consequences, and the olivopontocerebellar and striatonigral circuits' relative preservation
Rifampicin (antibiotic)	MBP-α-Syn model of mouse[30]	Reduction of α-Syn aggregation
Nocodazole (microtubule-depolymerizing agent)	CNP-α-Syn model of the mouse of MSA[31]	Nocodazole prevented the aggregate of soluble Syn fibrils but did not liquefy already formed aggregates, indicating that -III-tubulin is the primary factor in -Syn-aggregation.
Terazosin (α1-AR antagonist)	α1B-Adrenergic receptor overexpressing transgenic MSA model of mouse [32]	Long-term treatment significantly decreased α-Syn-aggregation and improved motor impairments.
Myeloperoxidase inhibitor (MPO)	PLP-α-Syn model of the mouse of MSA combined with 3-NP	Long-term therapy decreased -Syn-aggregation and enhanced motor impairments

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	administration[33]	Motor impairment was decreased, as were α-Syn aggregates that were present intracellularly, microglial stimulation was suppressed, and striatum degeneration, SNpc, Purkinje cells, pontine nuclei, and the inferior olivary complex was reduced.
Fluoxetine (selective serotonin reuptake inhibitor)	MBP-α-Syn model of the mouse of MSA[34]	Motor behaviour improvement, aggregation of α-Syn, astrogliosis, and demyelination decrease, elevated levels of GDNF and BDNF levels, and protection of neurons in the frontal cortex, hippocampus, and basal ganglia
Fluoxetine Olanzapine Amitriptyline	MBP-α-Syn model of the mouse of MSA[35]	Modulation of proinflammatory and anti-inflammatory cytokines, decrease of Syn accumulation in the basal ganglia, reduction of astrogliosis in the basal ganglia and hippocampus
Mesenchymal stem cells	PLP-α-Syn model of the mouse of MSA[36]	T-cell-specific cytokines IL-2 and IL-17, downregulation and relative retention of SN TH-positive neurons
	MPTP-3-NP double-toxin model of mouse [37]	Anti-inflammatory and anti-gliotic actions, as well as increased dopaminergic neuron survival in the SN and striatum

Cell-based interventions

As opposed to neuroprotective effects, restoration of neurons attempts to restore neurons that have died due to pathogenic events with new, functionally integrated neurons[38]. Two kinds of cell-based therapy

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have been investigated in MSA: (1) Levodopa dysfunction in MSA-P is fixed by embryonic striatal transplants into the host striatum of adults, and (2) distribution of stem cells of mesenchyma throughout the body to delay disease development.

Cell-based therapies for L-dopa failure

To determine if embryonic striatal cell transplantation can treat dopamine receptor loss and correct Levo-dopa failure, which is a major contributing cause to MSA-P-related progressive motor impairment, animal research has been conducted. In 1996, stereotaxic inj. of 6-OHDA into the bundle of the medial forebrain was tailed by an injection of QA into the ipsilateral striatum three to four weeks later, yielding one of the first rat neurotoxic MSA models. Contralateral apomorphine and ipsilateral amphetamine rotations were found, with the final decreasing after the QA lesion.

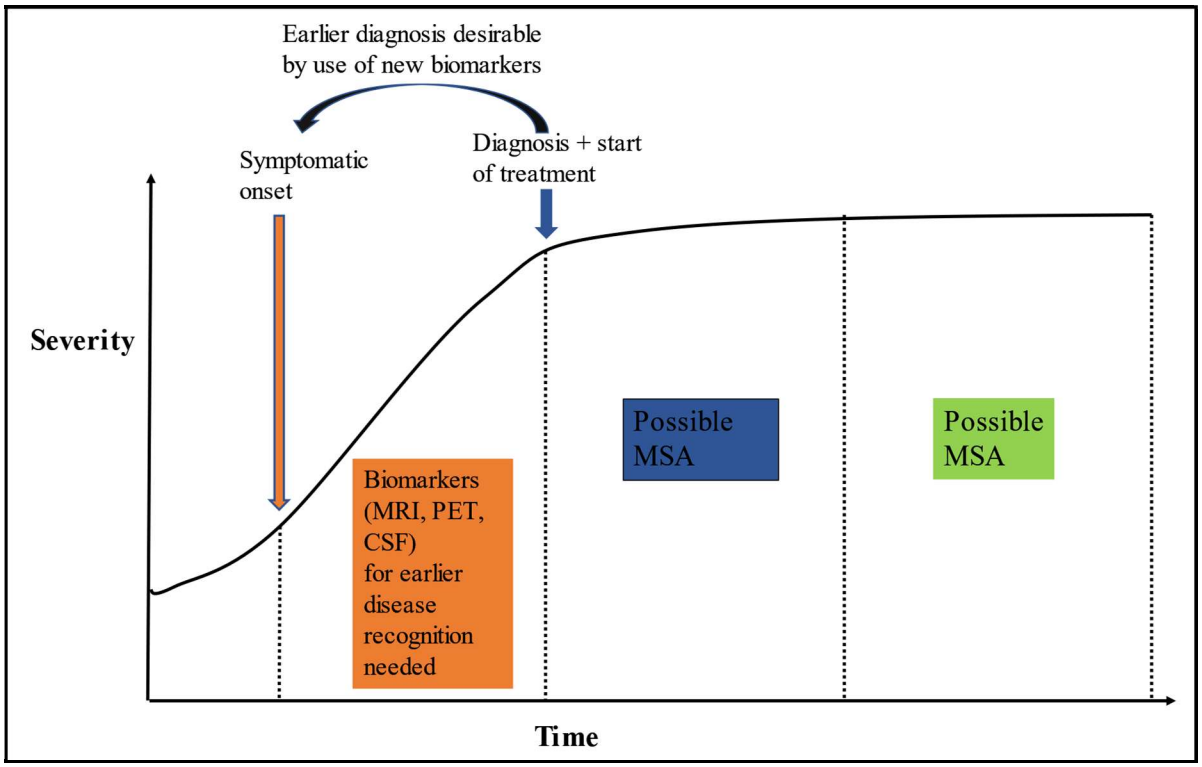

Figure 3 Biomarker-assisted early MSA diagnosis: a requirement for successful trial intervention.

Current MSA treatment bottlenecks and how to get over them

MSA studies have advanced rapidly over the previous decade as a result of many simultaneous advances; yet, it is clear that numerous difficulties must be addressed to accomplish cause-directed involvement, which would provide multiple-system atrophy patients with genuine modification of disease. Three of them are listed below. The fact that MSA is an orphan disease is one of the most significant drawbacks. As a result, the amount of research participants is restricted, and natural past research is frequently found to be underpowered. As a first start toward solving this challenge, several worldwide MSA networks such as the European and Japanese multiple system atrophy Study Groups (NAMSA, NNIPPS, EMSA) have been established. The lack of an economic impact of MSA makes it difficult to raise enough money for preclinical medication development and clinical trials. Two, over the last decade, disease recognition has improved as a result of established consensus criteria and the

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expansion of diagnostic tools, particularly better MR imaging techniques, which are being employed as surrogate markers in CT[39]. However, the ineffectiveness of initial stage MSA identification teaches us that enhancing criterion sensitivity through the recognition of motor and non-motor threatening indications (red flags) and neuroimaging of molecules techniques is vital for significant advancement[40]. Most interventional studies to date have been undertaken in patients with MSA who have participated in the script, assisted with the literature exploration and main organization, provided vital advice for the plan of the tables and figures, and assisted with amendments. The pathology section was heavily influenced by KAJ[41]. KS gave helpful suggestions for the tables and assisted with adjustments. MGS was tangled in the literature review and made significant aids to the modifications. WP assisted with the partition of the literature as well as amendments. GKW developed the research criteria, assisted with the partition of the literature, contributed to the major figure design, systematization, and table layout, and made the concluding modifications. All authors worked meaningfully on the work's writing and revisions, and have reviewed and approved the final edition[42].

COGNITIVE IMPAIRMENT

A phase of ageing that happens among typical cognitive decline and dementia is known as mild cognitive impairment (MCI). Issues with remembrance, speech, judgment, and objectivity are all frequent signs. Your chance of later-life dementia caused by Alzheimer's disease or other neurological illnesses increases if you have mild cognitive impairment[43].

- **Post-stroke cognitive impairment**
- **Cancer therapy cognitive impairment**

Post-stroke cognitive impairment

The cerebrovascular accident (CVA), often known as a stroke, is another greatest reason for death and adult disabilities globally. It is known as a malfunction of the brain brought on by a blockage of cerebral blood flow[44].

Mechanism of Cognitive Impairment

After a stroke, cognitive impairment has an unclear aetiology. Studies indicate that they might work synergistically to lessen post-stroke cognitive problems. AD or VCI brought on by a stroke may be the source of post-stroke cognitive problems Figure 4.

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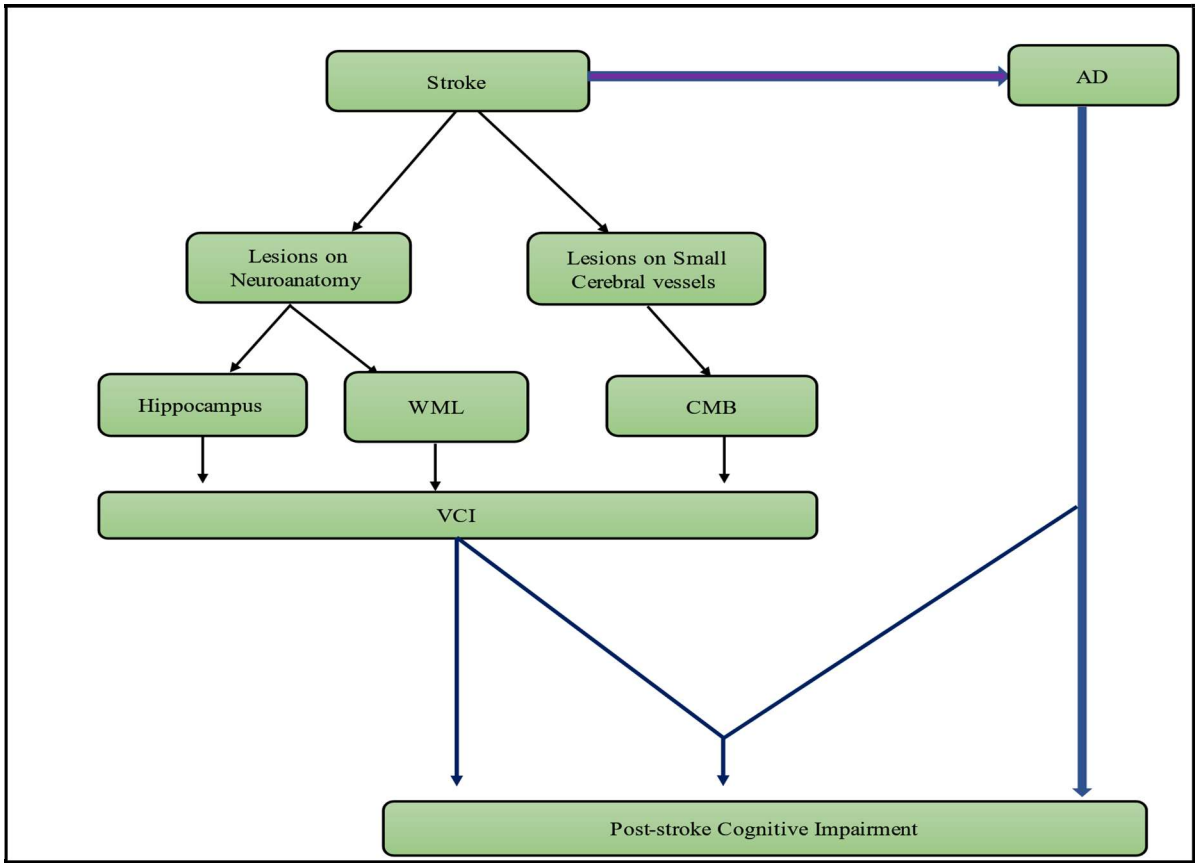

Figure 4 The major pathways that cause cognitive impairment after a stroke. AD stands for Alzheimer's disease; WML is for white matter lesion; CMB stands for cerebral microbleed, and VCI stands for vascular cognitive impairment.

Treatment for cognitive impairment

For post-stroke cognitive damage, there is presently no indisputably effective treatment. It has been demonstrated that several drugs for Alzheimer's disease can improve cognitive impairment following a stroke. Assessing the clinical value of these medications is challenging because there is uncertainty regarding global and daily function, despite research suggesting they can improve some cognitive domains, such as executive function. Clinical trial results, however, remain promising as prospective treatments for post-stroke cognitive impairment[45].

It is unclear how strokes affect cognitive function and dementia, and two substantially at odds hypotheses have been put out[46]. The very first theory focuses on the crucial part that stroke plays in cognitive impairment, provides evidence for the strong association between multiple strokes and post-stroke dementia, and outlines the prognostic significance of many stroke characteristics, including dysphasia, left hemisphere stroke, stroke intensity, haemorrhagic stroke, and infarct volume. As mentioned in the study's introduction, in this situation, the greatest defensive strategy for lowering the prevalence of dementia must be focused on providing efficient acute stroke care and preventing the recurrence of secondary stroke. The significance of vascular risk factors is emphasised by the alternate explanation Figure 5.

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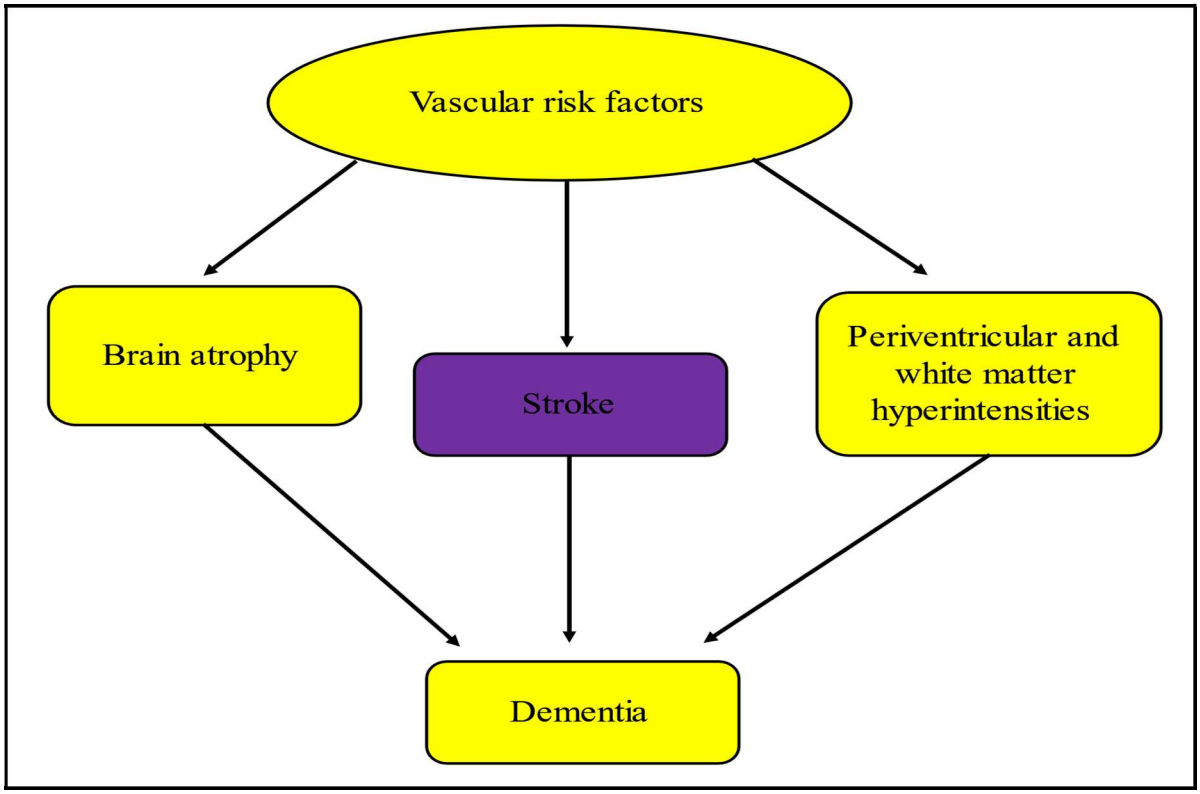

Figure 5 vascular risk factors' probable involvement in the onset of dementia in elderly persons.

Therefore, instead of being only the consequence of the stroke, poststroke dementia should be viewed as the product of pre-existing risk factors of vessels, alterations of white matter, and related pathology degeneration, along with the accumulation of amyloid plaque[47]. As an outcome, thorough therapy of vascular risk factors may be the most effective technique for preventing stroke and dementia in the elderly[48]. According to observational studies and clinical trials, high blood pressure is the risk factor for vasculature that is most strongly supported, suggesting that it is a major factor in the onset of dementia and cognitive decline. Several researchers have looked into the role of high blood pressure in cognitive decline, and high blood pressure was shown to indicate poorer cognitive outcomes many years later, especially in midlife, while other studies have found a J- or U-shaped link[49]. Hypertension has also been connected to executive function impairment, as well as subclinical infarcts and white matter hyperintensities (WMHs), which are pathogenically linked to VCI[50]. Even though the pathways underlying hypertension's disruptive consequences on elderly cognition are unidentified, it has been connected to the emergence of cerebrovascular disease pathogenesis and WMHs in the brain, as well as neuropathological characteristics of Alzheimer's disease, such as neurofibrillary tangles and amyloid plaques[51]. The link between hypertension and its consequences appears to be influenced by arterial stiffness[52]. There's also mounting evidence from clinical trials that using calcium channel blockers like nitrendipine and lercanidipine, as well as the perindopril–indapamide combination and telmisartan to stop heart disease and stroke lessens the danger of cognitive impairment[53]. Antihypertensive medicine, interestingly, may reduce the incidence of both VaD and AD[54]. Diabetes, dyslipidemia, obesity, atrial

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fibrillation, smoking, and alcohol use, among other vascular and stroke risk factors, could be therapeutic targets for stroke-related cognitive impairment in addition to hypertension[55]. Furthermore, there is proof that keeping optimal cardiovascular health from adolescence to mid-age is linked to improved cognition later in life. This conclusion supports the idea that intervention timing is important. Directing vascular risk factors may also be beneficial. since there appears to be a closer link between dementia and when vascular variables are assessed in midlife rather than later in life elderly age, implying that middle age is a significant phase. Notably, there is no proof that it has any positive impacts. Effects of antiplatelet drugs on cognition[56].

Cancer therapy cognitive impairment

Cancer treatment has advanced significantly over the previous century. Novel medicines have had a significant impact on survival. However, with improved long-standing cancer survival, the long-term implications of therapy are still unknown. Although the consequences of chemotherapy on cognition were first defined in the 1970s, it was only in the late 1990s that they became more widely recognized as a shared and important sign in cancer survivors[57]. Ageing is a key predisposing factor for cognitive deterioration as well as the most important risk factor for cancer. The Canadian Cancer Society's Steering Committee on Cancer Statistics estimates that 43 percent of new cancer diagnoses and 60 % of cancer deaths occur in those who grow older than 70 and over. Researchers are currently working to better understand cognitive impairment in the elderly as a result of cancer therapy[58]. The study was the first to look into the cognitive decline in people over 65 who were getting cancer therapy. Thirty-one women with breast cancer who were undergoing adjuvant chemotherapy had their brains tested before and after treatment. Deterioration in cognitive areas such as visual memory, psychomotor function, spatial function, and care was noted in 39 percent of patients Figure 6.

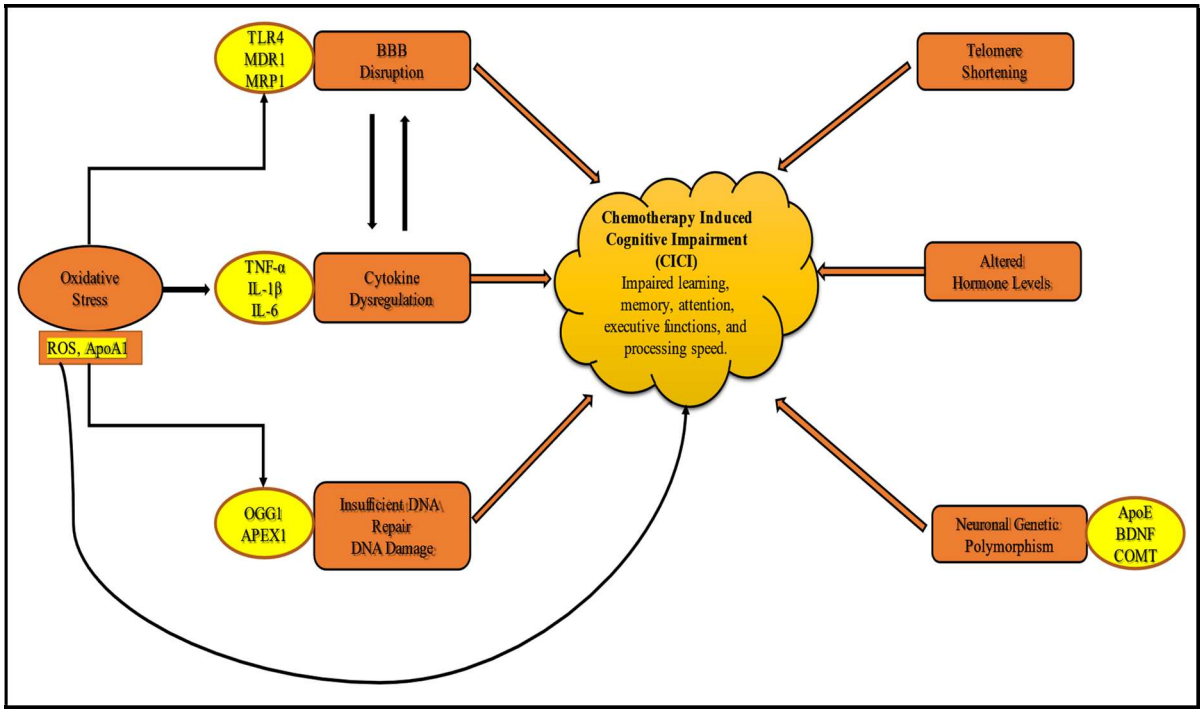

Figure 6 Mechanism of Cancer therapy cognitive impairment.

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Brain-directed cancer therapy and Ginkgo biloba for CNS cancer patients

Ginkgo Biloba (120 mg daily) was administered to 34 persons with brain malignancies who had completed radiation and were given it for 24 weeks. Significant gains were observed on cognitive tests examining processing supervisory function, memory, and speed. Though, this observation was restricted by the lack of a placebo control group and the fact that practice effects, which could explain test score improvement over time, were not taken into account[59].

Brain-directed cancer therapy and donepezil for patients with CNS cancer

The possible advantage is maintained by an open-label potential, single-arm phase 2 trial of donepezil in 24 individuals having tumours in the brain and a decline in cognition who had finished cranial irradiation[60]. After a 24-week regimen of donepezil, cognitive abilities such as focus and improvement of verbal memory dramatically. The findings were verified in a phase 3 randomised double-blinded controlled study undertaken by a similar group in a cohort of 198 brain cancer individuals who survived after cranial irradiation, which indicated that donepezil was better than placebo in enhancing cognitive functioning after a 24-week treatment[61]. After 24 weeks, there were considerable distinctions among the groups on the Grooved Pegboard for the leading hand, which measures dexterity and motor speed (least square mean scores 105.1/3.4 for donepezil vs. 117.0 [3.5] for placebo, p=0016), and the Amended Hopkins Verbal Learning Test (HVLT-R), which evaluates memory (least square mean scores for HVLT-R recognition, p=0.016). The HVLT-R discrimination least square mean scores for donepezil were 10.9 [0.2] vs. 10.3 [0.2] for the placebo, p=0.027; and 10.9 [0.2] for donepezil vs. 9.2 [0.2] for the placebo, p=0.007. Possibly most notably, this trial revealed a link between treatment impact and separate cognitive impairment, with individuals with more important memory impairments before therapy benefiting more from donepezil than individuals with fewer memory deficits before treatment. With a middle age of 11.1 years and 11 child brain tumour patients who had finished cranial irradiation more than 22 months before enrolment-eight (73 %) of whom had also received concurrent chemotherapy-Castellino and colleagues conducted an open-label pilot experiment. All individuals received age-appropriate doses of donepezil for 24 weeks[62]. Objective cognitive assessments were used to assess neurocognitive outcomes at baseline, 12, 24 and 36 weeks following the intervention. When compared to baseline, working memory, executive function, and visual memory all improved significantly following treatment. The Dellis-Kaplan Executive Function Test Tower Test showed the greatest improvement, going from a mean baseline scaled score of 8.3 to 11.7 at week 24 ($p<0{\cdot}001$). Furthermore, after a 12-week washout period, there was a trend toward a decrease in some cognitive domains. In a prior single-arm pilot, open-label research with 15 adult brain tumour patients who had finished cancer therapy or radio cancer therapy was reported. A day-to-day dose of donepezil (5 mg for 4 weeks, then 10 mg for 20 weeks) was given for 24 weeks, and cognitive evaluations were performed at baseline, 12 weeks, and 24 weeks following the intervention. After 12 weeks, there was a positive treatment impact, and after 24 weeks, there was a noteworthy positive result on visual memory, graphomotor speed, and attention [63].

Brain-directed cancer therapy and memantine for CNS cancer patients

Brown and colleagues randomly allocated 508 persons with metastases of the brain to have 24 weeks of placebo within 3 days of starting whole-brain radiation (20 mg daily) [64]. In the double-blind randomized controlled experiment, half of the patients had previously had chemotherapy, and a third

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took cancer therapy while participating in the investigation. Cognitive assessment at baseline, 8, 16, 24, and 52 weeks after treatment. Numerous results favoured the memantine group, even if the primary aim of reduced deterioration in delayed recollection was not met. Few persons experienced a failure in delayed recognition (HVLT-R delayed recognition median decline in standardised scores at 24 weeks 0 vs-1, p=0.0149), executive function (group scores not available), or processing speed (group scores not available), and memantine lowers the risk of cognitive failure (53.8 percent vs. 64.9 percent, HR 0.78; p=0.01) (group scores not available). Even though only 29% of all suitable patients did the 24-week evaluation, intent-to-treat research was conducted. Since this study used a comprehensive objective neuropsychological test battery, the results could be understood as demonstrating only minimal neuroprotective effects from memantine, albeit being statistically significant. The second investigation in this cohort, which found that dynamic especially in comparison to MRI may be a valuable biomarker for imaging for radioprotective characteristics of memantine, validated the results. More clinical trials are being carried out in this field, such as phase 2 or phase 3 studies to examine the properties of memantine on cognitive function in individuals who have undergone radiotherapy of the head or neck (NCT03342443) and a phase 3 study of patients who have undergone radiotherapy of the brain (NCT02360215). There is presently no data on memantine's impact on systemic chemotherapy-induced cognitive decline in non-CNS cancer patients Table 3[65].

Table 3 Chemotherapy-induced cognitive impairments are currently being studied in pharmacotherapy trials.

	Potential targets	Clinical trial registry numbers
CNS stimulants		
Methylphenidate[66]	Initiation position of the frontostriatal network	NCT02970500
Anti-dementia drugs		
Donepezil[67]	Safety of basal forebrain cholinergic system	NCT02822573
Memantine[68]	Glutamatergic neurotransmission	NCT03342443 NCT02360215
Potentially neuroprotective drugs		
Patients with brain-directed cancer therapy		
Lithium[69]	Safety against hippocampal neuron apoptosis	NCT01486459
Pioglitazone[70]	Anti-inflammatory, less oxidative neuron damage	NCT01151670
Ramipril[71]	Anti-inflammatory, less oxidative neuron damage	NCT03475186
Patients with systemic cancer therapy		
Fluoxetine[72]	Safety of dividing cells in the	NCT01615055

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	hippocampus	
Docosahexaenoic acid[73]	Functional recovery, lessening of microglia infiltration	NCT02517502
Ibuprofen[74]	Anti-inflammatory, fewer oxidative neuron damage	NCT03186638
Nicotine[75]	Glutamatergic neurotransmission	NCT02312934

VASCULAR DEMENTIA

The degenerative disease known as vascular dementia (VaD) affects cognitive functions by decreasing the blood supply to the brain. In addition to decision-making functions like thinking, planning, reasoning, judgement, and task execution, VaD persons may also experience delayed thinking, sadness and anxiety, forgetfulness, disorientation, and other symptoms. Output also tends to decline with task complexity. Around 17 to 20 percent of those with dementia have Vad, the 2nd most frequent type of dementia after Alzheimer's disease (AD). It affects older people more frequently[76]. A decrease in cerebral blood flow to the brain causes Vad, which might or might not be linked to a stroke, multi-infarct dementia, small vessel disease (SVD), which is characterised by multiple small strokes which is characterised by only main stroke with hippocampal injury, and vasculitic dementia, which is characterised by migraine-like pain in the head caused by blood vessel inflammation. Vad treatment is needed due to a lack of treatment alternatives, under-diagnosis, rising life expectations, and stable growth in the people suffering from risk issues such as metabolic syndrome, hypertension, diabetes, heart disease, and stroke.

Pathophysiology and molecular mechanisms of VaD

Before developing a viable animal model to test medicines, it's critical to understand the disease's pathophysiology. The pathophysiology and processes that underpin VaD are yet unknown. The clinical indications of VaD vary based on the aetiology and kind of VaD, as well as the location and amount of the infarction/damage. As a result, there is no consensus on specific symptoms or diagnostic procedures, and behavioural profiles and neuropsychological, as well as cognitive tests, are commonly performed. Chronic thromboembolic and hypoperfusion events cause a drop in hypoxia, CBF, oxidative stress, and inflammatory responses in VaD patients. Hypoperfusion-induced lesions are particularly vulnerable in the basal ganglia, periventricular WM, and hippocampus. Cognitive abnormalities are common in VaD when the prefrontal–basal ganglia pathway is disrupted (summary is given in Fig. 7). The nitric oxide synthase (NOS) pathway, reactive oxygen species, free radicals and malondialdehyde buildup are involved in the oxidative stress induced by hypoxia that results in mitochondrial malfunction (and vice versa), neuronal damage, and death[77]. Damage to the vessel, glial and endothelial occurs as an outcome of oxidative stress, foremost to neurovascular uncoupling and additional CBF reduction. Reactive oxygen species in excess can affect mitochondrial activity, leading to hypoxia and oxidative stress[78]. Cerebral hypoxia can cause cell necrosis and malfunction of microvessels, as well as vascular, endothelial dysfunction, blood-brain barrier leakage, and an increase in the inflammatory response of

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neurons[79]. MMPs (MMP 2,9), Interleukins (IL-1, IL-6), TLR4 (toll-like receptor 4), TNF- (tumour necrosis factor), and C-reactive protein infiltration promote permeability to the BBB when inflammatory factors such as matrix metalloproteinases (MMPs) and dysfunction of microvessels are present[80]. When these inflammatory substances enter the brain, they worsen WM injury (axonal loss, demyelination, degeneration of oligodendrocyte), promote degeneration of neurons and death of the cell, and increase neuroglial inflammation. By harming oligodendrocytes, glial production of inflammatory substances can worsen WM lesions and demyelination[81]. Because of its restricted supply of blood and inadequate collateral blood flow in deep tissues, cerebral WM is particularly vulnerable to hypoxia-induced injury[82]. WM damage in VaD is predominantly caused by demyelination, which is caused by hypoxia-induced oligodendrocyte destruction. Remyelination is reduced or hampered by the death of oligodendrocytes, as well as injury to oligodendrocyte progenitor cells[83]. Demyelination causes cognitive impairment by delaying neuronal signal transmission. Neurogenesis, synaptic plasticity, the proliferation of neuronal progenitor cells, and dendritic spine density are all affected by the inflammatory cascade in the hippocampus[84]. Learning and memory problems are the result of hippocampus-based learning[85]. Oxidative stress, microvascular dysfunction, endothelial and inflammation all contribute to the progression of cerebral injury. Increased BBB disruption, oedema, and neurovascular uncoupling, also neuronal damage, resulting from the interaction of oxidative stress and inflammation, which disrupts the neurovascular unit, a theoretical model that defines functional connections and signalling between capillaries, neurons, and glia in the brain[86]. The breakdown of neurovascular unit uncoupling and brain homeostasis is the outcome of a complicated molecular interplay between these systems[87]. Microvascular damage is caused by platelet stimulation and endothelial injury, which results in either adhesion, vascular blockage, vasoconstriction or thrombosis. Injury to the arteries that serve the deep WM of the brain results in white matter infarctions[88]. Known as CADASIL, the Notch3 gene mutation consequences in the rare VaD subtype (arteriopathy of cerebral autosomal dominant with subcortical infarctions and leukoencephalopathy). Apolipoprotein E (apoE) has garnered significant attention among the genes. While apoE4 allele carriers' explanation for almost 65-80% of all AD persons and its significance as a key risk issue has been extensively recognized in AD, there are various contradicting findings of its part in VaD. Recently, it was found that the hippocampus of the VaD brain contained cleaved apoE. It has been recommended that possessing apoE4 alleles increases your likelihood of developing VaD, however not to the same extent as AD. While the pathology of VaD sickness has been investigated to some extent and numerous factors leading to cognitive impairment have been found, there is still much to learn about the pathology and the larger image of disease process[89]. Additionally, markers that identify VaD from other forms of dementia are required.

Therapies and Treatment

Blood pressure-lowering therapies

The topic of whether reducing one of the major risk factors for vascular dementia, increased blood pressure, will lower the prevalence of vascular dementia, is both scientifically and therapeutically intriguing. Over 12,000 patients with hypertension but no cognitive impairment participated in three randomized, placebo-controlled studies to see if reducing blood pressure could lessen the danger of vascular dementia. In these investigations, there was no strong evidence that lowering blood pressure

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reduced the onset of cognitive impairment, including vascular dementia[90]. These investigations weren't flawless since antihypertensives had to be used on the control group of patients whose blood pressure often exceeded the predefined permissible ranges.

Validation therapy

Validation therapy is a set of nonpharmacologic procedures for treating demented people's disorientation and bewilderment[91]. Individuals and consideration of emotional states are highlighted in dealing with these empathy issues. Because of the recent focus on its validity and efficacy, the therapy was evaluated for this study. Meta-analysis information from three small randomized trials of dementia-affected people was discovered in the Cochrane database. In terms of cognitive or behavioural benefits, there were no meaningful effects. However, one study revealed that validation versus placebo improved behaviour, while another found that validation versus social contact improved depressive symptoms. Due to the less control of these researches, further research into the validation therapy may be beneficial in establishing whether these promising outcomes can be elaborated upon[92].

Currently, there is no therapy approved by FDA for VaD. As a result, various medications used to treat Alzheimer's disease and also reduce CVS risk factors are being utilized or researched. These treat mild to moderate cognitive impairment brought on by VaD while offering minimal advantages. The present therapeutic approaches are mostly aimed at slowing the progression of cognitive impairment induced by VaD. The subsequent is a quick rundown of the medicines used to treat VaD. Statins are medications that decrease cholesterol. Simvastatin (5 mg/kg for 4 weeks orally) was discovered to cognitive enhancement, lessen depression, bring blood serum TG to normal levels, and boost the numerous pyramidal neurons in rats receiving the HFD[93]. The ROCAS (Regression of Cerebral Artery Stenosis) CT found that Simvastatin (20 mg/day, twice a day for two years) could only slow the course of cerebral WM lesions in individuals with severe WM lesions[94]. The NMDA receptor is a key biological mechanism for controlling synaptic plasticity and memory performance. The FDA has approved the NMDA antagonist memantine for the management of Alzheimer's disease. In patients with mild to moderate VaD, memantine (10 mg twice a day for 28 weeks) therapy enhanced cognition[95]. NMDA receptor antagonists, on the other hand, are known to produce cognitive impairment and hallucinations[96]. Donepezil, an oral medication that works centrally to block acetylcholinesterase reversibly, appears to help people with Alzheimer's and Parkinson's disorder. According to two significant clinical trials, donepezil (5 or 10 mg/day, up to 54 weeks) may simply cross the blood-brain barrier, is well accepted in people, and recovers cognitive function. However, it should be used cautiously because it has the potential to cause digestive issues[97]. After a stroke, trophic factor angiogenesis, production, neurogenesis, and white matter reorganization are all improved by cell therapy, such as the transplant of endothelial progenitor cells, and HUCBCs (human umbilical cord blood cells) or BMSCs (bone marrow stromal cells). It may also help to alleviate cognitive impairment. In Alzheimer's mice, HUCBC therapy improves cognition and lowers amyloid-related neuropathology, as well as improves spatial memory in neonatal hypoxia-ischemia[98]. MSCs also lessen MSA patients' cognitive impairment by controlling longitudinal changes in cortical thickness Figure 7[99].

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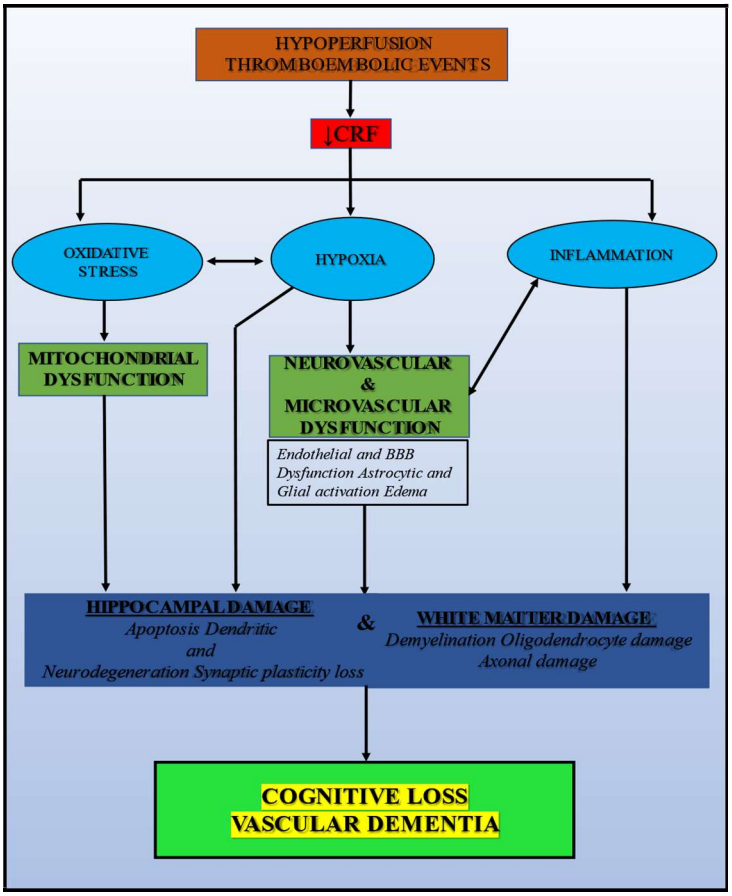

Figure 7 Summarises the numerous mechanisms thought to be involved in VaD pathogenesis.

TRAUMATIC BRAIN INJURY

Traumatic brain injury refers to any external mechanical force that results in a short-term or long-term impairment of physical, mental, and brain ability as well as a change in consciousness (TBI)[100]. TBI light-headedness, headache, forgetfulness, and vomiting, which may go away in days or weeks after the accident, but severe injuries can cause long-term behavioural and cognitive issues[101]. According to available data, head injuries raise the risk of neurodegenerative diseases like Parkinson's, Alzheimer's, and chronic traumatic encephalopathy[102]. Based on the intensity of the damage, TBI therapy involves medicines, cognitive therapy, or even surgery, such as a bilateral decompressive craniectomy[103]. This study highlights the molecular and cellular events that contribute to TBI pathogenesis. To create a novel treatment for TBI, possible pharmacological goals that have been reorganized in this study must be investigated.

Mechanism and Pathophysiology of traumatic brain injury

Following a primary biochemical, injury, molecular, and physiological processes may result in delayed and long-lasting secondary damage that may linger for hours or years. Excitotoxicity, oxidative stress, axonal degeneration, mitochondrial dysfunction, neuroinflammation, and apoptotic cell death are a few of the factors that lead to secondary injuries. Figure 8.

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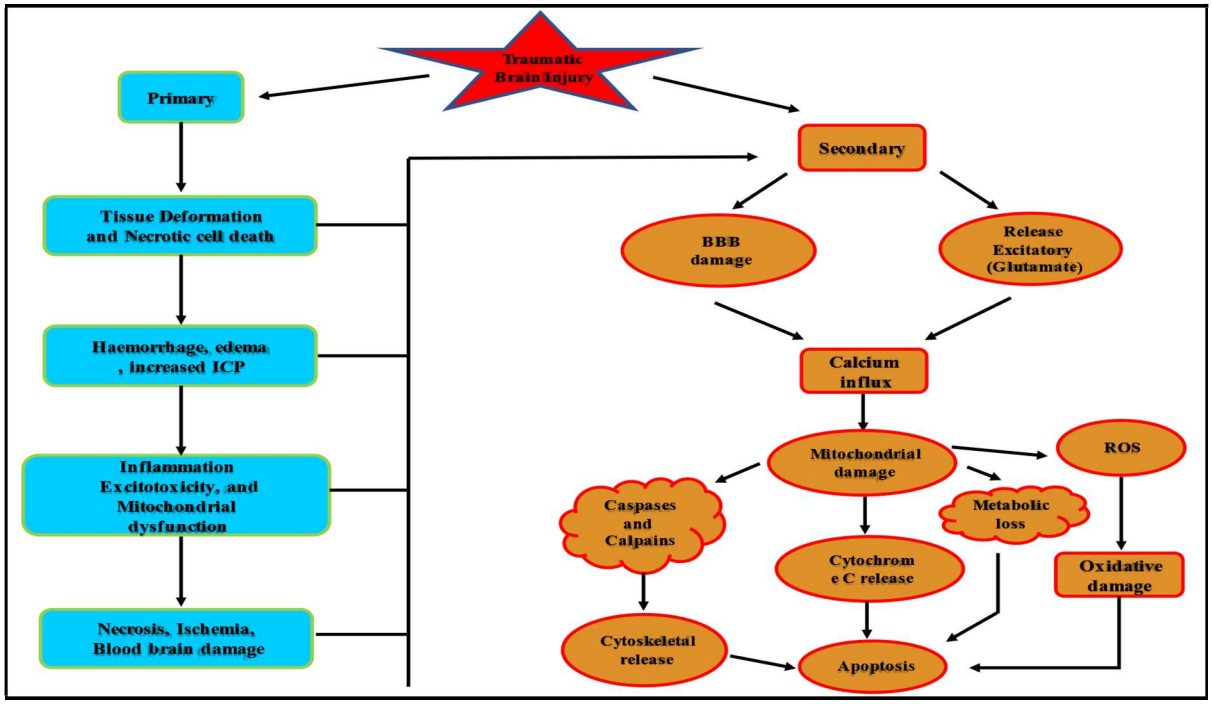

Figure 8 The pathophysiological mechanisms of primary and secondary brain injuries differ.

Excitotoxicity

Due to the BBB's disruption by TBI, additional neurotransmitters are released, and glutamate transporters-which are typically involved in the reuptake of glutamate failure[104]. Glutamate, like its multiple metabolites, attaches to the glutamate binding site and activates them. The membrane's Na, K, and Ca ions can enter through the NMDA and AMPA glutamate receptors to cause depolarization[105]. The overexpression of these receptors is encouraged by excessive glutamate release in TBI conditions, which disturbs ion homeostasis by enabling exogenous calcium and sodium ions to enter the cell[106]. GluN2B has been found in the cytosol at synapses and has been implicated in triggering excitotoxic responses[107]. Ca^{2+}/calmodulin-dependent protein kinase II, PKC, mitogen-activated protein kinases (MAPK), and protein phosphatases are among the downstream signalling molecules triggered by excessive intracellular Ca^{2+}. Excess calcium in the cytosol causes apoptotic proteins such as caspases, and calpain to activate, resulting in cell death[108]. The accumulation of reactive oxygen species also impairs mitochondrial activity (ROS). Cells are subjected to oxidative stress by excitatory neurotransmitters and excitotoxicity results in cell death. Directly afterwards trauma, stretch and shear forces brought on by brain damage promote glutamate-independent excitotoxicity via NMDA receptor stimulation[109]. One study also indicated that NMDA binding sites are mechanosensitive in terms of certain subunits and signalling pathways elaborate in modulating NMDA binding sites in reaction to mechanical stimuli. The GluN2B subunit was exposed to be a mediator of the mechanosensitive response[110].

Mitochondrial dysfunction

Mitochondrial dysfunction is a common complication of TBI that causes changes in physiological and metabolic function, eventually leading to cell death. Excessive $Ca2^{+}$ entry into mitochondria may affect

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the formation of ROS and depolarization of the mitochondrial membrane without ATP synthesis[111]. Excess ions invade mitochondria, causing ROS generation, mitochondrial membrane depolarization, and ATP synthesis suppression[112]. As a result, there is dysfunction in the oxidative phosphorylation and electron transport chains, which affects calcium control and metabolic efficiency[113]. The mitochondrial permeability transition pore (mPTP) is activated in response to stress. When the adenine nucleotide translocator protein binds to cyclophilin D, mitochondrial malfunction produces a structural alteration. This results in enhanced inner membrane permeability and mPTP opening. Apoptosis-inducing factors (AIF) and cytochrome c, among other mitochondrial proteins, are important in apoptotic cell death[114].

Oxidative stress

Secondary cell death and oxidative stress can result in higher amounts of free radicals, such as RNS and ROS. The excessive ROS produced disrupts mitochondrial function, causing lipid peroxidation damage to the mitochondrial membrane[115]. In reaction to the injured cells, the electron transport chain (ETC) produces more ROS following TBI. Ca^{2+} increase following TBI, on the other hand, stimulates the generation of NO by nitric oxide synthases (NOS)[116]. Excess NO combines with the free radical superoxide to create peroxynitrite (PN), which causes oxidative impairment even further. These ROS harm membranes of the cell by interacting with polyunsaturated fatty acids to create lipoperoxyl radicals, in addition to their effects on proteins and DNA[117]. Long-term excitotoxicity has also been linked to aberrant intracellular Ca^{2+} ion build-up. The continual release of ROS and LPO harms cerebral blood flow, causing plasticity of the brain and immunosuppression.

Neuroinflammation

TBI causes a variety of inflammatory and immunological tissue responses that are comparable to those seen in ischemia/reperfusion injury. Prostaglandins, free radicals, and inflammatory cytokines are all activated by primary and secondary mechanisms separately[118]. Polymorphonuclear leukocytes produced inflammatory mediators such as IL-1β, IL-6, and TNF-α in the post-mortem tissue of TBI patients, cerebrospinal fluid, and rat models 24 hours after the trauma[119]. The sustained release of cytokines revealed that the BBB's permeability is changed, resulting in oedema and neurological abnormalities. TNF-α, as a Fas intimate member, binds powerfully with the Fas ligand and stimulates caspases, resulting in apoptosis[120].

Axonal degeneration

Diffuse axonal injury (DAI) is caused by a rapid mechanical insult to neurons, which disrupts the axonal cytoskeletal network, which includes microtubules and neurofilaments[121]. Myelin sheath deterioration, damage of axonal transport, and transport of axonal protein accumulation separate acute axonal damage caused by trauma caused by sustained calcium-mediated proteolysis[122]. An extreme rise in axonal transport proteins causes axon swelling and cell and oligodendrocyte death over time[123]. The axonal markers -amyloid precursor protein (-APP) and neurofilament (NF) were found to be the hallmark of DAI in TBI tests 1 day after TBI, and retraction bulbs were mostly found in the pyramidal tracts and corpus callosum of the brain stem. The hippocampus, cingulum, and cortex have all been found to contain them[124].

Apoptotic cell death

Apoptosis of neurons, which manifests in the human hippocampus up to a year a TBI, is the hallmark of secondary brain injury[125]. Downstream proteases like caspases and calpain are stimulated by

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molecular pathways like extracellular signal-regulated kinase (ERK), Janus kinase/signal transducer and activator of transcription p38 MAPK (JAK/STAT), and others[126]. Intrinsic pathways (IP) and Extrinsic pathways (EP) are both involved in apoptosis (IP). IP combines mitochondrial depolarization of cytochrome c emissions with downstream caspase 3 activation via caspase 8 and 9 control, whereas EP integrates TNF-Fas connections with the relevant cell receptors[127]. However, in TBI, proteins of mitochondria such as AIF, Smac/DIABLO, and polymerase 1 are released into the nucleus as a consequence of caspase-independent apoptosis, that further stimulates upstream signalling molecules for neuronal and glial cell injury[128].

Pharmacological Treatment approach for traumatic brain injury

Neurorestoration cell-based therapy for TBI recovery

It has been demonstrated that neurovascular regeneration plays a crucial role in the restoration of brain function after injury[129]. The subgranular zone of the dentate gyrus (DG) and the subventricular region of the hippocampus both exhibit adult neurogenesis[130]. In models of animals, traumatic brain injury has been revealed to encourage the growth of neurons in the dentate gyrus and cerebral cortex[131]. When injected into animals, a G-actin sequestering protein termed thymosin β-4 (Tb4) boosted the proliferation of neural precursor cells in the cells (NPCs). It also promotes NPC differentiation and enhances angiogenesis. TBI is associated with angiogenesis and synaptogenesis, which may help in the recovery of TBI. It also causes a rise in vascular density in the brain's cortex. According to a new study, Tb4 activated peptide fragment and N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) improved the number of dendritic spines in the injured brain of a rat, enhancing neurogenesis and angiogenesis[132]. For CNS injuries and neurological conditions, stem cell therapy has emerged as a potential therapeutic option in recent years[133]. The most common technique of administration is a stereotactic injection of neural stem cells (NSCs) into the brain. TBI has also been the subject of research into embryonic stem cell (ESC) transplantation. The inflammatory response after TBI constrains the existence and transplanted ESCs integration[134]. However, there is a possibility of developing cancer. ESC transplantation has been demonstrated to enhance neurological results[135]. Many researchers have verified the broad benefits of stem cells in the treatment of spinal cord and brain damage[136]. Many studies have demonstrated the broad benefits of stem cells in the treatment of spinal cord and brain damage. For TBI recovery, various cell types have been employed. In animal models, the use of mesenchymal stem cells (MSCs) for traumatic brain injury recovery has been studied. MSCs came from the adipose tissue, umbilical cord and bone marrow[137]. MSC transplantation should take place within 24 hours following TBI. MSCs have been demonstrated to secrete growth factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor and fibroblast growth factor 2 (FGF-2) that can help advance neurological outcomes following a TBI[138].

Therapeutic objectives in traumatic brain injury: approaches

TBI's pathophysiology and molecular causes have been better understood because of extensive research. TBI injuries are irreversible, however, following an injury that develops over months or years can be repaired with treatments. Effective therapeutic medications must be taken during a subacute or chronic period due to the protracted injury period, which includes apoptotic cell death, neuroinflammation, excitotoxicity, oxidative stress, axonal degeneration, and neuroinflammation.

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Hyperosmolar therapy

In the event of a TBI, hyperosmolar treatment can be given as a bolus or as an infusion. The initial effects of mannitol are caused by changes in blood rheology. As blood rheology recovers and blood becomes less viscous, CBF increases[139]. The body's autoregulatory response to this ultimately limits CBF by transient vasoconstriction. Though mannitol has osmotic diuretic effects, this method for lowering ICPs is thought to occur after the primary action.

Enriched environment (EE) intervention for TBI recovery

The significance of neuro-rehabilitation in reintegrating TBI patients into a productive lifestyle is critical. Long-term depression is common among TBI sufferers. TBI patients' emotional well-being is improved significantly when they are exposed to favourable situations. A larger cage and more opportunities for sensory stimulation, social interaction, and exploratory activities are provided for the animals in an EE. Rats given an EE showed improvements in both neurobehavior and neuroanatomy. Rats given an EE showed improvements in both neurobehavior and neuroanatomy[140]. Multimodal therapies, including exposure to an EE, have had excellent effects in animal models of TBI. After brain ischemia, EE exposure has been demonstrated to increase spatial memory recovery[141]. Exposure to an EE has antidepressant effects in olfactory bulbectomized rats. EE has also been shown to improve the function and appearance of neural grafts in rats with striatal lesions[142]. Visually impaired mice have also been shown to restore some visual acuity after being exposed to an EE[143]. The preventive impacts of EE exposure before a TBI have also been found to be beneficial. Rats with injury to the spinal cord show functional recovery after being exposed to an EE[144].

EPILEPSY

The most prevalent, serious, and persistent neurological disorder, epilepsy affects 65 million people worldwide[145]. People with epilepsy face ignorance, prejudice, and the stress of living with a chronic random illness that can result in a loss of self-sufficiency in daily tasks[146]. Even though most cases of epilepsy may be successfully cured, there is a considerable treatment gap, particularly in low and middle-income nations where anti-seizures drugs are either unavailable or too expensive[147]. However, not all individuals gave a response to drug therapy, and there is mounting proof that surgery and other forms of treatment, including stimulation of neurons and nutrition, can be successful. Key aspects of seizures in children and adults were debated in two earlier conferences. This section focuses on recent developments[148].

The International League Against Epilepsy (ILAE) describes an epileptic seizure as "a transitory manifestation of signs related to aberrant extreme or synchronized neuronal activity in the brain. Seizures are defined as a “lasting brain predisposition to create epileptic seizures, with neurobiological, psychological, cognitive, and social implications”[149]. The conceptual definition can be challenging to execute in routine practice, hence the ILAE recently finalised an operational definition that is better suited for clinical usage. "At least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (ii) one unprovoked (or reflex) seizure with a risk of further epilepsy alike to the general reappearance danger after two unprovoked seizures (at least 60%) occurring within the next 10 years; and (iii) analysis of an epilepsy syndrome," according to the operational definition[150]. Individuals who have been seizure-free for at least 10 years and are no longer taking anti-seizure medications are deemed to have resolved epilepsy. This definition maintains the difference between provoked nonreflex (or

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acute symptomatic) epilepsy and unprovoked nonreflex (or spontaneous) epilepsy, which are epilepsy brought on by incidents that provisionally lower the seizure threshold but are unrelated to an enduring propensity and are therefore ineligible for an epilepsy diagnosis. Seizures that develop within 7 days of the trauma of the head with a metabolic disturbance, are examples of such seizures[151].

Mechanism and Pathogenesis of Epilepsy

Signalling roles of $ca^{2+}$and ros

In cell signalling, ROS play a significant role[152]. Mitochondria play a vital role in regulating Ca^{2+} homeostasis in cells and act as a Ca^{2+} buffer. Tricarboxylic acid (TCA) cycle enzymes such as succinate dehydrogenase, isocitrate dehydrogenase and maleate dehydrogenase are activated by physiological increases in mitochondrial Ca^{2+}[153]. Increased quantities of decreased oxidative phosphorylation substrates (NADH and FADH2) arise from their activation. As a result, a normal increase in mitochondrial Ca^{2+} causes higher respiratory chain activity amplified proton pumping, and, as a result, ROS production. The concept of ROS and Ca^{2+} crosstalk is based on the reciprocal interaction between Ca^{2+} modulated ROS generation and ROS modulated Ca^{2+} signalling. Ca^{2+} can influence ROS formation by merely stimulating the TCA cycle, which increases metabolic rate[154]. Nitric oxide can also be created by Ca^{2+} by activating the enzyme nitric oxide synthase. NO has been shown to block complex IV, which can cause ROS to be produced at the Q_0 site of complex III. Additionally, synaptic glutamate release caused by nitric oxide has been shown to increase excitotoxicity in neighbouring cells. Ca^{2+} may do this by increasing the electron flux during oxidative phosphorylation while also partially blocking the electron transport chain. If the electron transport chain is hindered, the likelihood of electron slippage to oxygen may increase[155].

Free radical homeostasis disruption plays a function in epileptogenesis.

The part of free radical homeostasis in brain illnesses is of considerable interest because CNS cells are especially vulnerable to the adverse effects of reactive oxygen and nitrogen species (RNS). Additionally, the CNS's antioxidant defence mechanisms are quite feeble. This is crucial because the brain has many mitochondria, exhibits high levels of aerobic metabolic activity, consumes a lot of oxygen, has a higher ratio of membrane surface area to cytoplasmic volume, and has a neural network that is susceptible to disruption[156]. The brain contains a lot of iron, and brain trauma creates iron ions that can promote the production of free radicals[157]. Also, superoxide radicals can be produced by the catecholamine auto-oxidation and xanthine oxidase enzyme in the cytoplasm[158]. Notably, antioxidants and repair capacity decline with ageing. Neurons are mainly vulnerable to oxidative assaults because they lack antioxidant enzymes like glutathione peroxidase (GPX) and catalase (CAT), as well as nonenzymatic antioxidants like glutathione (GSH) and vitamin E[159]. The two main opposing functioning neurotransmitters in the CNS are glutamate (excitatory) and the ɤ-amino butyric acid (GABA) (inhibitory). Glutamate is the main factor in the onset of oxidative stress and can be dangerous in higher concentrations[160]. Oxidative stress can affect a variety of biological component targets, including nucleic acids, lipids, proteins, and carbohydrates. When monosaccharide carbohydrates are oxyaldehydes, oxidised are produced, and these substances can cause protein aggregation[161]. Nucleic acid disruption may be triggered by free radicals. They can cause deletions and other changes by breaking strands of DNA or straight modifying purine and pyridine nucleotides[162]. Because of its decreased repair systems and deficiency of histones, as well as its proximity to the site of ROS

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formation, mtDNA is a much extra vulnerable aim for free radical damage. Mitochondrial malfunction may originate from mtDNA alteration, leading to cellular dysfunction. Lastly, RNA is the greatest vulnerable to oxidative damage since it is single-stranded, not covered by hydrogen bonds, and less protected by proteins. Proteins may be changed or gene expression may be dysregulated as a result of RNA damage[163]. Point mutations in the mitochondrial tRNALys gene are the source of the mitochondrial disease known as myoclonus epilepsy with ragged red fibres (MERRF) syndrome. Partial seizures are frequent in the mitochondrial encephalopathy with lactic acidosis and stroke-like episodes syndrome, which results from mutations in the mitochondrial tRNALeu gene[164]. Lipid peroxidation is caused by oxidative damage to polyunsaturated fatty acids in phospholipids of membranes (LP). LP damages cellular membranes, causing significant damage to their structure and function. Numerous by-products are created during this process, with malondialdehyde being the most well-known. Unsaturated hydroperoxides produced by the polyunsaturated fatty acids peroxidation can cleave down to yield different reactive aldehydes (MDA). Reactive aldehydes can form covalent bonds with proteins, altering their properties and harming cells[165]. Protein redox status is also important, as stated in the section on $Ca2^{+}$ and ROS signalling activities. Another effect of a rise in ROS production is a reduction in the action of the Na^{+}/K^{+}-ATPase, which is responsible for maintaining ionic gradients in membrane neurons. These electrical and chemical gradients produce the electrical activity needed for proper CNS functions. A reduction in the activity of Na^{+} /K^{+}-ATPase may lower the convulsive threshold, resulting in a rise in excitatory neurotransmitters like aspartate and glutamate or a decrease in inhibitory neurotransmitters like GABA. The intracellular area contains the majority of glutamate. Neurons may suffer damage from elevated glutamate concentration in the extracellular compartment. Increased glutamate extracellular concentrations have been related to a range of putative causes, including excessive release and defective cellular absorption, in the situation of CNS damage or disease. By directly inactivating glutamine synthetase (GS), ROS production can also enhance the onset of seizure activity by allowing an excessive rise in glutamate. The term excitotoxicity refers to neurotoxicity produced by excessive glutamate receptor activation, which can be triggered by glutamate receptor agonists or glutamate. Excessive activation of glutamate receptors, such as NMDA and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, results in an overwhelming rise in Ca^{2+} concentration in cytosol and mitochondria. Ca^{2+} levels in neuronal cells can sometimes reach dangerously high levels even before the damage. It is believed that long convulsions, like status epilepticus, release a adequate amount of ROS to overcome the antioxidant defences of the mitochondria. The majority of the time during the damage phase, the levels of Ca2+ are inadequate to result in death of cell. Later in the latent phase, however, Ca^{2+} remains increased, triggering a variety of properties mediated by secondary messengers and, as a result, causing long-term alterations in neurons, including death Figure 9. Ca^{2+} remains increased during the chronic phase if neuronal cells survive the latent period, and hence performs a unique function in keeping spontaneous recurring seizures. Overall, oxidative alterations may disrupt the function of receptors, enzymes, neurotransmitters, and structural proteins, resulting in abnormal neuroplasticity changes, cell decline, and eventually cell death[166].

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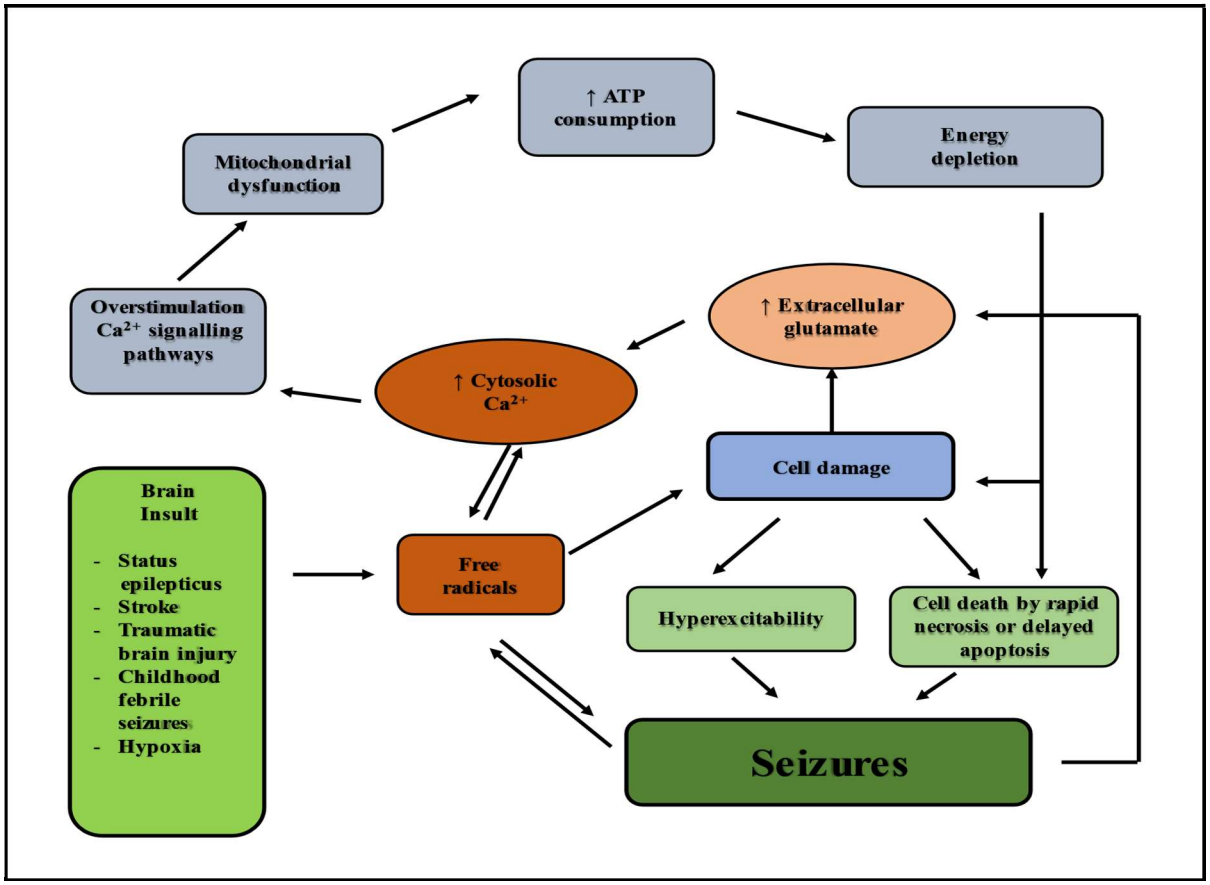

Figure 9 A schematic illustration of the predicted mechanism of damage of cell and epilepsy genesis is illustrated in acquired epilepsy. As a result of convulsions or an initial brain injury, free radicals build up. Increased levels of cytosolic Ca^{2+} and extracellular glutamate are associated with seizures, which cause dysfunction of mitochondria, rise in consumption of ATP, and reduction of energy. This is related to delayed apoptotic cell death and cell damage. Seizures are once more thought to be caused by cell death. Additionally, hyperexcitability might result in a reduced seizure threshold and a propagation reaction.

Therapies for Epilepsy

Precision therapies

Our knowledge of the molecular mechanisms underlying the aetiology of epilepsy has significantly risen in recent years. The most important advancements have been made in the study of seizure genetics, predominantly the identification of the gene mutations that account for a sizable fraction of cases of progressive and epileptic encephalopathies (DEEs)[167]. The discovery of an epileptogenic alteration enables the diagnosis (or creation) of precision-therapy drugs to target the useful defect that causes epilepsy in individuals. The utilisation of the ketogenic diet to cure seizures brought on by Glucose Transporter Type 1 (GLUT1) Deficiency Syndrome serves as an example of precision treatment. An additional energy source can be given to the brain to treat GLUT1 deficiency, which causes decreased glucose uptake in the brain and neuronal dysfunction[168]. Recent analyses suggest that the usage of drugs previously licenced for other purposes may be a part of precision medicine for epilepsy in persons with

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certain gene abnormalities. Everolimus is a repurposed drug that was previously discussed on this page for treating seizures brought on by TSC. There have been some methods for finding medications that can be used to treat monogenic epilepsies[169]. In certain circumstances, better results might be obtained without the use of additional pharmaceuticals by discontinuing treatments that, regrettably, worsen these patients' seizures. [170]. Precision therapies can help with seizures caused by metabolic, inflammatory, or immune-mediated factors as well as genetic abnormalities[171]. Although epilepsy precision therapies are still in their infancy, their use will undoubtedly rise as more data becomes available and better, more specialised medicines become available. In many patients with known gene mutations, targeted therapy for genetic seizures has been established to improve results; however, a more recent analysis provided a more sombre appraisal of their current impact[172].

Biomarker-guided therapies

In epilepsy research, the quest for biomarkers is still a prominent area. Biomarkers can be created using a mix of molecular, genetic, imaging, cellular, and electrophysiological measurements, as well as other clinical or laboratory data[173]. Biomarkers could be used to increase diagnostic precision, recognise ongoing epileptogenesis and its causes, forecast how specific treatments would affect seizures, gauge sensitivity to negative drug side effects, and more. To detect Han Chinese and other South Asian ethnic groups who are at high risk of carbamazepine-induced substantial cutaneous side effects, several biomarkers, like the HLA-B*15:02 antigen, are already employed in clinical practise[174]. Biomarker discovery and validation could improve treatment outcomes in a variety of ways, including therapeutic benefits. First, biomarkers could be utilized to recognize persons who are at high risk of acquiring epilepsy as a result of an epileptogenic insult, allowing them to be registered in clinical trials of potential antiepileptic drugs. Second, identifying biomarkers that predict seizure recurrence could help doctors decide whether to initiate or stop ASM therapy in individuals who have only had one seizure. Third, patients who are likely to react favourably to a given medication could be identified and enrolled in clinical trials for that drug, lowering the number of non-responders and preventing them from obtaining a placebo or inefficient therapy. Fourth, biomarkers have the potential to be utilised to monitor therapy response by informing doctors before a certain medication is administered to a patient whether it will be effective and safe. Last but not least, and most importantly, biomarkers may one day be able to inform doctors which ASM is greatest likely to treat seizures efficiently and with the fewest side effects. Therapy paradigms may be dramatically changed as a result. For instance, the utility of a treatment that is effective in completely controlling seizures in 5% of individuals with drug-resistant epilepsy would be significantly increased if we had biomarkers that could detect people who are receptive to it. To increase the likelihood of success, we would only provide that medication to receptive patients in such a situation[175]. In reality, it is uncommon for a single biomarker to offer the best data for any intended usage. More immediately, improvements will probably come from algorithms that combine clinical data with biomarkers. This technique can be greatly aided by the development of tools based on artificial intelligence[176].

Novel medications and the search for disease-modifying treatments

The small effect of second-generation ASMs on seizure outcomes in persons who are resistant to older drugs encourages continued research into newer, potentially more effective therapies Table 4.

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Table 4 A collection of investigational medications that are presently in CT as possible epilepsy therapies. The list is not exhaustive, and it excludes drugs that have been licensed for other uses but are now being evaluated for possible repurposing in epilepsy.

Anavex 2–73	Omaveloxolone (RTA 408)
Ataluren	OV 329
Carisbamate	Sec-butylpropylacetamide
CVL 865 (PF-03672865)	Soticlestat (TAK 935, OV935)
CX8998	Vatiquinone (EPI-743)
Ganaxolone	Vixotrigine (CNV 1014802)
Huperzyne A	XEN 496
JJ 40411813	XEN 1101
NBI 921352 (XEN 901)	

Many advances are currently assisting drug development, including a better understanding of epileptogenesis and seizure induction mechanisms to specific aetiologies, enhanced understanding of pharmacoresistant mechanisms, and the availability of disease-specific and pharmacoresistance models. These advancements are altering the paradigms for medication discovery and development[177]. A considerable paradigm shift has occurred concerning treating the original illness, i.e., precise etiologies and the molecular pathways associated with such etiologies, as opposed to focusing on medications to reduce seizures[178]. This approach will eventually lead to the development of innovative small molecules, reused pharmaceuticals, and other therapies based on cutting-edge technologies like gene therapy and antisense oligonucleotides. Some of these treatments need invasive administration techniques, which are also being researched for fresh applications of current medications[179]. A closely related paradigm shift is to address epileptogenesis and other disease symptoms specifically[180]. In syndromes with a continuous course, this kind of drug may be utilized to prevent epilepsy, reduce its development, and alter the onset or course of concomitant conditions including intellectual incapacity and other disorders. Extensive diversity of compounds has been taken to have antiepileptogenic effects in preclinical animals via antioxidant, anti-inflammatory and other mechanisms[181]. Phytocannabinoids, erythropoietin, melatonin, vitamins, and other dietary elements, as well as drugs currently approved for other signs, such as losartan, montelukast, metformin and ceftriaxone, are among the chemicals[182]. It has to be seen whether these features revealed in animal models translate into therapeutic benefit. It's important to note that several correct drugs targeted at specific causes of epilepsy may have effects that modify the condition, although it's likely that drugs that focus on a single molecular route won't treat all of the comorbidities associated with aberrant neural networks. As previously stated, the development of biomarkers to identify patients who respond to medications, detect epileptogenesis at an early stage, and assess treatment response may enhance clinical trials of the novel, investigational medicines[183]. Contrary to assertions to the contrary, proving that a prescribed chronic treatment initiated before the onset of seizures stops the incidence of epilepsy in individuals still getting the therapy does not demonstrate seizure protection because any ASM with a purely symptomatic effect could outcome in

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the same outcome. Similarly, seizure suppression may be enough to stop some comorbidities, such as the advancement of cognitive dysfunction. To provide definitive evidence that medicine is efficacious in avoiding epilepsy or has a straight disease-modifying effect, really new trial designs will be necessary[184].

SCHIZOPHRENIA

Schizophrenia is a complex, long-term mental health condition characterised by delusions, impaired cognitive ability, disorganised speech or behaviour, and hallucinations. The disease's initial onset and chronic nature make it a devastating illness for many sufferers and their families[185]. Disability is frequently produced by negative indications (characterised by loss or inadequacies) and cognitive symptoms (such as working memory, attention deficits, or executive function impairments). Positive signs including delusions, suspicion, and hallucinations can also lead to relapse[186]. There is an absence of consensus about pathophysiology, aetiology, and diagnostic criteria for schizophrenia due to the disorder's inherent variability. This page provides a brief explanation of schizophrenia and the available treatments[187].

Mechanism and Pathogenesis of Schizophrenia

Free radicals are supposed to play a part in the pathophysiology of schizophrenia[188]. Zhang and colleagues showed that lecithinized superoxide dismutase can protect against traumatic brain injury, lung injury, and colitis. As a result, lecithinized SOD has been suggested as a possible beneficial medication for a variety of disorders. Hypoxia/reoxygenation episodes characterize obstructive adenotonsillar hypertrophy, a long-term illness. This could lead to an imbalance in the antioxidant and ROS defence mechanisms[189]. They discovered that SOD activity was much higher before tonsillectomy than after tonsillectomy, and they speculated that oxidative stress increases this antioxidant enzyme, with these characteristics returning to normal following tonsillectomy. Persons with tonsillitis were also evaluated. Both authors found that SOD catalytic activity was reduced in the patient’s sera with chronic tonsillitis, but that SOD activity enhanced after tonsillectomy[190]. SOD catalytic activity was evaluated before and after tonsillectomy. They discovered a close link between tonsillar and erythrocyte SOD activities and SOD activity in the blood reduced during the 3-year study. In this scenario, the scientists found that the severity of local infections determines this[191]. Temporary hypoxic stress was used to study the activity of SOD and its alteration of mRNA for SOD in cultured glial cells. In glial cells, transient hypoxia boosted Mn-SOD activity but not Cu, ZnSOD activity. SOD mRNA expression was also increased in hypoxia-treated cells, with Mn-SOD mRNA levels rising faster than Cu, and Zn-SOD mRNA levels Figure 10 [192].

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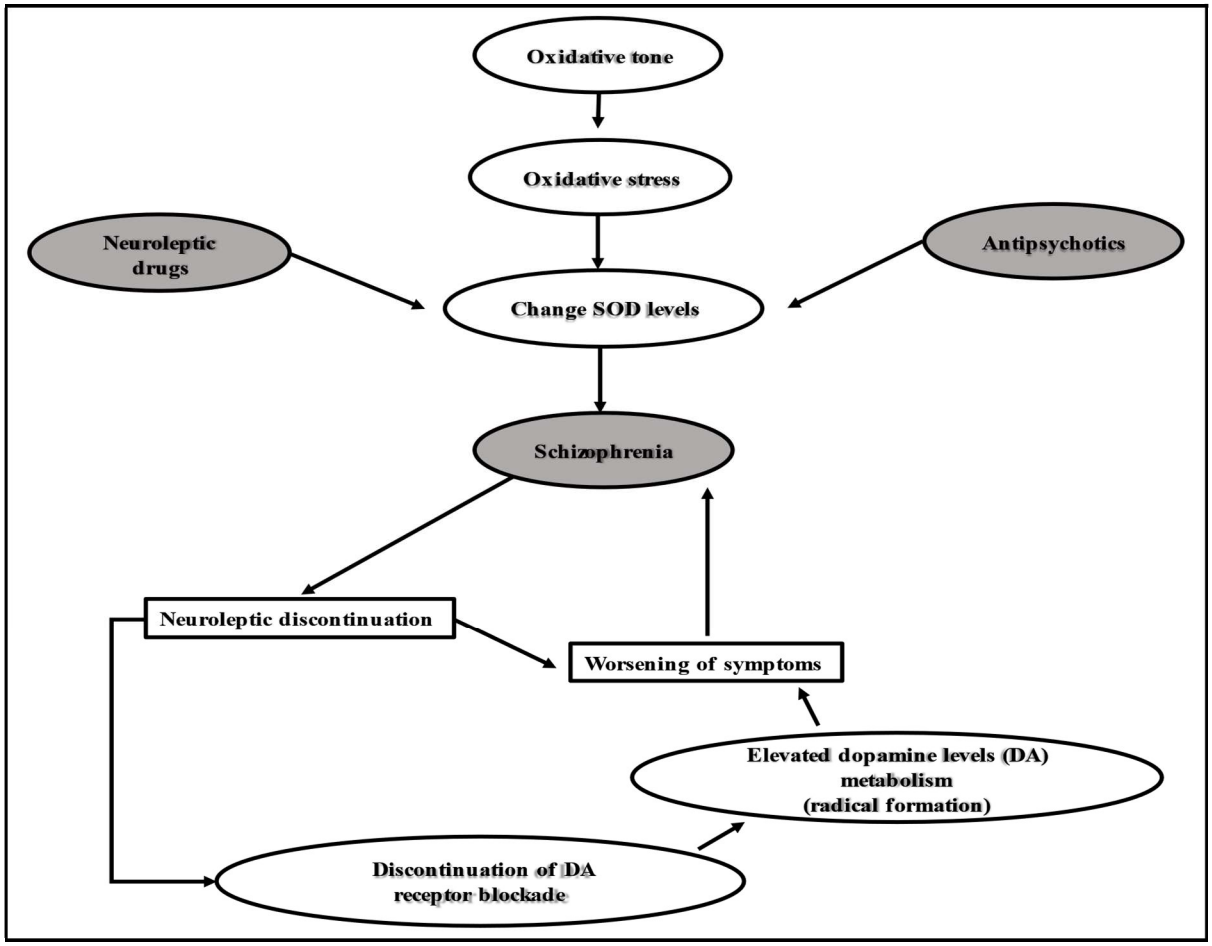

Figure 10 The mechanism of Schizophrenia. * Superoxide dismutase *(*SOD*)*

Therapies for Schizophrenia

Nonpharmacological therapy

For the individual to reintegrate into society, therapies try to address signs, lower recurrence and enhance adaptive functioning. For the best long-term results, nonpharmacological and pharmaceutical medications are required because people usually regain their baseline level of adaptive functioning. The cornerstone of treating schizophrenia is pharmacotherapy, although some patients may experience persistent symptoms. For instance, psychotherapy is a crucial form of non-pharmacological medicine[193].

Pharmacological therapy

In most schizophrenia patients, establishing effective rehabilitation programmes without the use of antipsychotic medicines is difficult. Because the bulk of illness-related brain abnormalities develops within five years of the initial acute episode, early medication treatment is crucial[194]. Illegal use of amphetamines and other CNS stimulants, along with alcohol and drug misuse, point to a poor prognosis. All three substances-alcohol, coffee, and nicotine can affect how drugs work. If a psychotic episode occurs suddenly, treatment should be begun shortly soon. Reduced hostility and an effort to reappearance the individual to regular functioning are the main objectives of the first week of treatment (e.g., sleeping and eating). Based on the individual's response at the beginning of treatment, the proper dosage should be adjusted[195]. Following acute phase treatment for schizophrenia, maintenance therapy

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should focus on enhancing socialisation and enhancing self-care and mood. Prolonging life is essential to help avoid a recurrence. Individuals who get pharmacological treatments experience a lower rate of relapse than those who do not 18% to 32% versus 60% to 80%, respectively[196]. The duration of medication therapy should be maintained for at least 1 year following the first psychotic episode[197]. Except for clozapine, second-generation (atypical) antipsychotics (SGAs) are the agents of choice for first-line treatment of schizophrenia, according to the American Psychiatric Association[198]. Because they produce fewer extrapyramidal effects, SGAs are generally preferred to FGAs. Diabetes mellitus, hyperlipidemia, and weight gain are all typical metabolic side effects of SGAs. The greater risk of cardiovascular death observed in schizophrenia patients may be caused by these side effects[199].

Augmentation and Combination therapy

Patients who do not respond to clozapine may be evaluated for augmentation therapy (with ECT or a mood stabilizer) or combinational therapy (with antipsychotics). When giving augmentation therapy, clinicians should follow the following guidelines:

• When used alone, augmenting medications seldom relieve the symptoms of schizophrenia, thus they should only be utilized in individuals who have not responded well to earlier therapies.
• The majority of individuals who benefit from augmentation therapy experience rapid improvement.
• The majority of individuals who benefit from augmentation therapy experience rapid improvement.

A mood stabiliser is a shared augmentation agent. Lithium, for example, improves behaviour and mood in certain individuals without having an antipsychotic effect. Combination therapy involves the administration of two antipsychotic medicines at the same time, such as an SGA and an FGA, or two distinct SGAs. When multiple antipsychotics are taken at the same period, the risk of serious side effects increases[200].

Subarachnoid Hemorrhage

Impulsive subarachnoid haemorrhage (SAH) contributes to 2 to 7 percent of all strokes, but a higher share of mortality and morbidity from stroke due to its younger mean age frequency and high mortality. A ruptured intracranial aneurysm (aSAH) is the most usual cause, accounting for 85 percent of cases. It affects 6 out of every 100000 people in wealthy countries each year, albeit the rate is decreasing[201]. This decline, which is largely related to reduced smoking and better high blood pressure treatment, could have a societal health impact comparable to the fall in case fatality that has happened in recent decades[202]. Contrary to popular opinion, the occurrence is higher in Japan than in Finland. The female predominance has no rational reason. From 52 years in 1973 to 62 years in 2002, the average age of onset has increased. This article examines the diagnosis and treatment of SAH with a focus on new advancements, the factors that contributed to these advancements, knowledge gaps, and areas for future research rather than updating guidelines[203].

Mechanism and Pathogenesis of Subarachnoid Hemorrhage

Transient global cerebral ischemia and associated diseases occur minutes following aneurysm rupture and are referred to as EBI. Its symptoms appear within the first 2 hours and last for 72 hours following the initial incident. SAH causes damage that goes beyond the haemorrhage site and is not limited to the location of the ruptured vessel. Shortly after SAH, signalling cascades are started, which causes the BBB to be disrupted as well as inflammatory reactions, damage to the cell, and oxidative stress. Following aneurysm rupture, intracranial pressure (ICP) rises quickly, reaching arterial pressure (about

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120 mmHg) in 1-2 minutes before levelling off slightly above baseline. Reduced cerebral perfusion pressure (CPP) caused by elevated ICP impairs cerebral blood flow (CBF) and jeopardises cerebrovascular autoregulation. Following SAH, there was a decline in CPP to practically nothing, followed by a decrease in CBF. Although the CPP returns to normal, the CBF remains low, indicating acute vasoconstriction within 6 hours. EBI is caused by global cerebral ischemia followed by progressive reperfusion. Early vasoconstriction has been reported to occur regardless of CPP or ICP alterations. Although a lower CPP isn't necessarily linked to a bad neurological outcome, a drop in CBF to less than 45% of baseline in the initial hour after SAH projected 100% death. The compensatory vascular responses of cerebral autoregulation retain oxygen and CBF in a myogenic and neurogenic dependent way[204]. SAH causes an immediate disruption of cerebral autoregulation due to a hemodynamic mismatch between neurons and arteries, resulting in lower CBF Figure 11. Oxidative stress contributes significantly to the emergence of EBI following SAH through the production of ROS radicals. The following ROS are formed quickly after SAH: superoxide anion, OH, H_2O_2, NO, and peroxynitrite (ONOO). After SAH, mitochondrial function is affected by hypoxia and oxygen deprivation, which causes the autooxidation of haemoglobin created by subarachnoid blood lysis. Hypoxia transformation of endothelial xanthine dehydrogenase, nitric oxide synthase activity, lipid peroxidation, and increased NADPH oxidase are also factors of elevated ROS levels. When injured cells' mitochondria are triggered by high levels of Calcium, sodium, and ADP, they release excessive ROS. ROS has been shown to cause harm to the neurovascular unit by causing LPO, and protein and DNA degradation. Inflammation, blood-brain barrier breakdown, and the liberation of vasoconstrictors are all caused by ROS. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) triggers a compensatory endogenous antioxidative response under physiological settings. These antioxidants, however, diminish 1 hour after SAH. The formation of EBI is greatly aided by the main signalling pathways, such as the cell death of apoptosis cascade and nuclear factor kappa beta (NF-B), which is triggered by intracellular ROS and upregulates nitric oxide synthase 2. The two main cells contributing to the inflammatory reactions in the CNS are microglia and astrocytes. After SAH, astrocytes can manufacture and secrete factors like chemokines and cytokines, causing EBI. Astrocytes can produce and emit substances like cytokines, whereas microglia cells are immune-competent and phagocytic. Free radicals trigger cytokine-secreting leukocytes, and extravascular haemoglobin and its lysates are other inflammatory mediators. EBI is strongly associated with the cytokines IL-1, IL-8, IL-6, IL-1, and TNF. Following SAH, IL-1, IL-6, and N-terminal kinase (JNK)-mediated induction raises MMP-9 expression, with an initial peak occurring around 6 h and a second peak occurring between 48 and 72 h. It is believed that the inflammatory cascade is initiated by the proteins extracellular signal-regulated kinase 1/2 (ERK1/2) and MAPK. Two additional mediators are NF-B, the main regulator of inflammatory transcription of the gene, and High-mobility group box-1, a possible predictor of functional outcome following SAH. It has been shown that chemokines including chemokine (C-C motif) ligand 5 (CCL5), monocyte chemotactic protein-1 (MCP-1), chemokine (C-X-C motif) ligand 1 (CXCL1), and fibroblast growth factor-2 (FGF2) stimulate blood-derived inflammatory cells, and their expression has been increased after[205]. Surface proteins that mediate leukocyte-endothelial contact and inflammation are known as adhesion molecules. After SAH, the number of leukocytes increases, which is linked to a worse result. Activated leukocytes can enter the brain parenchyma by adhering to intercellular adhesion molecule-1

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and lymphocyte function-associated antigen-1 (ICAM-1). Among the cell-surface receptors discovered following SAH are integrins, immunoglobulins, cadherins, and selectins. In the CSF and serum of people with SAH, there are higher concentrations of the soluble forms of cell adhesion molecule-1 (VCAM-1), P-selectin, vascular E-selectin, and ICAM-1.

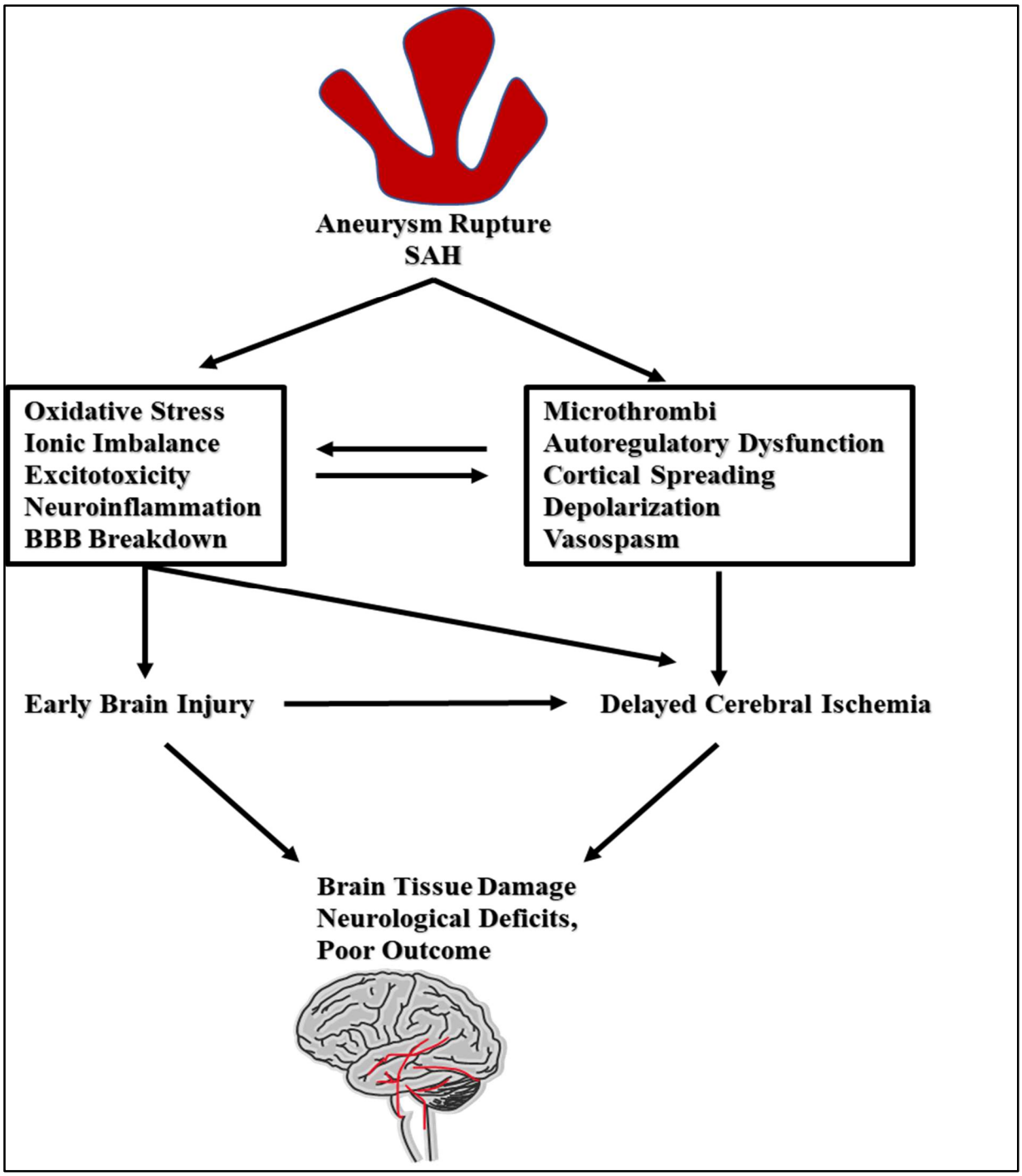

Figure 11 An overview of the pathophysiology of subarachnoid haemorrhage (SAH). The blood-brain barrier (BBB).

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Therapies for Subarachnoid Hemorrhage

An influx of immune cells

Inflammation has been linked to brain injuries and has been proposed as a primary contributor to brain damage following SAH. Increased cytokine levels have been observed in cerebrospinal fluid (CSF) and plasma after SAH[206]. SAH causes a rise in chemokines and pro-inflammatory cytokines in mice. Endothelial cells, microglia, leukocytes, and neurons produce chemoattractants and express adhesion molecules like selectins and integrins, which attract inflammatory cells like macrophages and granulocytes to the wounded brain[207]. Patients with SAH had higher levels of ICAM-1 and VCAM-1 (intercellular and vascular adhesion molecules 1) in their CSF and serum[208]. Furthermore, increased BBB permeability following SAH promotes the influx of peripheral immune cells into the brain. In the endovascular puncture model, matrix metalloproteinase 9 (MMP9) was found to be upregulated following SAH. MMP9 is a collagenase that enhances immune cell transport to the site of injury by destroying extracellular matrix tight junctions and basal membrane proteins (ECM)[209].

Early after SAH (within hours), neutrophils and macrophages enter the subarachnoid space, activating local microglia, astrocytes, and neurons. Neutrophils phagocytose RBC in the subarachnoid region before degranulating and dying. Additionally, neutrophils are present in the CSF of SAH patients. Their information shows that active macrophages/microglia may still be present in the endovascular puncture model three weeks after SAH, indicating that relocation to the lesion site and stimulation of these cells appear to be continuous inflammatory processes following SAH. Following SAH, T-cells also penetrate the injured area, but only two days later[210].

Rescue therapies

Rescue therapy such as forced intraarterial balloon angioplasty and hypertension medications is advised if DCI develops[211]. Even though induced hypertension is the principal treatment recommended by most guidelines, the evidence is of moderate to low quality[212]. The therapy of DCI with or without induced hypertension was examined in an RCT with 41 aSAH patients[213]. Although induced hypertension did not affect clinical outcomes, it increased the likelihood of serious adverse events by a factor of five. This could be because individuals with reduced oxygen transport to brain tissue have a benefit in the risk: benefit ratio of induced hypertension, but this benefit is obscured when individuals who do not have cerebral ischemia cannot advantage from induced high blood pressure included. Prospective observational studies or RCTs may be used to study induced hypertension. If induced high blood pressure is unsuccessful to relieve DCI or the individual cannot bear it, endovascular therapy with balloon angioplasty is typically considered.[214]. There is moderate to low quality evidence for these procedures, and no RCTs have been reported. Although these therapies are designed to reverse aVSP, the problem being treated with DCI does not need a VPS. Furthermore, in RCTs, lowering aVSP has not always resulted in better results. There is no agreement on which interventional methods should be used. A review of 55 investigations of endovascular therapies for aVSP found that the condition could be decreased but not better. These operations' dangers are likely under-reported, and they should be investigated further[215].

INTRACEREBRAL HEMORRHAGE

A common and deadly neurological disorder known as intracerebral haemorrhage (ICH) causes 10-20% of strokes in American and European countries and 25-35% of strokes in Asian countries[216]. ICH has a

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lesser prevalence than ischemic stroke, which has a prevalence of more than 70%, but it more than makes up for it in terms of morbidity and mortality: Only 20% of patients recover functional independence in the following 30 days, and death is 50% likely[217]. Only a small number of treatments for ICH have been proven to be beneficial over time, including evacuation of invasive hematoma, minimally BP control and hemostatic therapy[218]. The depressing outcomes of the Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation III trial, which evaluated minimally invasive evacuation accompanied by thrombolysis in individuals with ICH, served to further emphasise the unfortunate fact that ICH is the least easily curable type of stroke[219]. The MISTIE-III trial appeared to reinforce investigators' pessimism regarding the view of effective surgical hematoma evacuation after ICH, subsequently the disappointment of surgical hematoma evacuation investigations. However, progress has not been consistently absent in the sector, and we believe it is vital to look past the absence of apparent success in specific trials by considering the outcomes of the MISTIE-III and other finished clinical trials[220]. When a synthetic viewpoint is accepted, it becomes probable to study from the trials and apply what has been learned to create future work that is free of the constraints that afflicted its predecessors. In this review, we will describe the key treatments for ICH and outline the details of their disappointment in CT; with this foundation in place, we will recommend future avenues for achieving the potential of this research[221].

Intracerebral Hemorrhage Pathophysiological Mechanisms

Intracerebral haemorrhage produces brain damage via some pathophysiological processes, the most important of which are depicted in Figure 12. Blood that leaks from the relevant blood vessel form a hematoma, which grounds direct compression damage to the brain parenchyma and disturbs cellular construction. The hematoma causes a mass impact, which raises intracranial pressure and reduces cerebral perfusion, resulting in ischemic damage[222]. An accumulation in the parenchyma causes further harm as a result of the physiological reaction to the hematoma as well as direct toxicity of cells caused by both the accumulated hematoma and its breakdown by products[223]. Secondary ICH-mediated damage is the umbrella term for all of these pathways. Antiplatelet and anticoagulant use, the time between the onset of indications and baseline imaging, the volume of ICH on baseline imaging, and some signs of imaging, such as the blend sign, black hole sign, CT angiography spot sign and CT hypodensities, have all been found to be independent predictors of haemorrhage growth in studies[224]. Approximately 45% of patients undergo hematoma enlargement within 24 hours after symptom onset (particularly in the first six hours), leading to worsening of the mass impact and secondary damage caused by the hematoma, as well as neurological decline and poor outcomes[225]. Many medicines have been developed to target these processes; they are included below along with the molecular reason for their efficacy.

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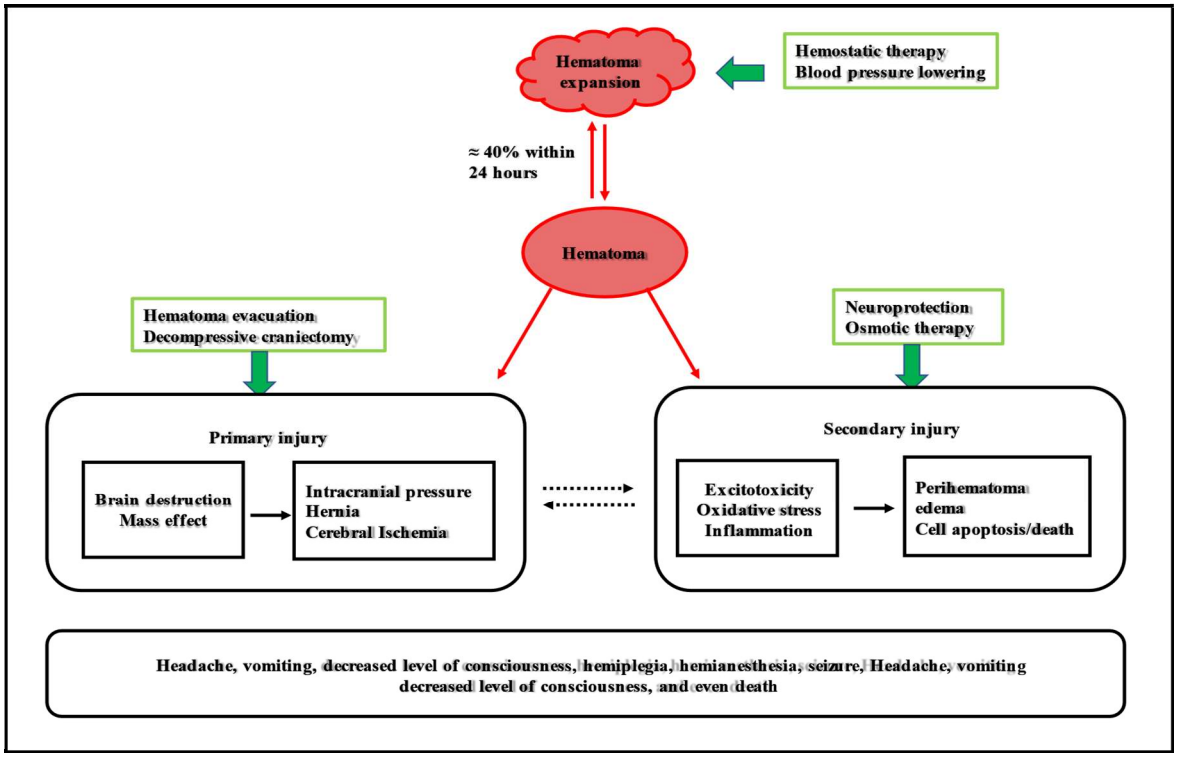

Figure 12 Intracerebral haemorrhage pathophysiological mechanisms and treatment options.

Treatment options for the hematoma and related mass effect

Since hematoma is the main factor contributing to brain injury, numerous treatments have been created to directly lessen its effects. These interventions range from mechanical removal to growth inhibition. To prevent hemostatic therapy (such as tranexamic acid, recombinant human factor VII and transfusion of platelet) hematoma expansion and BP management (such as the ATACH and INTERACT trials) have been investigated[226]. Surgical evacuation using minimally invasive (i.e., MITIE) and invasive (i.e., STICH) procedures have been employed to achieve mechanical removal[227].

Hemostatic therapy

Increased blood clotting capacity can decrease the progression of ICH and other bleeding disorders. As a result, ultra-early haemostatic treatment has been researched as a way to stop continuous bleeding and avoid hematoma expansion[228]. Recombinant human factor VIIa improves haemostasis by triggering the extrinsic pathway of the coagulation cascade, which speeds up coagulation[229]. According to a pilot study, recombinant human factor VIIa given within 4 hours of the ictus reduction in hematoma size may recover survival results in people with ICH after 90 days[230]. These results were not supported by the FAST trial, a multi-centre randomised trial in which ICH patients received recombinant human factor VIIa within four hours of the onset of symptoms. In this larger experiment, d factor VII may have increased the frequency of arterial ischemia episodes in addition to failing to enhance survival or functional results. Another hemostatic drug called tranexamic acid is widely used in clinical situations involving severe bleeding, like catastrophic cerebral haemorrhage[231]. Similar to factor VII a, tranexamic acid was discovered to be feasible in patients with ICH in small studies, but this commitment was not realised in a larger study. The TICH-2 study, a randomised controlled study with over 2300 people,

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discovered that tranexamic acid was unable to reduce mortality or enhance the efficacy of furosemide despite lowering early hematoma progress at 2 days and death at 7 days[232]. All three non-contrast computed tomography imaging signs-the blend sign, and the hypodensities-predicted hematoma expansion; the island sign, and the hypodensities all predicted poor functional outcomes in intracerebral haemorrhage individuals; and these signs did not indicate a better response to tranexamic acid treatment effectiveness[233]. Antiplatelet therapy is commonly utilized to treat ischemic cardiocerebrovascular disease, but it has the potential to enhance the incidence of ICH while also exacerbating its symptoms. As a result, platelet transfusion has been discovered as a treatment option in intracerebral haemorrhage and has been studied in patients with the acute intracerebral haemorrhage who are receiving antiplatelet medications[234]. These studies follow the same pattern as the other hemostatic medicines we discussed earlier. However, the PATCH trial discovered that transfusion of platelet in individuals with intracerebral haemorrhage on drug treatment raised the odds of death on day 90 and the percentage of patient populations who got serious adverse effects. Platelet transfusion was previously found to be safe in individuals with intracerebral hemorrhage and may show improved results in observational studies[235]. Furthermore, desmopressin has been shown to recover platelet activity in individuals with intracerebral haemorrhage who had low platelet activity or were on antiplatelet medications[236]. According to new guidelines issued by the Neurocritical Care Society, desmopressin is advised in individuals with intracerebral haemorrhage who are undergoing cyclooxygenase-1 inhibitors, however, clinical data are scarce. A significant randomised trial testing the effectiveness of desmopressin in individuals with ICH is underway. Its name is the Desmopressin for Reversal of Antiplatelet Drugs in Stroke Due to Haemorrhage (DASH) investigation[237]. The use of direct anticoagulation (OAC) medications orally (e.g., dabigatran, apixaban and rivaroxaban) in individuals with cardiocerebrovascular disorders is rapidly increasing, particularly in the elderly. New clinical concerns have emerged as a result of the widespread use of these medications in clinical practice, such as DOC-associated ICH. Reversal drugs have been studied in DOAC-related severe haemorrhages or patients requiring emergency surgery[238]. However, no particular analyses of ICH patients from these investigations have yet been issued. Only case reports have been issued on the use of particular reversal medications such as idarucizumab for the cure of DOC-related intracerebral haemorrhage. As a result, there is currently no evidence of the efficiency of reversal medications for DOAC-associated ICH[239]. In summary, hemostatic treatment has been shown to slow hematoma size in individuals with ICH, but it can also produce major thromboembolic complications, and earlier trials that used it failed to show a therapeutic advantage. The way these trials chose people for therapy could be one explanation for their poor results. The impacts of hemostatic treatment may be diminished if administered to all individuals with ICH regardless of how far along their condition is since hematoma growth only happens in less than half of all ICH patients. Considering these traits while selecting research subjects could increase the likelihood of success. The appearance of the spot sign in CT images and estimate scores can aid to recognize those who are at a complex risk of hematoma growth. The outcomes of studies based on this concept, however, have not been particularly positive: Recombinant human factor VII a was investigated in the SPOTLIGHT and STOP-IT trials in individuals with ICH who exhibited a spot sign on CT angiography, but only neutral results were discovered[240]. It is nevertheless crucial to identify those at risk as precisely as is practical in case future research examine the effects of haemostatic therapy in individuals with a

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higher risk of hematoma growth. Tranexamic acid, recombinant human factor VIIa, and other pro-coagulant drugs may not be safe and effective for use in individuals with ICH brought on by anticoagulation. Currently, a study is being conducted to see whether tranexamic acid can benefit ICH individuals taking non-vitamin K antagonists such rivaroxaban, dabigatran (clinicaltrials.gov NCT02866838).

Multiphasic therapy

Though the volume of hematoma is related to worse consequences in ICH individuals, hematoma prevention or reduction does not recover long-term functional results. This was shown in the INTERACT experiment, where the intensive BP control group's relative risk of hematoma expansion was 36 percent lower (33 percent or 12.5 mL), demonstrating that BP control can stop the progress of hematoma. The INTERACT -2 experiment, grounded on the INTERACT experiment, was intended to authorize the experimental advantages of aggressive BP control, but it was unsuccessful in doing so[241]. An alike discrepancy between clinical data and volumetric was seen in the MISTIE-III trial: On end-of-treatment CT, ICH volume was significantly reduced (12.5 mL vs. 43.7 mL), but there was no important change in results. It's problematic to resolve these findings by looking at these trials in isolation, but a larger look at the area of ICH study reveals a likely clarification: intracerebral haemorrhage causes damage not just by imposing its volume, but also by a variety of additional processes over various phases, counting the intricacies of secondary damage outlined above. As a result, treatments that focus on a specific mechanism in a single phase may be ineffective in changing long-term results. With this in attention, it seems likely that effective therapy for intracerebral haemorrhage will call for a multifaceted strategy proportional to the injury mechanism, with distinct interventional components used at different points during the ICH process. To prevent hematoma growth during the first several hours after ICH, methods including BP control should be adopted. If the hematoma still creates a mass effect, a minimally invasive hematoma evacuation procedure may be required to prevent mechanical harm. Neuroprotective methods could then be used to avoid subsequent damage and oedema that occur as a result of the main intracerebral haemorrhage process. As a result, treatments that focus on a specific pathophysiological mechanism in a single phase may be ineffective in changing long-term results. Furthermore, after patients with ICH have stabilized their state, rehabilitation should begin as soon as possible, and any comorbidities that may have a detrimental impact on prediction should be spoken as soon as likely. The INTERACT -3 study (the third, intensive care bundle with BP decrease in patients) is still ongoing. The Acute Cerebral Hemorrhage study (NCT03209258) (clinicaltrials.gov NCT03209258) attempts to see if there's a way goal-directed active management bundle (glycemic control, intense blood pressure lowering) management, pyrexia therapy, and anticoagulation reversal) in ICH is more successful than usual. As a result, it is an example of the diverse method that seems to form the anti-ICH technique with the most promise.

Conclusion

Multiple system atrophy, Cognitive Impairment, Vascular dementia, Traumatic Brain Injury, Epilepsy, Schizophrenia, Subarachnoid and Intracerebral Hemorrhage Disorders, Subarachnoid and Intracerebral Hemorrhage Disorders all pose a substantial health risk worldwide. These disorders are not only common, but they are also linked to considerable disability, poor psychosocial outcomes, and high financial consequences. Because of the scarcity of specialised treatment, new approaches to health care

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administration are required. Some of these strategies are presented, but only a handful have been evaluated for cost-effectiveness. Many areas of global neurology, like epidemiological research, need evaluations, and cost-effectiveness analyses, which require more data collecting. Pharmacotherapies have evolved significantly in the last two decades for all of these disorders, although they are still limited. Indeed, there is a significant treatment gap for these diseases, owing to the patient and healthcare system characteristics that are unlikely to improve without public and health-care professional legislation, education, and anti-stigma efforts. Fortunately, attitudes and awareness about the load are improving, and this improvement can help close the treatment gap and improve psychosocial results for persons affected by these diseases [242-287.]

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