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PHARMACOLOGY AND TOXICOLOGY OF NEUROLOGICAL DISEASE

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Abstract:

Ensuring that patients receive safe pharmaceuticals is largely dependent on pharmacovigilance, which is described by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem." We can learn more about a drug's side effects by a variety of techniques, such as database research, close observation, and unprompted reporting. The goal of increasing pharmacovigilance is being pursued through the development of new scientific and regulatory procedures. Scientifically, transparency and greater patient engagement are two key components; regulatory-wise, these include conditional approval and risk management strategies. An unpleasant and hazardous response that follows medicine after an intervention is known as an ADR. The two main categories of adverse reaction mechanisms are direct toxicity studies and hypersensitive responses brought on by changes in the pharmacokinetic and pharmacodynamic properties of pharmaceutical drugs. Direct toxicity responses can be explained by the toxic effects of a substance or its metabolites, which can manifest in different organ systems and cause physiological dysfunction, harmful chemical reactions, damage to DNA, or harm to tissues and cellular structures. Diseases affecting the brain, spine, and the nerves that link them are referred to as neurological illnesses. More than 600 disorders affect the neurological system, including less common conditions like front temporal dementia and more common ones like brain tumors, epilepsy, Parkinson's disease, and stroke. The World Health Organization (WHO) defines neurological disorders as those illnesses that impact the central and peripheral nervous systems, or the nervous system as a whole. The brain, spinal cord, cranial nerves, peripheral nerves, nerve roots, autonomic nervous system, neuromuscular junction, and muscles will all be affected by these diseases. Peripheral neuropathy and chemotherapy-induced brain damage are examples of neurological side effects that impact the brain and nervous system. The term "encephalopathy" refers to brain impairment.

Keywords: Parkinson’s disease, Stroke, Epilepsy, Brain tumor, Front temporal dementia.

Abbrevation list

ADR: Adverse drug reaction
WHO: World Health Organization
AD: Alzheimer disease
Ach: Acetyl Choline
AchEIs: Acetyl Choline esterase inhibitors
CNS: Central nervous system
ICD: Impulse control disorder
BBB: Blood brain barrier
SIADH: Syndrome of inappropriate antidiuretic hormone secretion
MS: Multiple sclerosis
TBZ: Tetrabenazine
PFC: Prefrontal cortex
DA: Dopamine
GO: Gingival overgrowth

NMS: Neuroleptic malignant syndrome
SJS: Stevens Johnson syndrome
TEN: Toxic epidermal necrolysis
RSL: Restless legs syndrome
WED: Willis Ekbom disease
OPD: Out-patient department
MAO-B: Monoamine oxidase type B

Introduction:

The study of diseases and disorders affecting the nervous system, which includes the brain, spinal cord, and peripheral nerves, is known as neurology. The word comes from the Greek word νεῦρον (neûron), which means "string, nerve," and the suffix -logia, which means "study of."(Source:) Nervous system ailments, either central or peripheral, are referred to as neurological disorders. Stated differently, they impact the neural-muscular junction, muscles, cranial nerves, peripheral nerves, nerve roots, vegetative nervous system, and brain. [1] These conditions include nerve system infections, brain tumors, traumatic nervous system disorders like head injuries, neurological disorders associated with malnutrition, epilepsy, Alzheimer's disease and other dementias, cerebrovascular diseases like stroke, migraine and other headaches, multiple sclerosis, Parkinson's disease, and other neurological disorders. Human voluntary daily movement is impacted as a result of these imbalances. The accomplishment of the human voluntary movement is actually much more complicated than it appears. Due to its intricate mechanism, numerous nerve structures are able to make ref lexive or decisional decisions. Then, using the nerve impulses meant for the musculoskeletal system, this mechanism "defines" and "controls" the motion. Additionally, it is well known that neurological disorders are the world's leading cause of disability and the second leading cause of death. [2-5]

Materials and Methods

1. Alzheimer Disease:

Dementia is a clinical condition characterized by a gradual decline in cognitive function, making it difficult for the affected individual to perform daily tasks. [6] Predominantly occurring dementias include Alzheimer's disease. [7] The development of AD is linked to a number of modifiable and non-modifiable risk factors. AD is a progressive multifactorial neurodegenerative brain condition without a recognized cause. Without a doubt, the biggest non-genetic risk factor is age. [8,9] The nerve cells in the brain are disrupted both structurally and functionally. The communication within brain circuits, which is crucial for memory and other cognitive functions, is impacted by early illness processes that also lead to synaptic Malfunctioning's of nerve cell.

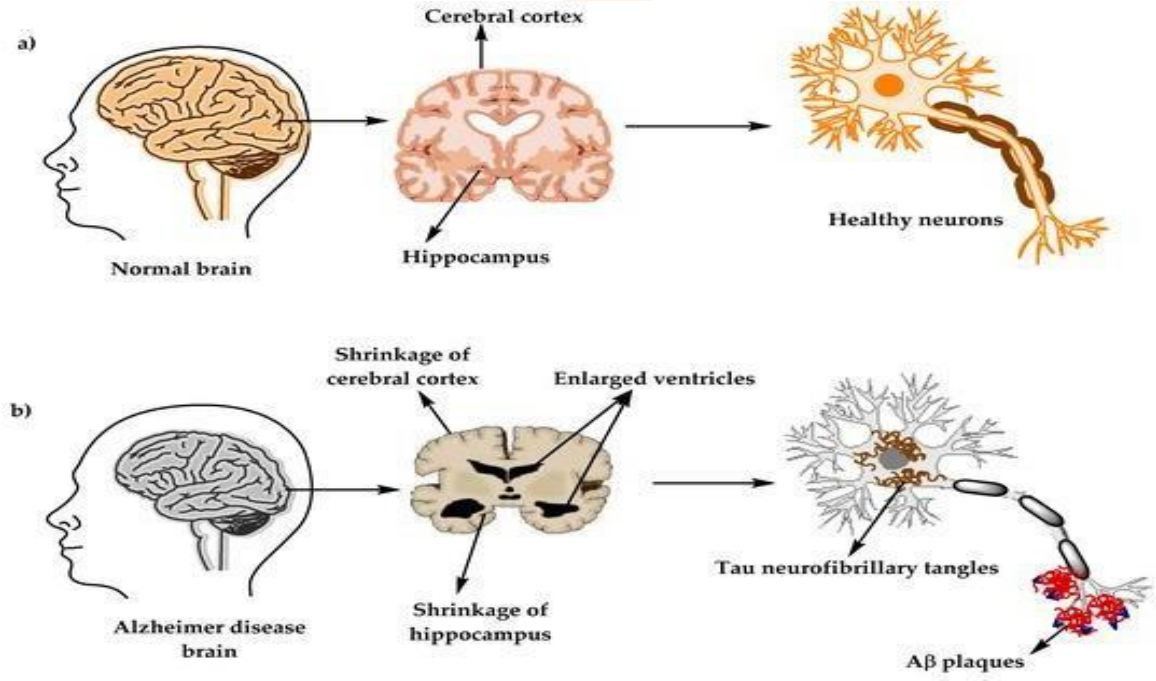

Fig.No.1: Showing structure (a)Normal and (b) Alzheimer affected brain.[11]

Adverse effect shown by Anti-Alzheimer agent: Acetylcholine esterase inhibitor:

Reduced levels of Ach in the brain are thought to be the cause of cognitive deficiencies associated with aging and Alzheimer's disease.[12] The gastrointestinal tract is the site of most AChEI cholinergic adverse effects. About 20 % of individuals using these drugs have been documented to experience these adverse effects, which are often moderate twelve. [13,14] The package inserts of the "second-generation" AChEIs that are currently on the market list nausea (11 %–47 %), vomiting (10 %–31 %), diarrhea (5 %–19 %), and anorexia (4 %–17 %) as side effects. Thirteen Clinicians are generally aware of these gastrointestinal adverse effects, which can be reduced by using longer titration times and taking these drugs with food.[15]

Clinical professionals who treat older patients should be aware of lesser-known adverse effects of AChEIs, which occur in less than 5 % of patients. [16] Asthenia, myasthenia, tremor, dizziness, headaches, bradycardia, orthostatic hypotension, syncope, gastrointestinal hemorrhage, seizures, extrapyramidal symptoms, rhinitis, fatigue, leg cramps, insomnia, abnormal dreams, and, very rarely, liver dysfunction including hepatitis are some of the potentially fatal side effects.[17,18] A few cases of agitation, aggressive conduct, and hallucinations have been reported; however, these symptoms have disappeared after therapy was stopped or the dosage was reduced. Thirteen Additionally, rivastigmine use has been linked to severe vomiting and esophageal rupture. [19]

2. PARKINSON'S DISEASE:

There are both motor and non-motor system symptoms associated with Parkinson's disease, an idiopathic disease of the neurological system. Though it can manifest in much younger people, it is a chronic, progressive neurodegenerative illness that primarily affects theelderly. This neurodegenerative illness is the second most prevalent one.[20]

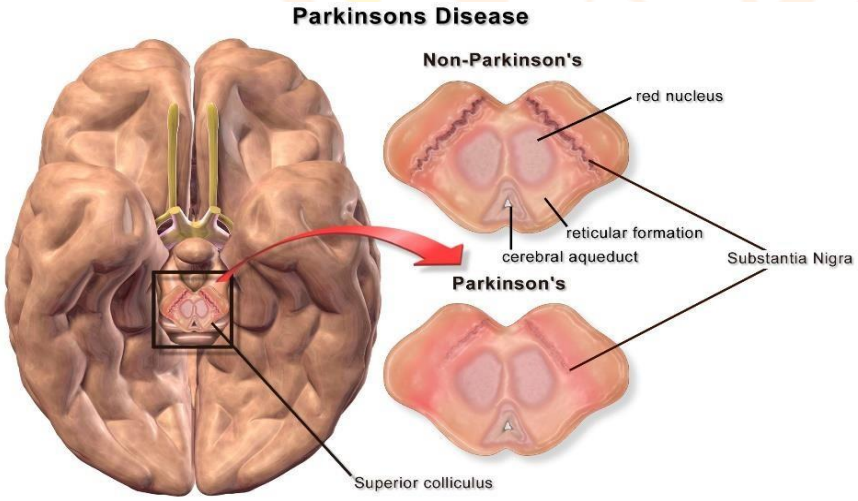

Fig.No.2: Pathophysiology of Parkinson Disease. [21]

Adverse effect shown by Anti-Parkionsons Agent

Levodopa:

Nausea, vertigo, headaches, and sleeplessness are typical side effects of levodopa therapy. If taking more carbidopa doesn't assist with nausea, domperidone may be useful. Increasing carbidopa is advised. Elderly patients require extra vigilance since they can be more vulnerable to the effects of the central nervous system (CNS). Confusion, hallucinations, delusions, psychosis, and agitation are among the most frequent side effects seen by elderly levodopa users [22-24]. Orthostatic hypotension and other gastrointestinal problems including nausea and vomiting are significant side effects as well. Anxiety and delusions are examples of neuropsychiatric traits that may arise from dopamine's "off-target" effects on extranigral brain areas. [25,26]

Dopamine Agonist:

Intense and impulsive behavioral disorders (impulse control disorder [ICD]) are a potential side effect of dopamine agonists that should be taken seriously. Hypersexuality, compulsive gambling, binge eating, obsessive shopping, pounding, and hoboism (compulsive Internet use, creative pursuits, and writing) are among the symptoms that may be present. [27– 33] Once dopamine agonists are started, it is critical that clinicians remain watchful for these issues.

Common side effects include dry mouth, sleeplessness, peripheral edema, constipation, fainting, hallucinations, nausea, vomiting, and sleepiness (which is caused by stimulation of the region postrema, which is located in the medulla at a place in which the BBB is disturbed).[34,35]

MAO-B inhibitors

MAO-B inhibitors are by and large very much endured, with gastrointestinal incidental effects being the most widely recognized concern. Opposite aftereffects incorporate joint torment, sorrow, weakness, dry mouth, sleep deprivation, wooziness, disarray, bad dreams, mind flights, influenza like side effects, heartburn, and migraine. [25],[35] Normal secondary effects incorporate obscured vision, dry mouth, blockage, sluggishness, trouble peeing, urinary maintenance, disarray, mental debilitation, mind flights, discombobulation, trouble gulping, dyskinetic developments, and memory weakness. Albeit dry mouth is recorded as a result of anticholinergic medications, lessening salivation is a helpful impact in patients on anticholinergic medications and can be utilized to treat this side effect. [35-37]

3. Epilepsy:

Epilepsy involves a disorder of the brain's neurons and circuits, resulting in an excessive amount of electrical activity and synchronous discharges. These discharges can manifest in a variety of ways, including interictal electrical discharges that can lead to prolonged or recurrent seizures, which are classified as a seizure disorder. Additionally, if a seizure occurs due to an acute event, such as a brain injury, electrolyte imbalance, or co- occurrence of diseases, it is not considered epilepsy, but rather a provoked seizure. [38,39]

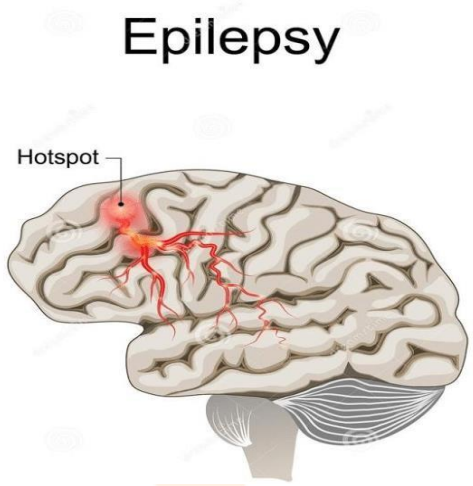

Fig.No.3: Electrical impulse (Hotspot) in brain. [40]

Adverse effect shown by Anti-Epilepsy Agents:

The most frequent side effects are incoordination, weariness, and poor balance. [41] Elderly people are disproportionately affected by these phenobarbital side effects. Irritability, appetite loss, aches in the muscles, bones, or joints, depression, and liver damage (though the latter is an uncommon outcome) are all known side effects that can occur when used long-term. Among them are weakness, vertigo, and a decline in focus and attention. [42] In example, falls and injuries can be caused by impaired coordination in older adults. Impaired driving abilities and a higher likelihood of traffic accidents are two additional impacts. [43-45] Diminished desire and problems with erection are common adverse effects. [46,47] In self-control issues and anxiety could arise. Hypotension and restricted breathing, sometimes known as hypoventilation, can happen during intravenous treatment. Vertigo, hunger changes, depersonalization, exhilaration, disorientation, and impaired vision are less common side effects. [48] Using valproic acid has been associated with a number of serious adverse reactions, including hepatotoxicity, psychosis, hallucinations, suicidality, anaphylaxis, hyponatremia, SIADH, pancreatitis, thrombocytopenia, pancytopenia, bleeding, erythema multiforme, polycystic ovarian syndrome, cerebral pseudoatrophy, encephalopathy, and coma. [49]

4. MULTIPLE SCLEROSIS:

MS is an inflammatory and autoimmune neurological illness that affects the central nervous system (CNS). MS assaults on myelinated axons in the central nervous system result in varying degrees of myelin and axon loss. [49-52]

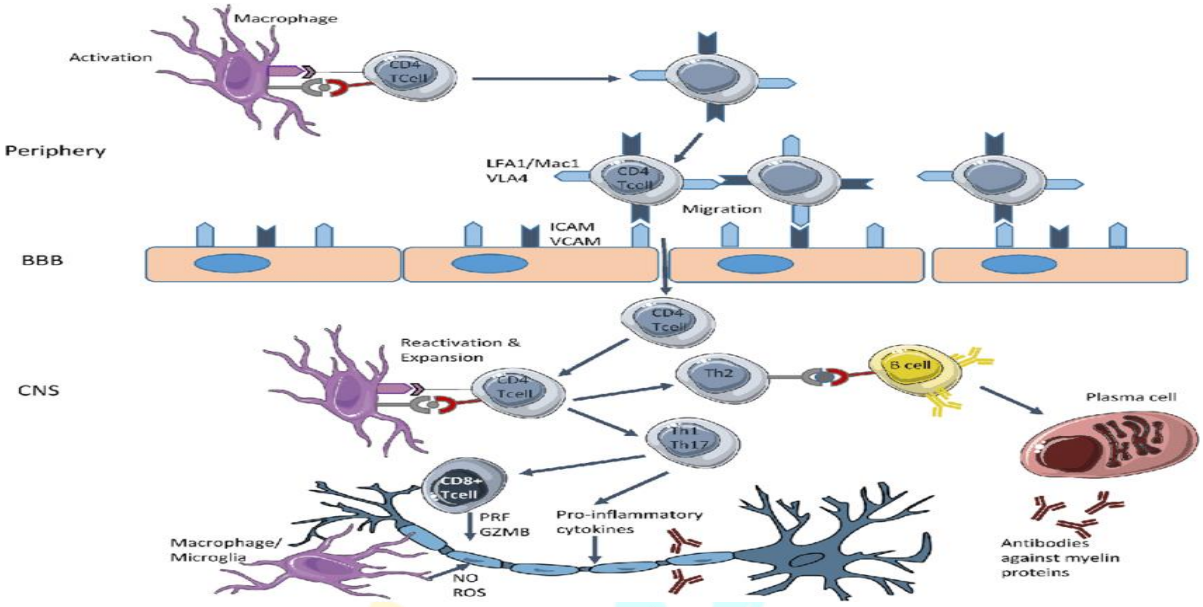

Fig.No.4: Schematic diagram of pathogenesis of multiple sclerosis. [53]

Adverse effect shown by drugs used in Multiple Sclerosis:

Beta-1 interferon, side effects are most commonly associated with flu-like symptoms, including headaches, chills, fever, muscle and joint pains, nausea, vomiting, lethargy, and diarrhea; they can also include mood changes, depression, difficulty focusing, and disorientation. It is likely that you will have flu-like symptoms. Less often seen adverse effects include tinnitus, dry lips, metallic taste, transient hair loss or thinning, pins and needles in the hands and toes, and difficulty falling asleep. [54,55] Overall, the majority of patients experience flu-like symptoms, which include fever, chills, sweating, muscle aches, and fatigue [56]; skin reactions, such as soreness, redness, pain, bruising, or swelling at the injection site [56]; anxiety and depression; liver problems; and blood problems, such as a potential drop in the patient's white blood cell, red blood cell, or clotting factor levels. Severe decreases in levels have been demonstrated to cause patients to become less resilient to infections, feel lethargic or sluggish, or bleed or bruise easily; thyroid problems, where patients' thyroid function may fluctuate; and allergic reactions, where some patients developed rash, hives, skin bumps, or itching while taking Rebif. Additional individuals have reported experiencing severe allergic responses, such as dyspnea or light-headedness. [56] It has been noted that an unusual adverse effect of taking Rebif is retinal vascular problems, such as anaphylaxis. [56] g., cotton wool spots, blockage of the retinal vein or artery, and retinopathy); [55-57] other risks include hepatobiliary diseases and rare instances of severe liver dysfunction, such as liver failure requiring liver transplantation

5. Huntington's Chorea:

As of right now, the first documented description of a patient with Huntington's choreais found in Waters's 1842 account. Still, Huntington's chorea was not formally identified until 1872, after George Huntington gave a talk outlining the condition. Here is a neurological disease that runs in families; symptoms include dementia, behavioral and mental abnormalities, and undesired choreatic movements. It usually shows up in middle age. [58]

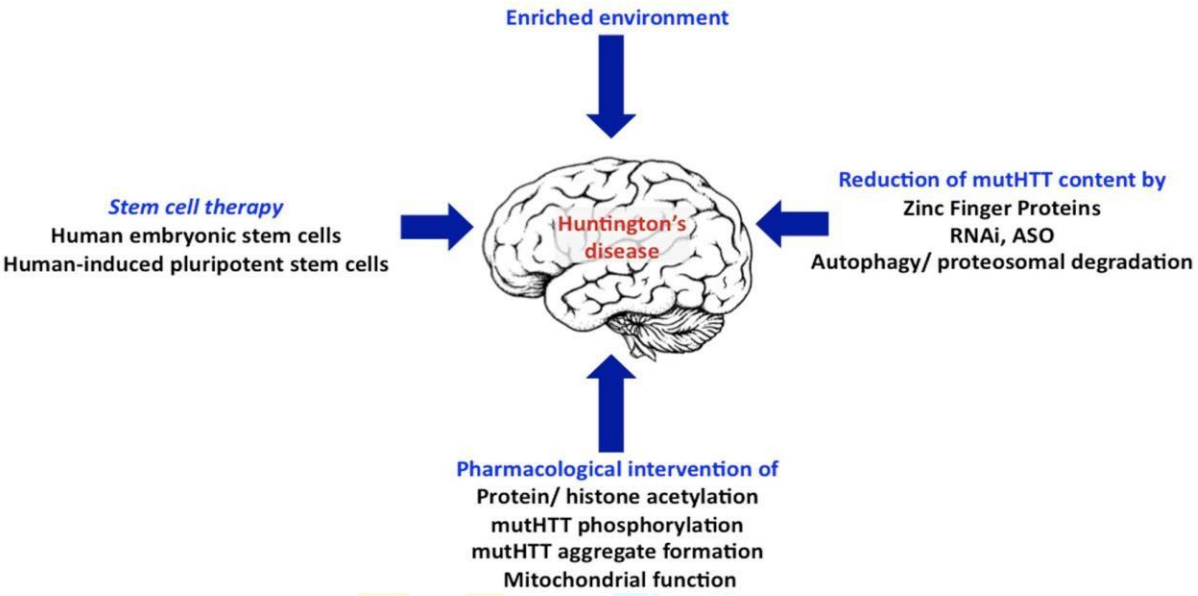

Fig.No.5: Etiology of Huntington's Disease. [59]

Adverse effect shown by Anti-Huntington's Chorea Agents:

The common adverse effects of TBZ that can be managed include somnolence, acute akathisia, insomnia, tiredness, agitation, depression, anxiety, nausea, diarrhea, and parkinsonism. Tyrosine titration or dose decrease can be utilized to treat these side effects. [60,61] Because of this, these adverse effects are known as dose-limiting adverse effects. [62] Panic episodes, orthostatic hypotension, psychological problems, problems with balance and gait, hallucinations, disorientation, "trance-like/zombie"-like symptoms, blurred vision, headaches, paraesthesia , paranoia, pharyngeal spasm, and soreness are some other, less frequent adverse effects.[63] Because it may induce depression or worsen pre-existing depression, TBZ is sold with a black box warning. [64]

6. Stroke:

The fast onset of clinical indications of localized or global disruption of cerebral function, which last for more than twenty-four hours and/or culminate in death with no other evident cause of death than vascular brain origin, characterizes a stroke.[64–66] The pathophysiology of stroke is further complicated by events such as complement activation, oxidative stress, loss of homeostasis, inflammation, energy failure, acidosis, elevated intracellular calcium levels, excitotoxicity, cytokine-mediated cytotoxicity, free radical- mediated toxicity, and disruption of the blood–brain barrier. [67-71]

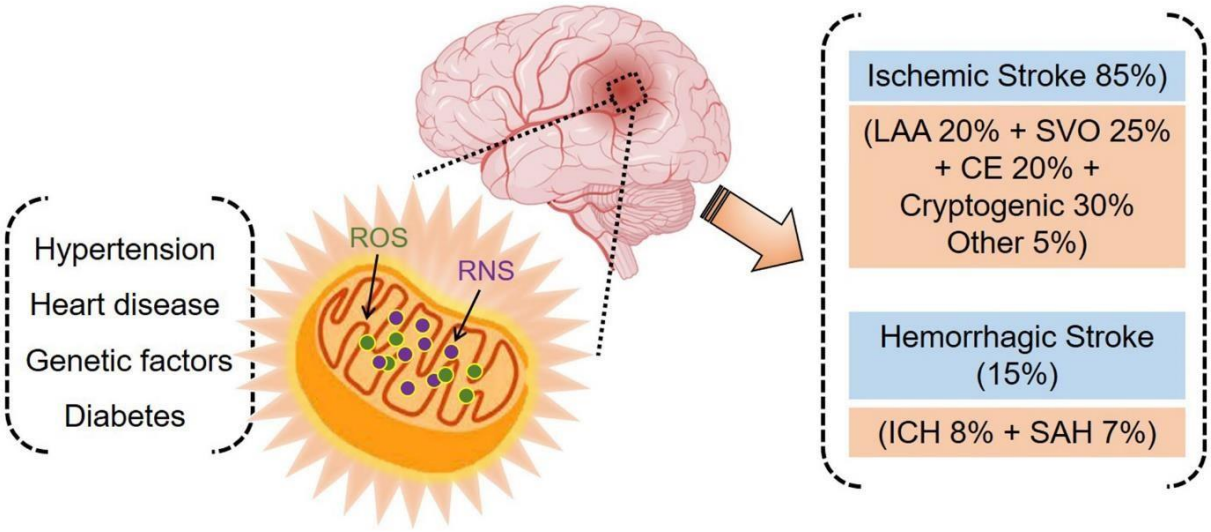

Fig.No.6: Oxidative stress plays a crucial role in the pathophysiology of stroke (both ischemicand hemorrhagic), and it is linked to diabetes, heart disease, hypertension, and hereditary factors. Stroke and related risk factors.[72]

Adverse effect of Aspirin:

Numerous meta-analyses of aspirin data demonstrate that, although it may possibly contribute to a trend toward increased rates of bleeding and gastrointestinal problems, aspirin lowers the risk of serious adverse cardiovascular events among diabetics without cardiovascular disease. Bleeding from gastroenteritis is the most frequent adverse effect of aspirin. [73-77]

7. Psychosis:

Combining several psychiatric symptoms that lead to a detachment from reality is called psychosis. Currently accepted theory states that a far greater, variable percentage of individuals may have at least one psychotic symptom in their lives, even if only 1.5 % to 3.5 % of people will fit the diagnostic criteria for a psychotic disease. [78] A frequent characteristic of several medical, neurologic, neurodevelopmental, psychiatric, and neuropsychiatric disorders is psychosis. It is the distinguishing characteristic of psychotic illnesses such as schizophrenia spectrum, co-occurring with many mood and drug use disorders,[81] and a difficult symptom of several medical and neurological diseases. Medical practitioners now prioritize treating psychosis as it may cause extreme anguish for both patients and their loved once . [79,80]

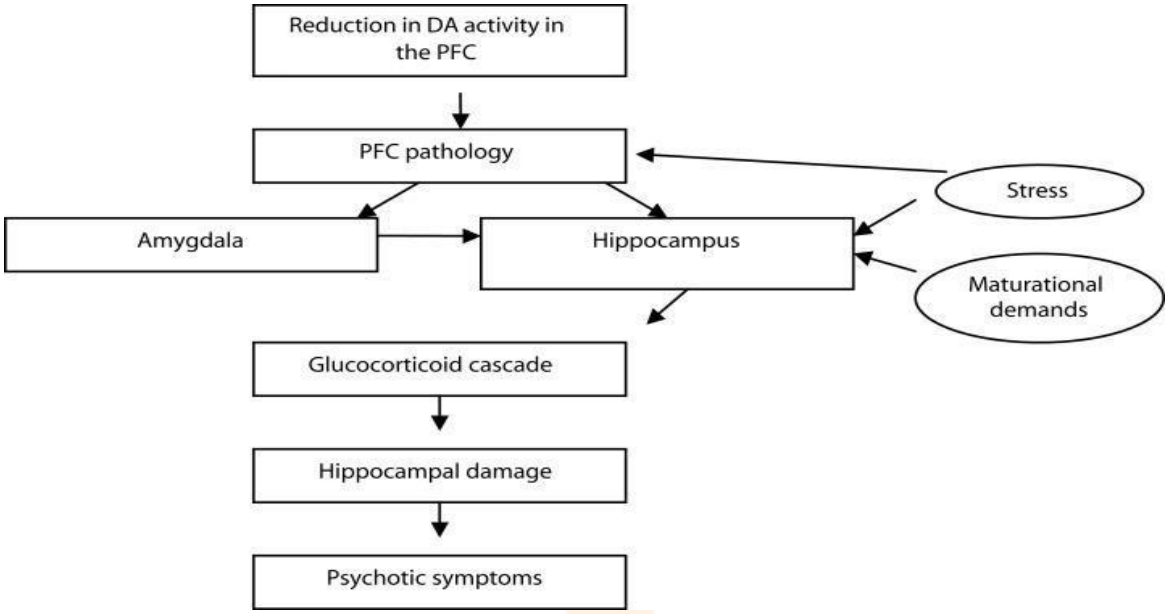

Fig.No.7: An initial model of psychosis that takes into account disease in the prefrontalbrain. PFC stands for prefrontal cortex; DA stands for dopamine.[82]

Adverse effect of Anti-Psychosis:

When antipsychotics are administered or dosed increased, dystonia's usually develop hours to days later, nearly frequently in the first five days. [83] Prevalence varies greatly depending on risk factors and certain medications. [84] The most important risk factor, with a relative risk of almost six, is a history of extrapyramidal side effects [85]. Two more obvious risk factors are male sex and young age. [85-87] laryngospasm, a very painful and agonizing tonicdeviation of the eyes that can become recurring or chronic, and oculogyric crisis, a rare but potentially fatal condition, are the two most alarming presentations. [88-90]

Toxicity:

Gingival overgrowth

Includes all clinical conditions characterized by gingival hypertrophy. In the dental office, this type of enlargement is a unique complaint that can be attributed to a variety of factors. The antiepileptic medication phenytoin has been closely linked to GO among medications that cause it. [91] It wasn't until 1939. [92] when GO was first linked to long-term phenytoin usage. In addition to treating epilepsy, this drug is still often given to treat neuralgias and heart arrhythmias.[93] Considerable gingival changes are thought to occur in between 30 % and 50 % of phenytoin-using individuals. [94] GO has also been linked to other anticonvulsants. However, reports of gingival alterations in adult patients following long-term administration of valproic acid, carbamazepine, phenobarbital, and vigabatrin have been extremely infrequent.[95–97] Gouty eyes can also be a serious side effect of other medication families, including the immunosuppressant cyclosporine A and several calcium channel blockers (dihydropyridines, diltiazem, and verapamil). [98]

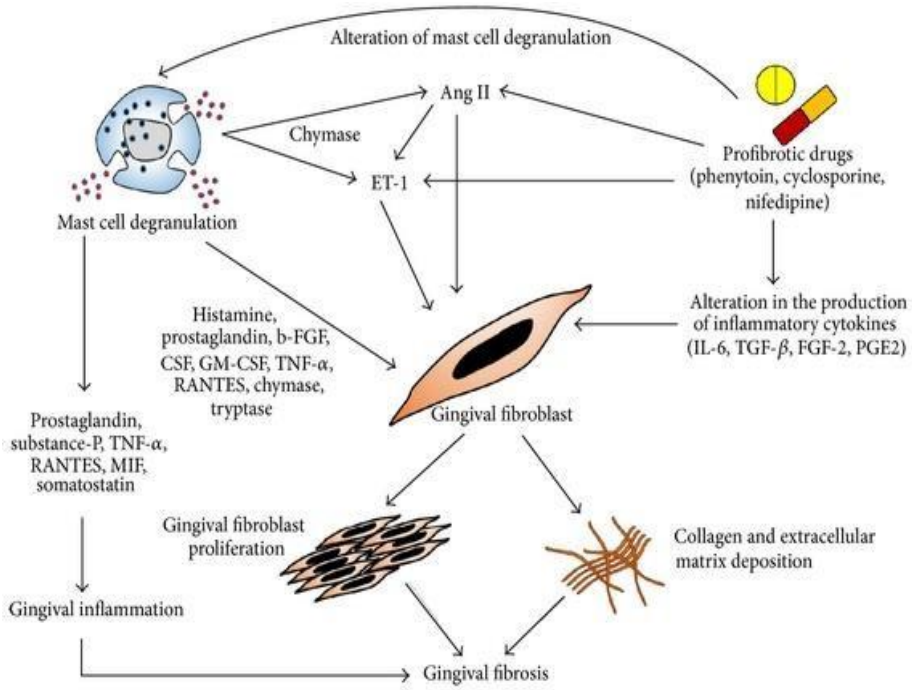

Fig.No.8: Drugs like phenytoin affect on mast cell and induced Gingival overgrowth.[99]

Aplastic Anemia

Is a hematopoietic stem cell disease marked by hypocellular bone marrow and pancytopenia of the peripheral blood. [100,101] One unique side effect of the medication is aplastic anemia. The most popular and extensively utilized anticonvulsant for treating and preventing partial seizures, generalized seizures, and status epileptics is phenytoin.[102] phenytoin seldom causes hematological issues, such as macrocytosis, agranulocytosis, granulocytopenia, leukopenia, and pancytopenia. [103,104] phenytoin has a dose-dependent action. The exact cause of drug-induced aplastic anemia is yet unknown, but toxic, reactive metabolites of many different substances may be important. Covalent attachment of the intermediates to cell macromolecules produces an electrophilic metabolite, which can be harmful to bone marrow via a number of different routes. [105,106]

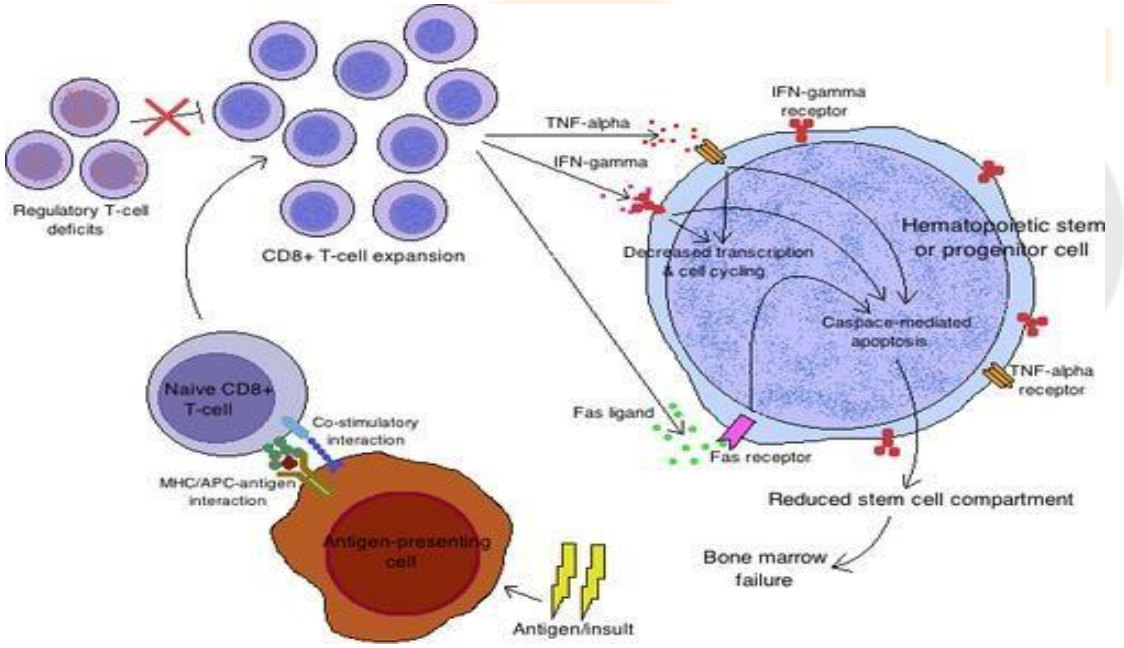

Fig.No.9: The apoptotic process of hematopoietic stem or progenitor cells in the bone marrow of patients with aplastic anemia is immunopathogenic.[107]

Serotonin syndrome

The associated illness that is most frequently diagnosed is serotonin syndrome. [108-110] With a similar appearance to NMS, this is typically brought on by the use of selective serotonin reuptake inhibitors.[110] Shivering, hyperreflexia, myoclonus, and ataxia are typical symptoms of these individuals that are not frequently observed in NMS patients. [111,112] In serotonin syndrome, nausea, vomiting, and diarrhea are also often reported symptoms of the prodrome; they are infrequently reported in NMS. When rigidity and hyperthermia do occur, they are not as severe as in NMS patients. Although serotonin syndrome symptoms often develop more quickly than those of NMS, both disorders have varying and overlapping start times. [113] (See "Serotonin syndrome (serotonin toxicity)".

Anti-Parkinson medication withdrawal

In addition, NMS has been observed in parkinsonian patients receiving dopamine agonist treatment or stopping L-Dopa, as well as when switching between agents and reducing dosages.[114-118]Possible precipitants include dehydration, surgery, and infection.[118-119].This condition, frequently referred to as acute akinesia, neuroleptic malignant-like syndrome, parkinsonism hyperpyrexia syndrome, or the malignant syndrome in Parkinson disease, may be distinguished from NMS.[119,120].There have been reports of more severe instances and even fatalities in this illness. [119],[122,123], although some reporting a better prognosis and milder clinical symptoms and laboratory results. [121] Thirty-one percent of a group of ninety-three patients failed to regain their previous baseline. [118]

Stevens-Johnson Syndrome (SJS)

Is an inflammatory mucocutaneous medication response that can be fatal [124–126].
Erythema multiforme major, or SJS, is a condition that falls between toxic epidermal necrolysis and erythema multiforme minor. The former is characterized by targetoid cutaneous lesions that cover less than 10 % of the body surface area, while the latter affects 30 % to 100 % of the skin surface[127].Although skin biopsies and direct immunofluorescence tests of the skin are necessary to rule out other disorders such autoimmune bullous disease, the initial diagnosis ofSJS is based on clinical presentation. [128,129]

Drug implicated	No. of cases	Drug implicated	No. of cases
Anticonvulsant		Paracetamol	1
Carbamazepine	18	Diclofenac sodium	1
Phenytoin	3	**Antibiotic**	
Phenobarbitone	1	Aminoglycosides	1
NASIDS		Ampicillin	1
Ibuprofen	1	Cotrimoxazole	1
Mefenamic acid	1	Ofloxacin	1

Table No.1: Drugs that have been linked to SJS/TEN. [130]

Reye syndrome

Reye syndrome is an uncommon juvenile condition that can be deadly. It is characterized by fatty liver failure and abrupt noninflammatory encephalopathy. This conditionwas initially characterized in 1963 by Australian pathologist R.D.K. Reye. In the early 1970s, the US launched a nationwide monitoring program for Reye syndrome, which resulted in stringent guidelines for children's aspirin usage. In children, Reye syndrome usually begins with vomiting and bewilderment and progresses quickly to coma and death. This condition frequently manifests in the days after recuperating from a viral infection that required aspirin treatment. Reye syndrome may also be predisposed to or develop as a result of inborn errors of metabolism, particularly those involving the metabolism of fatty acids, drug responses, and toxins. Both laboratory tests and clinical indicators support this diagnosis. There isn't a Reye syndrome-specific test, though. [131,132]

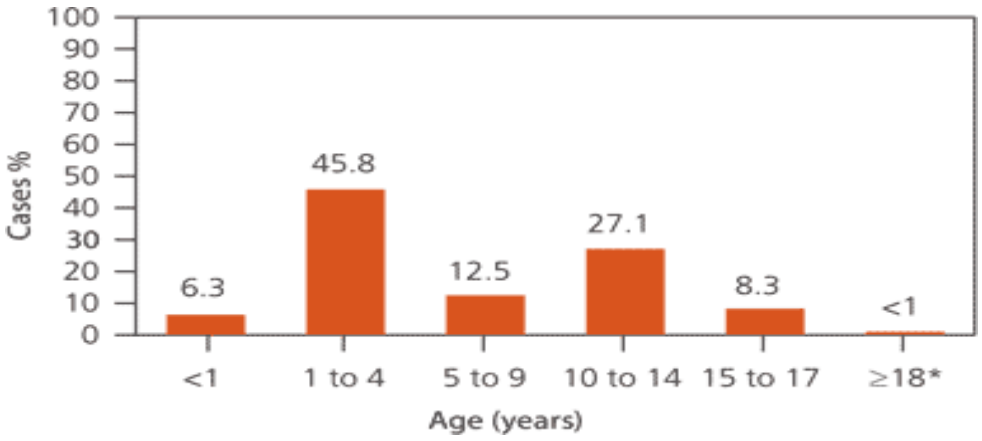

Fig.No.10: Bar graph displaying the age-specific percentage of cases of Reye syndromereported. Age-Specific Share of Recorded Reye Syndrome Cases. [133],[134]

Restless legs syndrome (RLS):

Sleep disturbances are common in neurological sensory-motor disorders such as restless legs syndrome (RLS) and Willis-Ekbom disease (WED).[135] Patients describe it as a painful compulsion to move their legs when they are immobile.[135] A painful feeling frequentlyfollows the want to move. Moving the patient can temporarily alleviate both symptoms, but if they stop moving, the patient may experience relapses.[136] Prolonged durations of exercise may give little to no relief from symptoms in really severe cases of RLS.[137] Functional impairmentis therefore often experienced by patients in their daily life if RLS is not well managed.[138] Numerous studies have highlighted primary-care physicians' lack of awareness to adequately diagnose the disorder. [139-141] As a result, this leads to a patients' symptoms beingattributed to other medical conditions, such as peripheral neuropathy, leg cramps, and anxiety. [142]

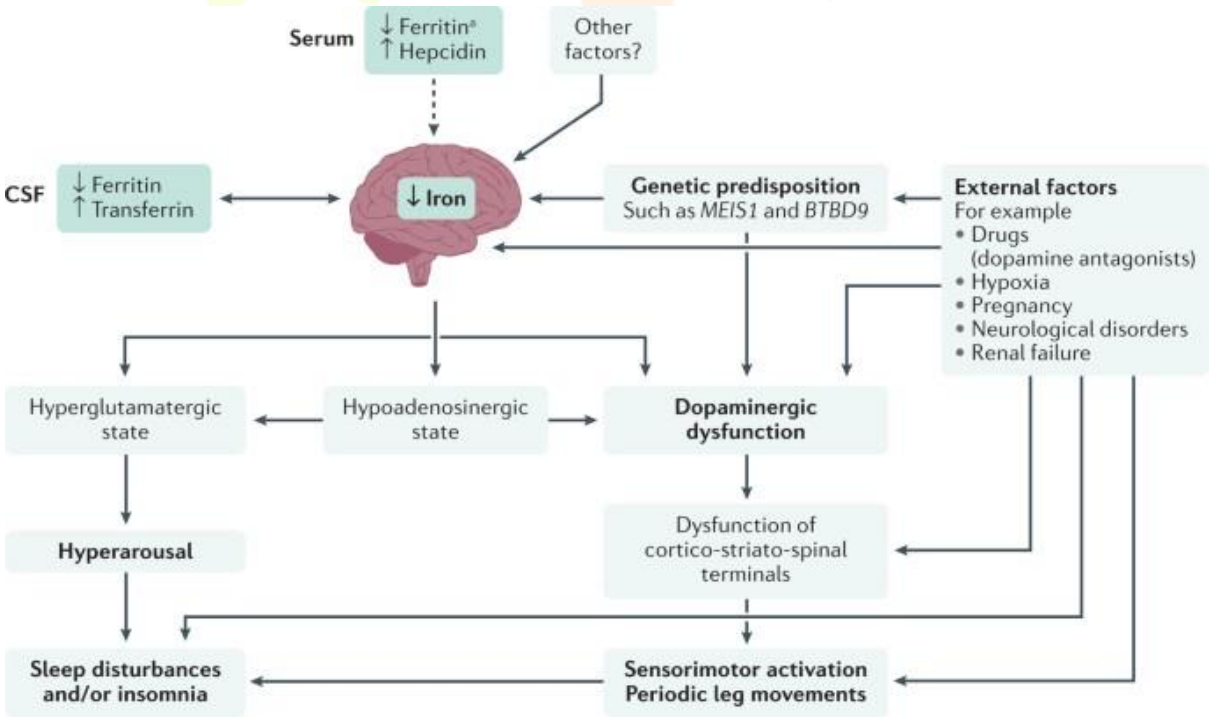

Fig.No.11: Pharmacology behind the restless leg syndrome.[143]

Hirsutism:

Hirsutism is defined as the presence of terminal coarse hairs in females in a male-like distribution. It affects around 5-10 % of women [144],[145] and is a common presenting complaintin the dermatological outpatient department (OPD) for cosmetic reasons. It is not only imperative to identify the cause of hirsutism but also important to know how to recommend the right treatment based on the main causative factor. The most important determinant in making the diagnosis is a change in the form and rate of hair growth. A technique has been developed to assess hirsutism with video equipment and computer software.[146] Digital imagingof hair development is recorded, which demonstrates a significant difference in hair form and growth rate between hirsute and non-hirsute women.

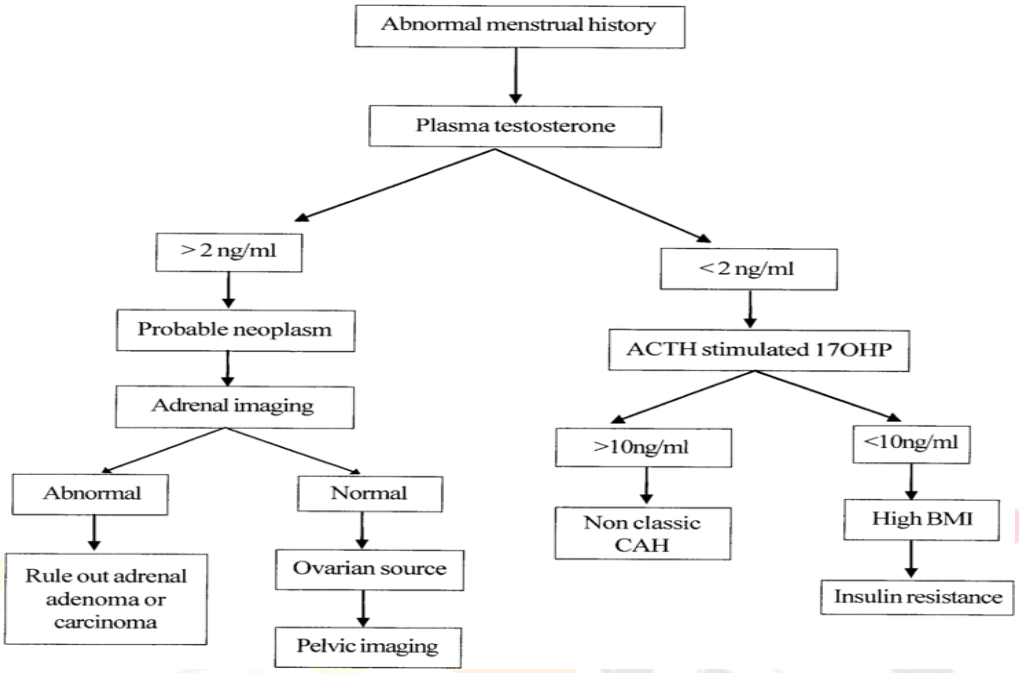

Fig.No.12: Methodology for Hirsutism diagnosis[147]

CONCLUSION:

Neurological disorder included epilepsy, Alzheimer disease, multiple sclerosis, Parkinson disease also stroke We provide the summary of neurological disorders and some drugs with their adverse effect. Some drugs cause serious effect. Pharmacovigilance plays important role to report toxicity and adverse effect. So it will help to reduce toxicity of drug and increases safety of medicine.

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REFERENCES

1. Accreditation Council for Graduate Medical Education. ACGME program requirements for graduate medical education in family medicine. Family Medicine. 2017 Jul 1.

2. Feigin VL, Abajobir AA, Abate KH, Abd-Allah F, Abdulle AM, Abera SF, Abyu GY, Ahmed MB, Aichour AN, Aichour I, Aichour MT. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Neurology. 2017 Nov 1;16(11):877-97.

3. Feigin VL, Vos T, Alahdab F, Amit AM, Bärnighausen TW, Beghi E, Beheshti M, Chavan PP, Criqui MH, Desai R, Dharmaratne SD. Burden of neurological disorders across the US from 1990-2017: a global burden of disease study. JAMA neurology. 2021 Feb 1;78(2):165-76.

4. Chin JH, Vora N. The global burden of neurologic diseases. Neurology. 2014 Jul 22;83(4):349-51.

5. Erkkinen MG, Kim MO, Geschwind MD. Clinical neurology and epidemiology of the major neurodegenerative diseases. Cold Spring Harbor perspectives in biology. 2018 Apr 1;10(4):a033118.

6. Gilman S. Oxford American handbook of neurology. Oxford University Press; 2010 May 18.

7. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DC. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007 Oct 29;29(1-2):125-32.

8. Ott A, Breteler MM, Van Harskamp F, Claus JJ, Van Der Cammen TJ, Grobbee DE, Hofman A. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. Bmj. 1995 Apr 15;310(6985):970-3.

9. Querfurth HW, LaFerla FM. Mechanisms of disease. N Engl J Med. 2010;362(4):329 -44.

10. Selkoe DJ. Alzheimer's disease is a synaptic failure. Science. 2002 Oct 25;298(5594):789-91.

11. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: Causes and treatment. Molecules. 2020 Dec 8;25(24):5789.

12. Cummings JL, Kaufer D. Neuropsychiatric aspects of Alzheimer's disease: the cholinergic hypothesis revisited. Neurology. 1996 Oct 1;47(4):876-83.

13. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology. 1998 Jan 1;50(1):136-45.

14. Cummings JL. Use of cholinesterase inhibitors in clinical practice: evidence-based recommendations. Focus. 2004 Apr;11(2):131-252.

15. Agronin ME, Kluwer PW. Alzheimer Disease and Other Dementias: A Practical Guide.

16. Menezes MD, McCarter R, Greene EA, Bauman NM. Status of propranolol for treatment of infantile hemangioma and description of a randomized clinical trial. Annals of Otology, Rhinology & Laryngology. 2011 Oct;120(10):686-95.

17. Inglis F. The tolerability and safety of cholinesterase inhibitors in the treatment of dementia. International journal of clinical practice. Supplement. 2002 Jun 1(127):45- 63.

18. Gauthier S. Cholinergic adverse effects of cholinesterase inhibitors in Alzheimer's disease: epidemiology and management. Drugs & aging. 2001 Nov;18:853-62.

19. Patel BB, Holland NW. Adverse effects of acetylcholinesterase inhibitors. Clinical Geriatrics. 2011;19(1):27-30.

20. Sherer TB, Chowdhury S, Peabody K, Brooks DW. Overcoming obstacles in Parkinson's disease. Movement disorders. 2012 Nov;27(13):1606-11.

21. Moore DJ, West AB, Dawson VL, Dawson TM. Molecular pathophysiology of Parkinson's disease. Annu. Rev. Neurosci.. 2005 Jul 21;28:57-87.

22. Trenkwalder C, Kuoppamäki M, Vahteristo M, Müller T, Ellmén J. Increased dose of carbidopa with levodopa and entacapone improves "off" time in a randomized trial. Neurology. 2019 Mar 26;92(13):e1487-96.

23. Poewe W, Chaudhuri KR, Bergmann L, Antonini A. Levodopa–carbidopa intestinal gel in a subgroup of patients with dyskinesia at baseline from the GLORIA Registry. Neurodegenerative disease management. 2019 Feb;9(1):39-46.

24. Patel AB, Jimenez-Shahed J. Profile of inhaled levodopa and its potential in the treatment of Parkinson's disease: evidence to date. Neuropsychiatric Disease and Treatment. 2018 Nov 2:2955-64.

25. National Collaborating Centre for Chronic Conditions. Symptomatic pharmacological therapy in Parkinson's disease. Parkinson's Disease. London: Royal College of Physicians. 2006:59-100.

26. Nord M. Levodopa pharmacokinetics-from stomach to brain: A study on patients with Parkinson's disease. Linköping University Electronic Press; 2019 Jan 7.

27. Atmaca M. Drug-induced impulse control disorders: a review. Current clinical pharmacology. 2014 Feb 1;9(1):70-4.

28. Baumann-Vogel H, Valko PO, Eisele G, Baumann CR. Impulse control disorders in Parkinson's disease: Don't set your mind at rest by self-assessments. Eur J Neurol. 2015;22(4):603–9

29. Moore TJ, Glenmullen J, Mattison DR. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. JAMA internal medicine. 2014 Dec 1;174(12):1930-3.

30. Sáez-Francàs N, Andrés GM, Ramírez N, de Fabregues O, Álvarez-Sabín J, Casas M, Hernández-Vara J. Clinical and psychopathological factors associated with impulse control disorders in Parkinson's disease. Neurología (English Edition). 2016 May 1;31(4):231-8.

31. Seeman P. Parkinson's disease treatment may cause impulse-control disorder via dopamine D3 receptors. Synapse. 2015;69(4):183–9.

32. Van Eimeren T, Ballanger B, Pellecchia G, Miyasaki JM, Lang AE, Strafella AP. Dopamine agonists diminish value sensitivity of the orbitofrontal cortex: a trigger for pathological gambling in Parkinson's disease?. Neuropsychopharmacology. 2009 Dec;34(13):2758-66.

33. Weintraub D, Claassen DO. Impulse control and related disorders in Parkinson's disease. International review of neurobiology. 2017 Jan 1;133:679-717.

34. Samii A, Nutt JG, Ransom BR. Parkinson's disease. Lancet. 2004;363(9423):1783 – 93.

35. Goldenberg MM. Medical management of Parkinson's disease. Pharmacy and Therapeutics. 2008 Oct;33(10):590.

36. Vizcarra JA, Sánchez-Ferro Á, Maetzler W, Marsili L, Zavala L, Lang AE, Martinez- Martin P, Mestre TA, Reilmann R, Hausdorff JM, Dorsey ER. The Parkinson's disease e-diary: Developing a clinical and research tool for the digital age. Movement Disorders. 2019 May;34(5):676-81.

37. Ahlskog JE. Slowing Parkinson's disease progression: Recent dopamine agonist trials.Neurology. 2003;60(3):381–9.

38. Gallucci Neto J, Marchetti RL. Aspectos epidemiológicos e relevância dos transtornos mentais a ssociados à epilepsia. Rev Bras Psiquiatr. 2005; 27:323-8. doi: 10.1590/S1516- 44462005000400013.

39. Calabresi PA. Diagnosis and management of multiple sclerosis. American family physician. 2004 Nov 15;70(10):1935-44.

40. Jana R, Mukherjee I. Deep learning based efficient epileptic seizure prediction with EEG channel optimization. Biomedical Signal Processing and Control. 2021 Jul 1;68:102767.

41. Anderson GD, Hakimian S. Pharmacokinetic factors to consider in the selection of antiseizure drugs for older patients with epilepsy. Drugs & aging. 2018 Aug;35:687- 98.

42. Suddock JT, Cain MD. Barbiturate toxicity.

43. Ballenger JC. Benzodiazepine receptor agonists and antagonists. Comprehensive textbook of psychiatry. 2000:2317-24.

44. Lieberman JA, Tasman A. Handbook of psychiatric drugs. John Wiley & Sons; 2006 May 16.

45. Stone KL, Ensrud KE, Ancoli-Israel S. Sleep, insomnia and falls in elderly patients. Sleep medicine. 2008 Sep 1;9:S18-22.

46. Rapoport MJ, Lanctôt KL, Streiner DL, Bédard M, Vingilis E, Murray B, Schaffer A, Shulman KI, Herrmann N. Benzodiazepine use and driving: a meta-analysis. Journal ofClinical Psychiatry. 2009 May 1;70(5):663.

47. Orriols L, Salmi LR, Philip P, Moore N, Delorme B, Castot A, Lagarde E. The impact of medicinal drugs on traffic safety: a systematic review of epidemiological studies. Pharmacoepidemiology and drug safety. 2009 Aug;18(8):647-58.

48. Evans RJ, Miranda RN, Jordan J, Krolikowski FJ. Fatal acute pancreatitis caused by valproic acid. The American Journal of Forensic Medicine and Pathology. 1995 Mar 1;16(1):62-5.

49. Hauser SL. Multiple sclerosis and other demyelinating diseases. Harrison's principles of internal medicine. 1994;2287.

50. Goldenberg MM. Multiple sclerosis review. Pharmacy and therapeutics. 2012 Mar;37(3):175.

51. TOMASELLO L, ALIBRANDI A, RAFFAELE M, GALLETTA S, CASELLA C, BUCCAFUSCA M. Measuring quality of life in patients with relapsing-remitting MS (RRMS). NEUROLOGICAL SCIENCES. 2016;37:414-.

52. Bruyn GW. Handbook of clinical neurology (Vol. 4). Amsterdam: North. 1968.

53. Elkhodiry AA, El Tayebi HM. Scavenging the hidden impacts of non-coding RNAs inmultiple sclerosis. Non-coding RNA Research. 2021 Dec 1;6(4):187-99.

54. Cheraghmakani H, Samaee HR, Ghazaeian M. Interferon Beta-1a Cardiomyopathy ina Patient with Multiple Sclerosis: Case Report. Multiple Sclerosis and Related Disorders. 2020 Sep 1;44:102219.

55. National Institutesof Health. A service of theUS National Library of Medicine. AnnualReport. 2012.

56. Panitch H, Goodin DS, Francis GF, Chang P, Coyle PK, O'connor P, Monaghan E, LiD, Weinshenker B. Randomized, comparative study of interferon β-1a treatment regimens in MS: the EVIDENCE trial. Neurology. 2002 Nov 26;59(10):1496-506.

57. Goodin DS, Bates D. Treatment of early multiple sclerosis: the value of treatment initiation after a first clinical episode. Multiple Sclerosis Journal. 2009 Oct;15(10):1175-82.

58. Shakir R. The struggle for stroke reclassification. Nature Reviews Neurology. 2018 Aug;14(8):447-8.

59. Huang WJ, Chen WW, Zhang X. Huntington's disease: Molecular basis of pathology and status of current therapeutic approaches. Experimental and therapeutic medicine. 2016 Oct 1;12(4):1951-6.

60. Chen JJ, Ondo WG, Dashtipour K, Swope DM. Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature. Clinical therapeutics. 2012Jul 1;34(7):1487-504.

61. Chitnis S, Karunapuzha CA. Tetrabenazine in Huntington's disease chorea. Clinical Medicine. Therapeutics. 2009 Jan;1:CMT-S2134.

62. Frank S. Tetrabenazine: the first approved drug for the treatment of chorea in US patients with Huntington disease. Neuropsychiatric disease and treatment. 2010 Oct 5:657-65.

63. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology. 1997 Feb 1;48(2):358-62.

64. Kaur N, Kumar P, Jamwal S, Deshmukh R, Gauttam V. Tetrabenazine: spotlight on drug review. Annals of neurosciences. 2016 Sep 9;23(3):176-85.

65. Ahmed HG, Alquwaiay FK, AlDhamadi HF, Alquwaiay DA, Alshammari A, Alsunitan HH. Stroke-associated comorbidities in Saudi Arabia. International Journal of Pharmaceutical Research & Allied Sciences. 2020 Apr 1;9(2).

66. Hosseinzadeh SA, Mazhari S, Najafi K, Ahmadi M, Aghaei I, Niazi M, Shabani M. Impact of anodic transcranial direct current stimulation (TCDS) on changes in movement and life–related functions in patients with chronic ischemic stroke: A clinicaltrial. Entomol. appl. sci. lett. 2018 Aug 1;5(3):13-20.

67. Woodruff TM, Thundyil J, Tang SC, Sobey CG, Taylor SM, Arumugam TV. Pathophysiology, treatment, and animal and cellular models of human ischemic stroke. Molecular neurodegeneration. 2011 Dec;6:1-9.

68. Gelderblom M, Leypoldt F, Steinbach K, Behrens D, Choe CU, Siler DA, Arumugam TV, Orthey E, Gerloff C, Tolosa E, Magnus T. Temporal and spatial dynamics of cerebral immune cell accumulation in stroke. Stroke. 2009 May 1;40(5):1849-57.

69. Suh SW, Shin BS, Ma H, Van Hoecke M, Brennan AM, Yenari MA, Swanson RA. Glucose and NADPH oxidase drive neuronal superoxide formation in stroke. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2008 Dec;64(6):654-63.

70. Qureshi AI, Ali Z, Suri MF, Shuaib A, Baker G, Todd K, Guterman LR, Hopkins LN.Extracellular glutamate and other amino acids in experimental intracerebral hemorrhage: an in vivo microdialysis study. Critical care medicine. 2003 May 1;31(5):1482-9

71. Wang J, Fields J, Zhao C, Langer J, Thimmulappa RK, Kensler TW, Yamamoto M, Biswal S, Doré S. Role of Nrf2 in protection against intracerebral hemorrhage injuryin mice. Free Radical Biology and Medicine. 2007 Aug 1;43(3):408-14

72. Kumar V, Bishayee K, Park S, Lee U, Kim J. Oxidative stress in cerebrovascular disease and associated diseases. Frontiers in Endocrinology. 2023 Feb 17;14:1124419.

73 Levonorgestrel I. Drugs and Lactation Database (LactMed)[Internet]. Bethesda (MD): National Library of Medicine (US). 2019:63-7.

74 Handa O, Takayama S, Mukai R, Suyama Y, Majima A, Fukui A, Omatsu T, Naito Y. A review of the mechanism and prophylaxis of acetyl salicylic acid-induced injury of the small intestine. Free Radical Research. 2018 Dec 2;52(11-12):1266-70.

75 Kosinski P, Sarzynska-Nowacka U, Fiolna M, Wielgos M. The practical use of acetylsalicylic acid in the era of the ASPRE trial. Update and literature review. Ginekologia polska. 2018;89(2):107-11.

76 Navaratnam K, Alfirevic Z, Pirmohamed M, Alfirevic A. How important is aspirin adherence when evaluating effectiveness of low-dose aspirin?. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017 Dec 1;219:1-9.

77 Weltermann T, Schulz C, Macke L. Effect of frequently prescribed drugs on gastric cancer risk. Best Practice & Research Clinical Gastroenterology. 2021 Mar 1;50:101741.

78 van Os J, Hanssen M, Bijl RV, Vollebergh W. Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison. Arch Gen Psychiatry. 2001 Jul;58(7):663-8.

79 Jellinger KA. Cerebral correlates of psychotic syndromes in neurodegenerative diseases. Journal of cellular and molecular medicine. 2012 May;16(5):995-1012.

80 Ismail Z, Nguyen MQ, Fischer CE, Schweizer TA, Mulsant BH, Mamo D. Neurobiology of delusions in Alzheimer's disease. Current Psychiatry Reports. 2011 Jun;13:211-8.

81 Sultzer DL, Leskin LP, Melrose RJ, Harwood DG, Narvaez TA, Ando TK, MandelkernMA. Neurobiology of delusions, memory, and insight in Alzheimer disease. The American Journal of Geriatric Psychiatry. 2014 Nov 1;22(11):1346-55.

82 Fiorentini A, Sara Volonteri L, Dragogna F, Rovera C, Maffini M, Carlo Mauri M, A Altamura C. Substance-induced psychoses: a critical review of the literature. Current drug abuse reviews. 2011 Dec 1;4(4):228-40.

83 Phillips LJ, McGorry PD, Garner B, Thompson KN, Pantelis C, Wood SJ, Berger G. Stress, the hippocampus and the hypothalamic-pituitary-adrenal axis: implications for the development of psychotic disorders. Australian & New Zealand Journal of Psychiatry. 2006 Sep;40(9):725-41.

84 Tarsy D. Neuroleptic-induced extrapyramidal reactions: classification, description, and diagnosis. Clinical Neuropharmacology. 1983 Jan 1;6(1):9-26.

85 van Harten PN, Hoek HW, Kahn RS. Acute dystonia induced by drug treatment. Bmj. 1999 Sep 4;319(7210):623-6.

86 Keepers GA, Casey DE. Use of neuroleptic-induced extrapyramidal symptoms to predict future vulnerability to side effects. The American journal of psychiatry. 1991 Jan 1;148(1):85-9.

87 Aguilar EJ, Keshavan MS, Martinez-Quiles MD, Hernández J, Gómez-Beneyto M, Schooler NR. Predictors of acute dystonia in first-episode psychotic patients. The American journal of psychiatry. 1994 Dec 1;151(12):1819-21.

88 Raja M. Managing antipsychotic-induced acute and tardive dystonia. Drug safety. 1998 Jul;19(1):57-72.

89 Koek RJ, Pi EH. Acute laryngeal dystonic reactions to neuroleptics. Psychosomatics. 1989 Jan 1;30(4):359-64.

90 Gardner DM, Abidi S, Ursuliak Z, Morrison J, Teehan MD, Tibbo PG. Incidence of oculogyric crisis and long-term outcomes with second-generation antipsychotics in a first-episode psychosis program. Journal of Clinical Psychopharmacology. 2015 Dec 1;35(6):715-8.

91 McLeod DE, Stoeckel D, Contreras J, Reyes E. Severe postpartum gingival enlargement. Journal of periodontology. 2009 Aug;80(8):1365-9.

92 Kimball OP. The treatment of epilepsy with sodium diphenyl hydantoinate. Journal of the American Medical Association. 1939 Apr 1;112(13):1244-5.

93 Güncü GN, Çağlayan F, Dinçel A, Bozkurt A, Saygı S, Karabulut E. Plasma and gingival crevicular fluid phenytoin concentrations as risk factors for gingival overgrowth. Journal of periodontology. 2006 Dec;77(12):2005-10.

94 Modéer T, Domeij H, Anduren I, Mustafa M, Brunius G. Effect of phenytoin on the production of interleukin-6 and interleukin-8 in human gingival fibroblasts. Journal of oral pathology & medicine. 2000 Nov;29(10):491-9.

95 Dahllof G, Preber H, Eliasson S, Ryden H, Karsten J, Modéer T. Periodontal condition of epileptic adults treated long-term with phenytoin or carbamazepine. Epilepsia. 1993 Sep;34(5):960-4.

96 Gregoriou AP, Schneider PE, Shaw PR. Phenobarbital-induced gingival overgrowth? Report of two cases and complications in management. ASDC Journal of Dentistry for Children. 1996 Nov 1;63(6):408-13.

97 Katz J, Givol N, Chaushu G, Taicher S, Shemer J. Vigabatrin-induced gingival overgrowth. Journal of clinical periodontology. 1997 Mar;24(3):180-2.

98 Dongari-Bagtzoglou A. Drug-associated gingival enlargement. Journal of periodontology. 2004 Oct 1;75(10):1424-31.

99 Subramani T, Rathnavelu V, Yeap SK, Alitheen NB. Influence of mast cells in drug-induced gingival overgrowth. Mediators of inflammation. 2013 Jan 1;2013.

100 Putri IA. PROFIL PENGGUNAAN ANTIPSIKOTIK DAN ANTIANSIETAS PADA PASIEN SKIZOFRENIA RAWAT INAP DI RUMAH SAKIT JIWA MUTIARA SUKMA PROVINSI NTB TAHUN 2021. Journal of Village and Local Community.2022 Jun 30;1(1):59-80.

101 Gerson WT, Fine DG, Spielberg SP, Sensenbrenner LL. Anticonvulsant-induced aplastic anemia: increased susceptibility to toxic drug metabolites in vitro. Blood. 1983May 1;61(5):889-93.

102 WILLIAMS L. PRINCIPLES of PHARMACOLOGY THE PATHOPHYSIOLOGIC BASIS OF DRUG THERAPY T hird E dition.

103 Foye WO. Foye's principles of medicinal chemistry. Lippincott williams & wilkins; 2008.

104 Verrotti A, Scaparrotta A, Grosso S, Chiarelli F, Coppola G. Anticonvulsant drugs and hematological disease. Neurological Sciences. 2014 Jul;35:983-93.

105 Handoko KB, Souverein PC, Van Staa TP, Meyboom RH, Leufkens HG, Egberts TC, Van Den Bemt PM. Risk of aplastic anemia in patients using antiepileptic drugs. Epilepsia. 2006 Jul;47(7):1232-6.

106 Al Qahtani SA. Drug-induced megaloblastic, aplastic, and hemolytic anemias: current concepts of pathophysiology and treatment. Int J Clin Exp Med. 2018 Jan 1;11(6):5501-12.

107 Carbone JR. The neuroleptic malignant and serotonin syndromes. Emergency Medicine Clinics. 2000 May 1;18(2):317-25

108 Bodner RA, Lynch T, Lewis L, Kahn D. Serotonin syndrome. Neurology. 1995 Feb1;45(2):219-23.

109 Ener RA, Meglathery SB, Decker WA, Gallagher RM. Serotonin syndrome and other serotonergic disorders. Pain medicine. 2003 Mar 1;4(1):63-74.

110 Haddow AM, Harris D, Wilson M, Logie H. Clomipramine induced neuroleptic malignant syndrome and pyrexia of unknown origin. BMJ. 2004 Dec 2;329(7478):1333-5.

111Lejoyeux M, Fineyre F, Ades J. The serotonin syndrome. The American journal of psychiatry. 1992 Oct.

112 Sternbach H. The serotonin syndrome. Am J Psychiatry. 1991 Jun 1;148(6):705-13.

113Werneke U, Jamshidi F, Taylor DM, Ott M. Conundrums in neurology: diagnosing serotonin syndrome–a meta-analysis of cases. BMC neurology. 2016 Dec;16(1):1-9.

114 Shalev A, Hermesh H, Munitz H. Mortality from neuroleptic malignant syndrome. The Journal of clinical psychiatry. 1989 Jan 1;50(1):18-25.

115Velamoor VR. Neuroleptic malignant syndrome: recognition, prevention and management. Drug Safety. 1998 Jul;19(1):73-82.

116Wu YF, Kan YS, Yang CH. Neuroleptic malignant syndrome associated with bromocriptine withdrawal in Parkinson's disease—a case report. General hospital psychiatry. 2011 May 1;33(3):301-e7.

117 Wijdicks EF. Neuroleptic malignant syndrome. UpToDate. Updated May. 2014;30. 118Takubo H, Harada T, Hashimoto T, Inaba Y, Kanazawa I, Kuno S, Mizuno Y, Mizuta E, Murata M, Nagatsu T, Nakamura S. A collaborative study on the malignant syndrome in Parkinson's disease and related disorders. Parkinsonism & Related Disorders. 2003Apr 1;9:31-41.

119Onofrj M, Thomas A. Acute akinesia in Parkinson disease. Neurology. 2005 Apr 12;64(7):1162-9.

120Mizuno Y, Takubo H, Mizuta E, Kuno S. Malignant syndrome in Parkinson's disease: concept and review of the literature. Parkinsonism & Related Disorders. 2003 Apr 1;9:3-9.

121 Serrano-Dueñas M. Neuroleptic malignant syndrome-like, or—dopaminergic malignant syndrome—due to levodopa therapy withdrawal. Clinical features in 11 patients. Parkinsonism & related disorders. 2003 Jan 1;9(3):175-8.

122. Sechi G, Tanda F, Mutani R. Fatal hyperpyrexia after withdrawal of levodopa. Neurology. 1984 Feb 1;34(2):249.

123. Newman EJ, Grosset DG, Kennedy PG. The parkinsonism-hyperpyrexia syndrome. Neurocritical Care. 2009 Feb;10:136-40.

124Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, Wu JY, Chen YT. A marker for Stevens–Johnson syndrome. Nature. 2004 Apr 1;428(6982):486-

125Ruiz-Maldonado R. Acute disseminated epidermal necrosis types 1, 2, and 3: study of sixty cases. Journal of the American Academy of Dermatology. 1985 Oct 1;13(4):623 - 35.

126Hussain W, Craven NM. Toxic epidermal necrolysis and Stevens-Johnson syndrome.Clinical medicine. 2005 Nov 11;5(6):555.

127Kumar G, Fadel HJ, Beckman TJ. 36-year-old man with productive cough and diffuserash. InMayo Clinic Proceedings 2006 Jul 1 (Vol. 81, No. 7, pp. 945-948). Elsevier.

128 Leaute-Labreze C, Lamireau T, Chawki D, Maleville J, Taieb A. Diagnosis, classification, and management of erythema multiforme and Stevens–Johnson syndrome. Archives of disease in childhood. 2000 Oct 1;83(4):347-52.

129Paquet P, Pierard GE. Erythema multiforme and toxic epidermal necrolysis: a comparative study. The American journal of dermatopathology. 1997 Apr 1;19(2):127 - 32.

130Devi K, George S, Criton S, Suja V, Sridevi PK. Carbamazepine-The commonest causeof toxic epidermal necrolysis and Stevens-Johnson syndrome: A study of 7 years. IndianJournal of Dermatology, Venereology and Leprology. 2005 Sep 1;71:325.

131 Mund ME, Gyo C, Brüggmann D, Quarcoo D, Groneberg DA. Acetylsalicylic acid as a potential pediatric health hazard: legislative aspects concerning accidental intoxications in the European Union. Journal of occupational medicine and toxicology.2016 Dec;11(1):1-5.

132Brannelly NT, Hamilton-Shield JP, Killard AJ. The measurement of ammonia in humanbreath and its potential in clinical diagnostics. Critical reviews in analytical chemistry.2016 Nov 1;46(6):490-501.

133Peters LJ, Wiener GJ, Gilliam J, Van Noord G, Geisinger KR, Roach ES. Reye's syndrome in adults. A case report and review of the literature. *Arch Intern Med.* 1986;146(12):2401-2403.

134Sullivan KM, Belay ED, Durbin RE, Foster DA, Nordenberg DF. Epidemiology of Reye's syndrome, United States, 1991–1994: comparison of CDC surveillance and hospital admission data. *Neuroepidemiology.* 2000;19(6):338-344

135Garcia-Borreguero D, Kohnen R, Silber MH, Winkelman JW, Earley CJ, Högl B, Manconi M, Montplaisir J, Inoue Y, Allen RP. The long-term treatment of restless legs syndrome/Willis–Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep medicine. 2013 Jul 1;14(7):675-84.

136Earley CJ. Restless legs syndrome. New England Journal of Medicine. 2003 May 22;348(21):2103-9.

137Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW,Zucconi M, Ferri R, Trenkwalder C, Lee HB, International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis–Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep medicine. 2014 Aug 1;15(8):860-73.

138Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Archives of internal medicine. 2000 Jul 24;160(14):2137-41.

139Carlos K, Prado LB, Carvalho LB, Prado GF. Willis–Ekbom disease or restless legs syndrome?. Sleep Medicine. 2015 Sep 1;16(9):1156-9.

140Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population:the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep medicine. 2004 May 1;5(3):237-46.

141Trenkwalder C. Restless legs syndrome: overdiagnosed or underdiagnosed?. Nature Clinical Practice Neurology. 2007 Sep;3(9):474-5.

142Cotter PE, O'Keeffe ST. Restless leg syndrome: is it a real problem?. Therapeutics and Clinical Risk Management. 2006 Dec 30;2(4):465-75.

143Ekbom K, Ulfberg J. Restless legs syndrome. Journal of internal medicine. 2009 Nov;266(5):419-31.

144McKnight E. The prevalence of "hirsutism" in young women. Obstetrical & Gynecological Survey. 1964 Dec 1;19(6):988-92.

145Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. The Journal of Clinical Endocrinology & Metabolism. 1961 Nov 1;21(11):1440-7

146Gruber DM, Berger UE, Sator MO, Horak F, Huber JC. Computerized assessment of facial hair growth. Fertility and sterility. 1999 Oct 1;72(4):737-9.

147Loriaux DL. An approach to the patient with hirsutism. The Journal of Clinical Endocrinology & Metabolism. 2012 Sep 1;97(9):2957-68.