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A REVIEW ARTICLE ON NOVEL DRUGS USED IN PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease is the most common Neuro-degenerative disorder. Several new medications are discovered, most of which are variations of previously existing products, such new dosage forms of already-approved products, or cost-saving generic formulations have been proposed. These new products contribute to the public health, safety of the people, greater access to medication, more consumer choice, and a competitive marketplace that enhances affordability and quality and care. However, these new approvals that we refer to as novel drugs are among the more truly innovative products that often help in advance clinical care to another level. This article includes study of existing drugs and novel drugs in the Parkinson's disease treatment and also describes their medicinal chemistry i.e understanding its structure, synthesis, structural activity relationships, mechanism of action, therapeutic uses, adverse effects etc. These drugs are competent in various areas to satiate, make them suitable for its therapeutic use and for drug formulations and discoveries

KEYWORDS: Neuro-degenerative disorder, new approvals, medicinal chemistry, novel drugs, synthesis, structural activity relationship, medication

INTRODUCTION

A loss of dopamine-generating cells in the brain that results in a complex array of symptoms is called as Parkinson's disease (PD) but it is primarily associated with progressive loss of motor control. Major cause of disability among the elder is Parkinson's disease. After Alzheimer's.

Common diagnostic criteria generally require the initiation of antiparkinson's medication before the diagnosis can be confirmed. This ambiguity can be confusing for primary care physicians, disease, currently the second most common neurological degenerative disorder affecting worldwide is Parkinson's disease. Young-onset Parkinson's disease is a condition where an individual under 40 years of age may develop PD. It is difficult to diagnose PD.

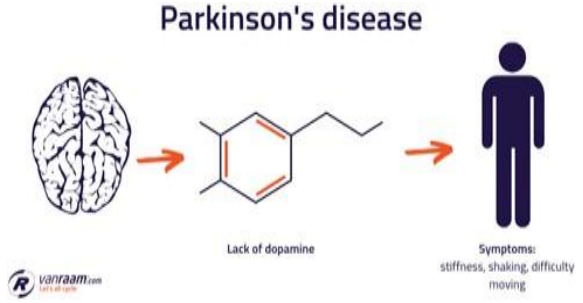


Fig. 1: Parkinson's disease. Especially when the disease presents without the characteristic tremor. Some- times PD condition in which no tremors occur may be mistaken for a Parkinson disease is often manageable in primary care.[1]

Objective

This article provides a discussion regarding recent development of drug medications to treat parkinsons disease. The main objective is to search the recent novel drugs used and to make out the

Parkinson disease condition whose main features are:

- Slowed movement
- Balance
- Gait & balance problems.[1]

Drugs used in PARKISON DISEASE THERAPY, and to give a detail information specifying the drugs and NOVEL DRUGS approved so far, for the treatment of this Neuro- degenerative disorder and describe about the chemistry.

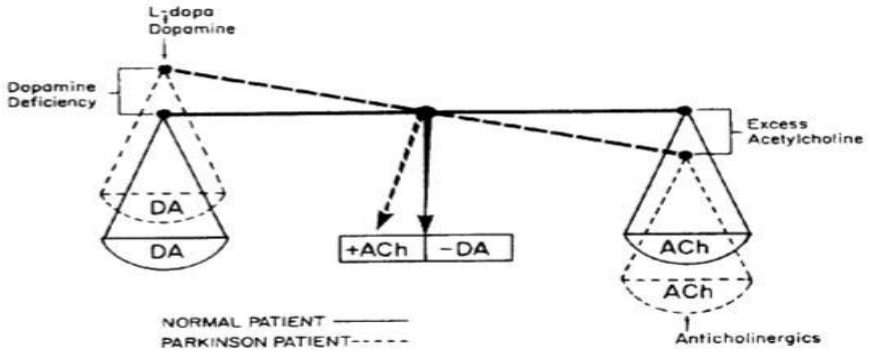


Fig. 2: Schematic representation of the imbalance b/w excitatory neurotransmitter Ach and the inhibitory neurotransmitter dopamine in basal ganglia.

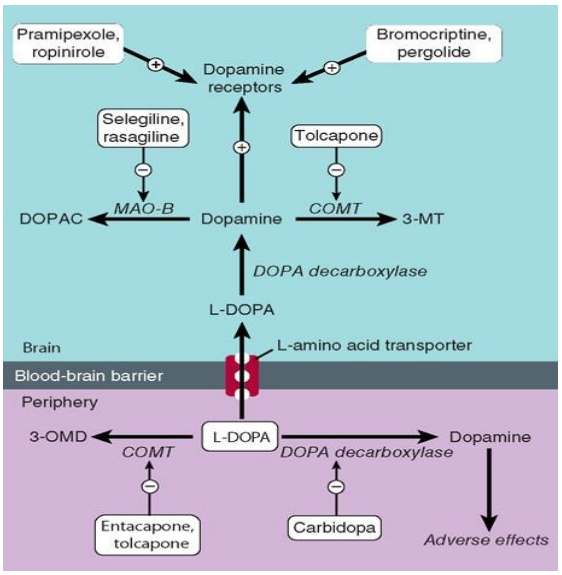
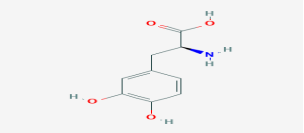
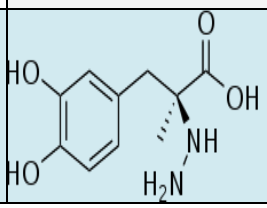


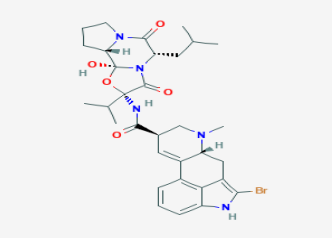
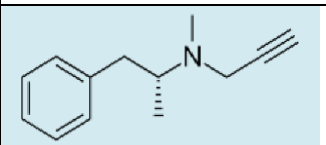
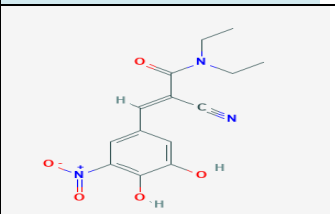
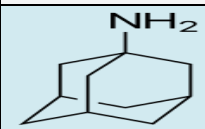
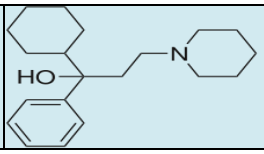
Fig-3: Mechanism of Action of Dopamine.

General Mechanism of Action

Parkinson's disease is a progressive neurodegenerative disorder with motor defects due to the imbalance between the dopaminergic (inhibitory-D2, excitatory-D1 receptors). These are amplified by K+ channels, respectively. Parkinson's disease is characterized by dopamine deficiency. Levodopa is considered to act through D1 and D2 receptors present in the straitum and it regulates the activity of the two pathways having opposite effects on the thalamic input to the motor cortex.[2]

Classification of Anti Parkinson's Drugs.[3]

Drugs affecting Brain Dopaminergic system			
Class	**Examples**	**IUPAC**	**Structure**
Dopamine precursor	**Levodopa**	(2S)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid	
Peripheral decarboxylase inhibitors	**Carbidopa** Benserazide	(2S)-3-(3,4-dihydroxyphenyl)- 2-hydrazino-2- methylpropanoic acid	

Dopaminergic agonists	**Bromocriptine** Ropinrole Pramipexole	(6aR,9R)-5-bromo-N-[(1S,2S,4R,7S)-2-hydroxy-7-(2-methylpropyl)-5,8-dioxo-4-propan-2-yl-3-oxa-6,9-diazatricyclo[7.3.0.02,6]dodec an-4-yl]-7-methyl-6,6a,8,9- tetrahydro-4H-indolo[4,3- fg]quinoline-9-carboxamide	
MAO-B inhibitors	**Selegeline** Rasageline	(R)-N-methyl-N-(1-pheny lpropan-2-yl)prop-3-yn-1- amine	
COMT inhibitors	**Entacopone** Tolcopone	(E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)- N,N-diethylprop-2-enamide	
Glutamate (NMDA)receptor agonist(Dopamin e facilitator)	**Amantadine**	Adamantan-1-amine	
Drugs Affecting Brain Cholinergic System			
Central anticholinergics	**Trihexylphenidyl** Procyclidin Biperiden	(RS)-1-Cyclohexyl-1-phenyl- 3-(1-piperidyl)propan-1-ol	
Antihistaminics			
	Orphenadrine Promethazine	N,N-dimethyl-2-[(2- methylphenyl)- phenylmethoxy]ethanamine	
Miscallaneous Drugs			
Antidepressents	Amitryptillin e Trazadol	3-(10,11-dihydro-5H- dibenzo[a,d]cycloheptene- 5-ylidene)-N,N-dimethylpropan-1-amine	
Vitamin-E	Tocopherol	2,7,8-trimethyl-2-(4,8,12- trimethyltridecyl)-3,4- dihydrochromen-6-ol	
Glutamate release inhibitor	Lamotrigine	6-(2,3-dichlorophenyl)- 1,2,4-triazine-3,5-diamine	
Glutamate release antagonist	Remacimide	2-amino-N- (1,2diphenylpropan-2- yl)acetamide	
Glialderived neurotrophic factor	GDNF		

Novel Drug or a New Molecular Entity (NME) it is an active compound, complex, molecule that previously has not been approved by the FDA/EMA. This is different from a previously approved drug that has received approval for a different but new condition. This is also different from a generic drug which is a generic (typically) off-patent formulation of the same NME but produced by an alternative company. In order to minimize these clinical complications, novel compounds have been developed. Novel drugs and bio products for the treatment of PD should address dopaminergic neuro protection to reduce premature neuro degeneration in addition to enhancing dopaminergic neurotransmission.[4]

Many of the new drugs have been introduced for the treatment of Parkinson's Disease in which some of them are discussed here briefly i.e

1. Istradeyfylline
2. Nilotinib 3.Safinamide
3. Isradipine
4. Ionosine
5. Stalevo
6. Idazoxan
7. Mirtazapine
8. Apomorphine Infusions
9. Rotigotine Skin patches
10. Pimavanserin

Istradefylline

Istradefylline, or KW6002, was developed by ***Kyowa Hakko Kirin in Japan*** for the treatment of Parkinson's disease as an adjunct to standard therapy. Unlike

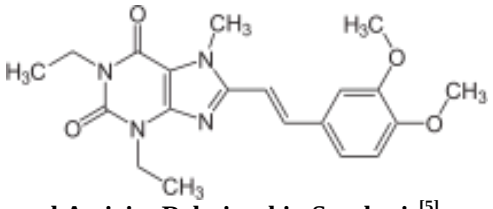
standard dopaminergic therapies for Parkinson's.

Istradefylline targets adenosine A2A receptors in the basal ganglia. This region of the brain is highly involved in motor control. Istradefylline is indicated as an adjunct treatment to [levodopa] and [carbidopa] for Parkinson's disease. This drug was first approved in Japan on 25 March 2013. Istradefylline was granted **FDA approval on 27 August 2019**.[5] **Istradefylline**, sold under the brand name **Nourianz**.[7]

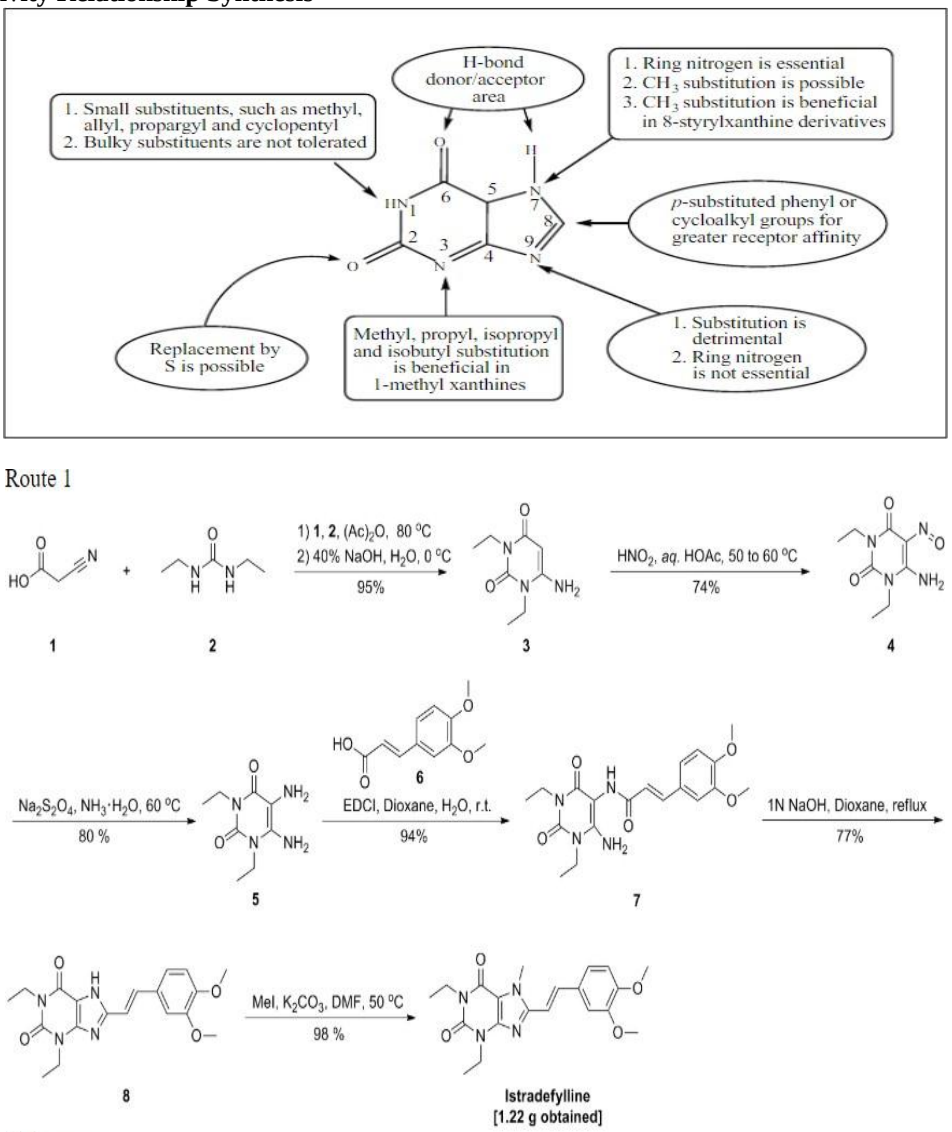
IUPACname: 8-[(*E*)-2-(3,4- dimethoxyphenyl)vinyl]-1,3-diethyl-7- methyl-3,7-dihydro-1*H*-purine-2,6-dione.[6]

Molecular formula: $C_{20}H_{24}N_4O_4$ **Molecular weight:** 384.42 g/mol.

Structure



Structural Activity Relationship Synthesis[5]



Route 1

Reference:

Fig. 5: SAR of Istradeyfylline.

Mechanism of action

Istradefylline is a selective adenosine A2A receptor

antagonist used in addition to carbidopa and levodopa for the treatment of "off" episodes. The precise mechanism of action of the drug is unknown but it is presumed to reduce the over activity of the striatal pathway, restoring the balance of basal ganglia.[6]

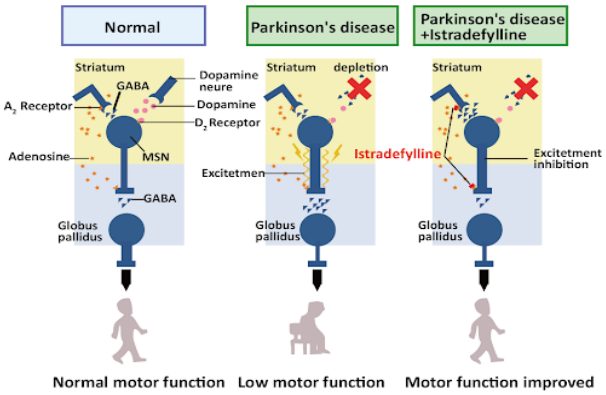


Fig-4: Motor function in PD.

Therapeutic uses

Istradefylline is used by people with Parkinson's disease taking carbidopa/levodopa to reduce the amount of "off" time (periods of slow movement or stiffness.[8]

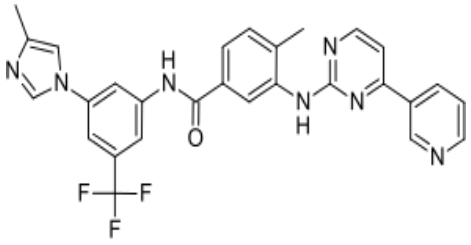
Adverse effects[7]

- Involuntary muscle movements,
- dizziness,
- constipation,
- nausea,
- hallucinations, and
- Insomnia

Nilotinib

Nilotinib by Novartis is a potential new treatment for Parkinson's disease (PD).[9] A clinical trial investigating the repurposed cancer drug Nilotinib in people with Parkinson's disease finds that it is reasonably safe and well tolerated. Researchers also report finding an increase in dopamine, the chemical lost as a result of neuronal destruction, and a decrease in neurotoxic proteins in the brain among study participants. Finally, they say Nilotinib, a tyrosine kinase inhibitor, potentially halts motor and non-motor decline.[10]

Structure



IUPAC name: 4-methyl-N-[3-(4-methyl- 1H-imidazol-1-yl)- 5-(trifluoromethyl) phenyl]-3- [(4-pyridin-3- ylpyrimidin-2-yl) amino]benzamide.

Molecular formula: C28H22F3N7O

Molecular weight: 529.52 g/mol

Mechanism of action: Nilotinib blocks the non-receptor Abelson (Abl) tyrosine kinase, but its exact mechanism of action in Parkinson's disease is still under investigation. The hope is that this approach could slow down or stop Parkinson's progression. The results of the first safety study should be available soon.[10]

Synthesis

The5-bromo-3-(tri fluoro methyl) phenyl amine was reacted with 4-methyl-1H- imidazole in the presence of cesium carbonate and cuprous iodide to obtain 3-trifluoromethyl-5-(4-methyl-1H-imidazol- 1- yl) phenyl amine(4). Ethyl 3-amino-4- methyl benzoate was reacted with cyanamide to obtain the guanidine, which cyclized with 3-dimethylamino 1-(3- pyridinyl) -2- propylene-1-one to provide ethyl4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino] benzoate(8). Compound 8 was subjected to Boc protection, hydrolysis, amidation and then condensation with compound 4 to give 4methyl-N-[3-(4-methyl-1H-imidazol-1- yl)-5- (trifluoromethyl) phenyl]-3-[N-tert butoxycarbonyl-[4-(3-pyridinyl)-2-pyrimidinyl] amino] benzamide(10). After deprotection, nilotinib was obtained.[11]

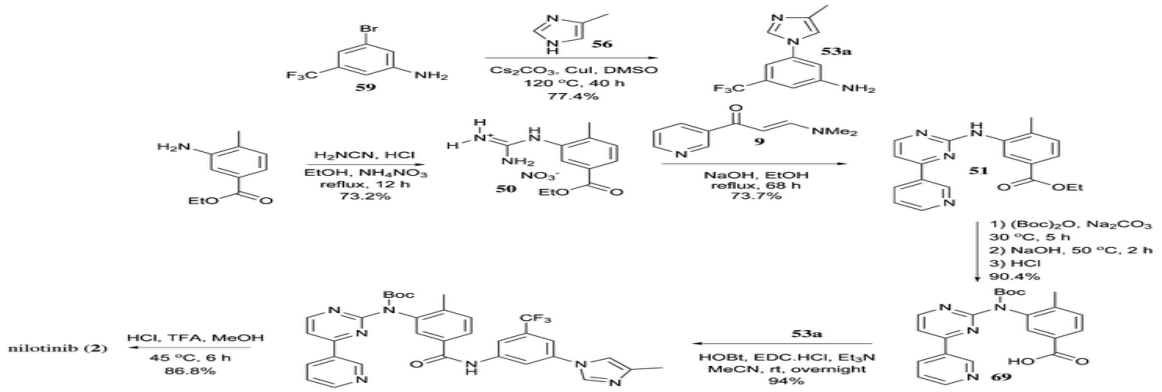


Fig-6: Synthesis of Nilotinib.

Therapeutic uses

Parkinson's disease and experimental Parkinsonism.[69] Idazoxan, as an adjunct Nilotinib is used in the treatment of Parkinson disease.

Nilotinib is used to treat a certain type of blood cancer (chronic myelogenous leukemia-CML). It works by slowing or stopping the growth of cancer cells.[12]

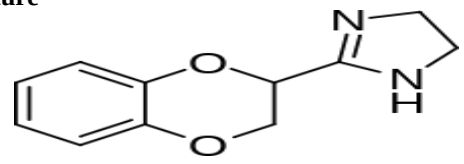
Adverse effects

- Itching,
- Headache,
- Nausea,
- Fatigue,
- Tiredness,
- Joint or muscle aches or pain,
- Back Pain,
- Diarrhoea,
- Constipation.[13]

IDAZOXAN

It has been proposed that Idazoxan in combination with L-dopa may provide a novel approach to the treatment of Parkinson's disease that will not only reduce the dyskinetic side effects, but extend the anti-parkinsonian actions of L- dopa. The a2-adrenoceptor antagonist idazoxan may improve motor symptoms in to dopamine replacement, may prove useful in the treatment of parkinsonian patients at all stages of disease progression.[14]

Structure[15]



IUPAC Name: (±)-2-(2,3-dihydro-1,4- benzodioxin-2-yl)-4,5-dihydro-1H- imidazole.

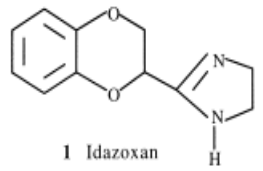
Molecular formula: C11H12N2O2 **Molecular weight**: 204.225g.[15]

Mechanism of action

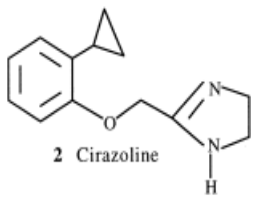
Idazoxan enhances the anti parkinsonian actions of levodopa and reduces dyskinesia in MPTP treated primates. It has been shown repeatedly that stimulation of the noradrenergic system will enhance memory retrieval idazoxan, increases firing of noradrenergic neurons of the locus coeruleus twofold at a dose that has no detectable effect on overt behavior such as locomotor activity.[16]

Structural activity relationship

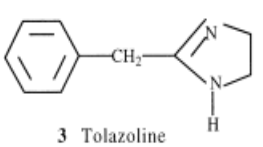
Although at the α1-adrenoreceptor all the compounds displayed a significant agonist activity, at the α2-adrenoreceptor they showed either agonist or antagonist activity depending on the nature of the phenyl substituent. The qualitative structure–activity relationship led us to the conclusion that the oxygen atom in the side-chain is essential for α1-agonist activity, while the cyclopropyl ring is not, and may be replaced by several groups. Of the groups studied, isopropoxy appears to be the best. Instead, the same substitution (i.e., isopropoxy for the cyclopropyl ring) at α2-adrenoreceptors causes a reversal of activity. On the other hand, the cyclopropyl ring seems to be important for α1-selectivity.[17]



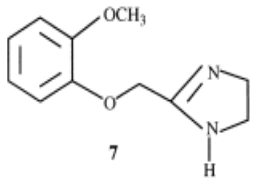
1 Idazoxan



2 Cirazoline



3 Tolazoline



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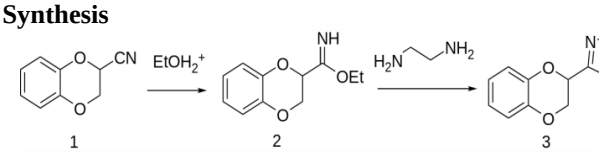
Synthesis



Therapeutic uses

- It has antidepressant effect but has not been reached the market
- Antipsychotic
- In pathogenesis of schizophrenia.[15]

Adverse reactions

Dyskinesia is a frequent and disabling side effect in patients with Parkinson's, Idazoxan actually extends L-DOPA's anti parkinsonian benefits.[17]

Isradipine

Isradipine Fails to Slow Early Parkinson Disease Progression in Phase 3 Study.[19]

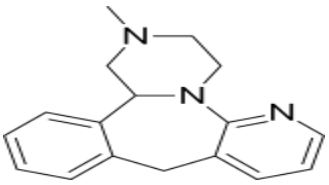
Isradipine is a medication currently used to treat high blood pressure and goes by the brand name of **DynaCirc®.** It is classified as a calcium channel blocker. Isradipine caught the attention of researchers for Parkinson's disease (PD) when data from large clinical studies showed that people taking isradipine had a lower risk of developing PD. It is thought that in dopamine neurons in the brain, neurons which die in Parkinson's disease, the entry of calcium in these neurons over time leads to damage. Isradipine blocks the activity of specific channels in the neuron that allow the calcium to enter, thus preventing the death of the neurons (nerve cells) that produce dopamine and may slow the progression of PD.

It is not yet known if Isradipine has beneficial effects on PD. Data from the trial will provide more information on its effectiveness in people with PD. In addition, low blood pressure is a common symptom of PD, so this medication may worsen the condition.[18]

MIRTAZAPINE

Pramipexole (Mirapex®) is a drug that is effective at alleviating movement deficits associated with Parkinson's disease. However, pramipexole can induce compulsive behaviours and behavioral addictions, such as problem gambling, in some patients. **Mirtazapine**, an atypical antidepressant reduces the effects of drug addiction in pre-clinical models and in humans. This study aims to determine if mirtazapine can reduce pramipexole- induced gambling-like behavior in a model of PD, while leaving the motor benefits intact.[20] Psychotic symptoms often occur as a complication in Parkinson's disease patients, and a set of criteria for Parkinson's disease with psychosis (PDPsy) has been established. Mirtazapine improved the patient's refractory psychotic symptoms, especially her visual hallucinations, without worsening her motor symptoms.[21]

Structure[22]



IUPACname:(±)-2-Methyl- 1,2,3,4,10,14b-hexahydropyrazino[2,1- *a*]pyrido[2,3-*c*],[2]benzazepine **Molecular formula:** $C_{17}H_{19}N_3$ **Molecular weight:** 263.35 g/mol.[22] **Mechanism of action:**

- Blockade of pre-synaptic alpha 2 receptors, which causes the increase in the release of nor- epinephrine from the nor- adrenergic nerve endings and of serotonin from serotonergic nerve endings.
- Blockade of 5HT-2A Presynaptic receptors.
- Blockade of H1 receptors. (It is not known which of this two actions more important for the antidepressant effect.).[23]

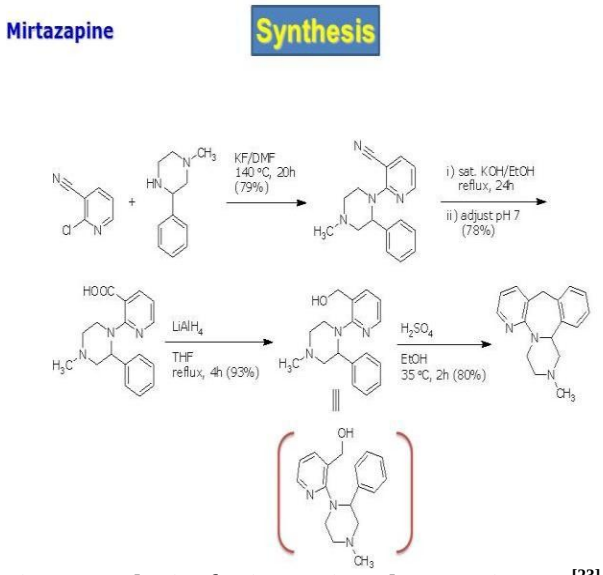


Fig. 7: Synthesis of Mirtazapine Therapeutic uses.[23]

Synthesis

- Psychosis related Parkinson therapy
- Antidepressant

Adverse reactions[23]

- Sedation and drowsiness.
- Constipation, appetite stimulation, Weight gain.

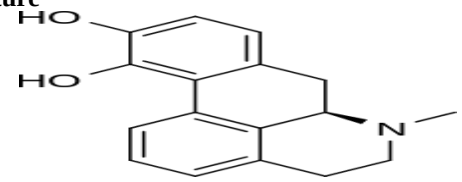
Contraindications

- REMERON (mirtazapine) Tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.[24]
- Starting REMERON in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.[24]

Apomorphine INFUSION

Apokyn (apomorphine) is used by injection to treat loss of body movement control in patients with advanced Parkinson's disease between doses of levodopa treatment. It has the same effect as dopamine, a naturally occurring chemical messenger found in the brain.[26]

Structure[26]



IUPAC Name: (6a*R*)-6-methyl-5,6,6a,7- tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline- 10,11-diol

Molecular formula: C17H17NO2 **Molecular weight:** 267.332g/mol.[26] **Mechanism of action**

Apomorphine's R-enantiomer is an agonist of both D_1 and D_2 dopamine receptors, with higher activity at D_2. Apomorphine improves motor function by activating dopamine receptors in the nigrostriatal pathway, the limbic system, the hypothalamus, and the pituitary gland It also increases blood flow to the supplementary motor area and to the dorsolateral prefrontal cortex (stimulation of which has been found to reduce the tardive dyskinesia effectsof L-DOPA). Parkinson's has also been found to have excess iron at the sites of neurodegeneration; both the R- and S-enantiomers of apomorphine are potentiron chelators and radical scavengers. Apomorphine also reduces the breakdown of dopamine in the brain (though it inhibits its synthesis as well).[19][20] It is a powerful up regulator of certain neural growth factors,[21] in particular NGF and BDNF, epigenetic dow n regulation of which has been associated with addictive behaviour in rats.

Apomorphine causes vomiting by acting on dopamine receptors in the chemoreceptor trigger zone of the medulla; this activates the nearby vomiting center.[26]

Structural activity relationship

- The side chain of dopamine (DA) is flexible (rotation around β- carbon phenyl bond).
- Compounds with catechol ring & amino-ethyl moiety of DA are held in rigid conformation are synthesized. Ex: Apomorphine.
- It has structure similarities in trans- α- rotamer conformation**.**

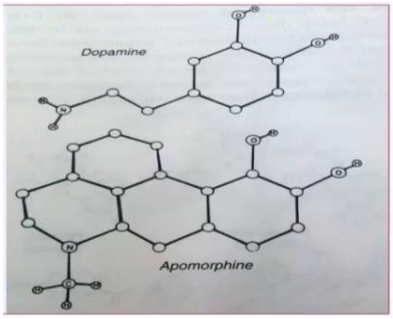
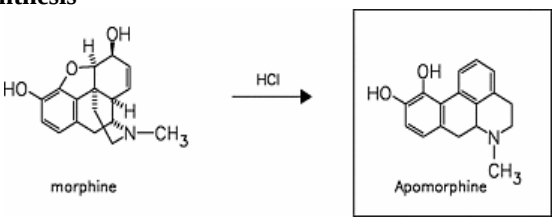


Fig-8: Structure of Apomorphine.

Synthesis[25]



Therapeutic uses: Apokyn may be used up to five times a day as a small injection under the skin, using a device similar to the one used for insulin injection in people with diabetes. Apokyn starts working as early as 10 minutes after the injection, with most people feeling relief from the "off" episode within 20 minutes. It usually lasts for up to 90 minutes, so it's important patients not stop taking their other Parkinson's medications.[25]

Adverse reactions: Apokyn should not be taken with medicines for nausea, vomiting, or irritable bowel syndrome, as serious side effects may occur, such as severely low blood pressure and loss of consciousness.[25]

Contraindications

- The main and absolute contraindication to using apomorphine is the concurrent use of adrenergic receptor antagonists; combined, they cause a severe drop in blood pressure and fainting
- IV administration of apomorphine is highly discouraged, as it can crystallize in the veins and create a blood clot (thrombus) and block a pulmonary artery (pulmonary embolism).[26]

DISCUSSION

Parkinson's disease was found in ancient era. It was described in ancient writing. There is no exact treatment for PD but different medications are available which are used to treat PD. The treatment includes plant based treatment, medicinal drugs such as dopamine which replaces with dopamine replacement therapy, surgical treatment such as deep brain stimulation (DBS). These symptoms are tested by medication with levodopa. According to researchers there is hope for development for method which not only cures PD but also help to control development of PD. The treatment is becoming more sophisticated as there are new methods are developed as NOVEL DRUGS FOR PARKINSON which lead a path to treat this neurodegenerative disorder, many drugs have been discovered and this play an essential role in preventing the disease. This novel drugs along with their medicinal chemistry based on its structure, synthesis, SAR'S, mechanism of action, therapeutic uses, Adverse effects and contraindications etc. are discussed above in the theory which is beneficial in drug design and modulation.

SUMMARY

Parkinson's disease is the most common Neuro-

degenerative disorder. Several new medications are discovered, most of which are variations of previously existing products, such new dosage forms of already-approved products, or cost-saving generic formulations the NOVEL DRUGS for its treatment have been proposed. This thesis describes regarding the PARKINSON DISEASE and its history, genetics, the commonly used drugs for its treatment and their medicinal chemistry and also it describes about the newly discovered drugs for the treatment of this disorder along with their medicinal chemistry. This approach was discussed to make out a brief idea regarding the drugs used nowadays most commonly to treat the disease and the main goal was to study regarding drugs to get a clear idea about its chemistry which used for its formulation and in various other aspects.

CONCLUSION

In conclusion, the approach has been applied to understand the aetiology of PD and to detect its genetic causes as well as treatment strategies. Based on the robust and efficient method applied in this study, which was performed without dimensionality reduction, more biologically valuable results have been obtained.

In this study, some drugs have been proposed as novel treatments for PD. Parkinson's disease is most common type of movement disorder seen in clinical practice. Early diagnosis can be made with high index of suspicion. Most of the patients respond to dopa agonists or L- dopa preparations.

Parkinson's disease is an incurable disorder that has proved challenging to manage and treat with current therapies.

Disease modification is the ultimate goal for drug development but has, so far, remained elusive.

Several NOVEL DRUGS has been developed and are found useful for the treatment and prevention of Parkinson's disease as discussed above i.e Istradeyfylline, Nilotinib, Safinamide, Stalevo, Idaoxazon, Ionosine, Mirtazapine, and it also provides a brief explanation regarding their medicinal chemistry.

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FIGURES

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