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MAO-A INHIBITORS - NEW HORIZONS- A REVIEW

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ABSTRACT

Objective: The study mainly focussed on identifying newer therapeutic agents available in the category of selective MAO-A inhibitors after 2000s, since these drugs found their way out of prescription due to the "Cheese Reactions". The study also aimed on the efficacy of the newer drugs with the available data on comparison with the conventional therapy. **Outcome:** The present study reviews on advancements and pharmacokinetic comparison of newer treatment options available in MAO-A Inhibitors with low tendency to produce "Cheese Reactions". This can be an innovative approach in prescribing alternative antidepressants which is to be explored in future.

KEYWORDS: Newer MAO-A Inhibitors, Cheese Reactions, antidepressants.

1. INTRODUCTION

Monoamine oxidase inhibitors (MAO Inhibitors) are medications prescribed for management of depression, neurological and psychiatric illnesses. It is an Antidepressant class of drug. Monoamine oxidase functions as catalysts for oxidative deamination of monoamines, (neurotransmitters such as serotonin and histamine, as well as the catecholamines such as dopamine, norepinephrine, and epinephrine). MAO-A and MAO-B are the two main isoenzymes of MOA. Norepinephrine, epinephrine, dopamine, tryptamine, and tyramine are all oxidized by both isoenzymes but serotonin is oxidized by MAO-A alone.

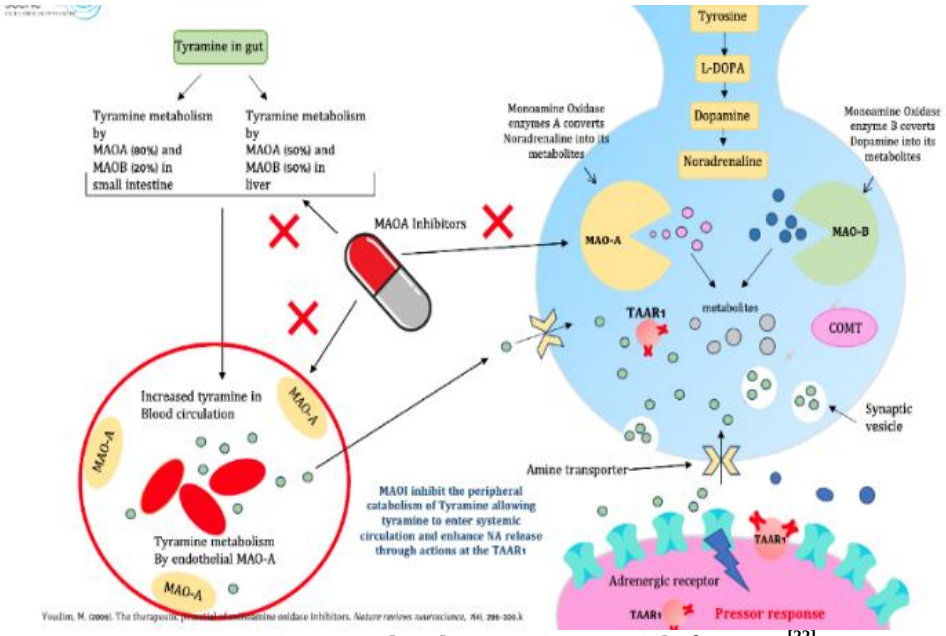


Figure 1: The Therapeutic potential of MOAI.[22]

Monoamine Oxidase Innhibitors function by inhibiting the enzyme MAO, result in accumulation of substrates such as the monoamine and catecholamine neurotransmitters, along with tyramine taken-up by some foods. The antidepressant effect of the MAOIs' is mainly due to the accumulation of serotonin, norepinephrine and dopamine in the synaptic clefts of Central Nervous system which is mainly dependent on the inhibition of

MAO-A, with MAO-B inhibitors being devoid of antidepressant activity.

This effect is likely due to the heterogenicity of isoenzyme distribution in the brain.[6] Table 1 shows the classification of the MAOIs based upon their class and selectivity.

Hypertensive crisis or the "cheese reaction" is a significant and potentially fatal side effect of MAOIs. This adverse event occurs when taking MAOIs along with sympathomimetic amines such as tyramine found in some fermented foods like cheese.[7] As the intestines contain very little MAO-B, it is important to note that selective MAO-B inhibitors do not have such an adverse effect.[8] The development of Reversible Inhibitors of selective MAO-A(RIMA) also avoided this issue. MAO-A inhibitors successfully block enough MAO-A in the brain also showing a low enough affinity to allow its displacement by tyramine from intestinal MAO-A.[9]

2. METHODOLOGY

2.1. Research In MAO-A Inhibitors

In the quest to find the ideal MAO-A Inhibitors, many parent compounds have also been explored though structural optimizations. Purpurin, an anthraquinone, found in the madder's roots, has a wide range of biological activities, such as the inhibition of xanthine oxidase, antifungal and antioxidant activity.[10] In 2017, Lee *et al.*[23] found that MAO-A inhibition was effectively and selectively accomplished by purpurin (IC50 = 2.50 μM) during the screening of target-based natural products using human MAO-A and MAO-B. The results showed that purpurin is a selective and reversible inhibitor of MAO-A, thus it can be regarded as a novel potential lead compound for the development of novel reversible inhibitors of MAO-A.[11] In addition, Yelekçi *et al.*[12] and Kare *et al.*[13] also used this method to design and analyse MAO-B inhibitors.

Receptor based approach has been used regularly by scientists in the pharmaceutical industry as well as in academic laboratories over the past four decades which is critical for the discovery and optimization of early lead compounds.[14]

This article focuses mainly upon the newer drugs which are under the clinical research pipeline and some drugs recently approved by the US FDA in the category of selective MAO-A inhibitors.

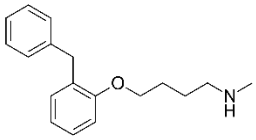
Reversible inhibitors of monoamine oxidase A (RIMAs) are a subclass of MAOIs that selectively and reversibly inhibit the activity of MAO-A enzyme.

RIMAs are used clinically in the treatment of depression and dysthymia, though they have not gained widespread clinical prescription worldwide. Because of their reversibility and selectivity, RIMAs are safer than the older MAOIs like phenelzine and tranylcypromine.[15]

Several selective reversible inhibitors of MAO-A are used outside USA; but only *moclobemide* is currently approved for use within and outside the United States by the FDA. These selective reversible inhibitors of MAO-A used outside USA are further described below.

1. Bifemelane (Alnert, Celeport) (available in Japan)

1.1. Physical and Chemical Properties



IUPAC Name: [4-(2-benzylphenoxy) butyl] (methyl)amine
(Molecular Weight: 305.84 g/mol)
The drug Bifemelane hydrochloride, an antidepressant of category MAO inhibitor. Reverses Tetrabenazine induced catalepsy in mice and increases locomotor activity in MPTP-treated marmosets.[16]

1.2. Clinical study information

Yamagami S et al studied the therapeutic efficacy, utility and safety of bifemelane hydrochloride in 52 elderly patients with depression. A 50mg oral tablet dosage form was given three times daily for 8 consecutive weeks. The final global improvement rating was 80.8 % and global utility rating was 73.1% for all patients. The improvement rates on the Hamilton depression rating scale (HAM-D) were more than 60% for depressed mood, guilt, suicide, middle insomnia, delayed insomnia, psychotic anxiety, gastro-intestinal symptom, hypochondriasis, depersonalization and derealization. The values of Psychoneurotic rating scale for doctor's use were more than 60% for tension, agitation, irritability and excitement, phobia, depression, hypochondria and nocturnal delirium in psychotic symptoms, and insomnia in addition to palpitation in somatic symptoms for global symptoms evaluated.

After treatment with this drug, a significant decrease was also observed in the symptoms covered by the Self-rating depression scale of Zung.[24] There were no Adverse drug reactions or abnormal laboratory values encountered in the trial. Therefore, bifemelane hydrochloride was suggested as a valuable treatment regimen for geriatric depression.[1]

1.3. Toxicological information

Acute Toxicity

Oral-rat Lethal Dose 50(LD50): 1080mg/kg; Intra-Peritoneal(IPR) -RAT LD50: 130mg/kg[25]; Subcutaneous(SCU)-RAT LD50: 513mg/kg; Intravenous(IVN)-rat LD50: 40400ug/kg[26]; oral-mouse Ld50: 400mg/kg[27]; IPR-mouse LD50: 105mg/kg[28]; SCU-mouse LD50: 313mg/kg[26]; IVN-MOUSE LD50: 35300ug/kg[26]; ORAL-RAT Lowest published toxic dose: 11375mg/kg[26]; Oral – rat , Lowest published toxic dose: 9100mg/kg.[29]

1.4. Symptoms based on Routes of exposure

Inhalation

There may be shortness of breath with a burning sensation in the throat. Exposure may cause coughing or wheezing. Absorption through the lungs can occur causing symptoms similar to those of ingestion. There may be shortness of breath.

Ingestion

There may be soreness and redness of the mouth and throat. Nausea and stomach pain may occur. Blood may be vomited. There may be vomiting and diarrhoea.

Skin

Irritation or pain may occur at the site of contact. There may be redness or whiteness of the skin in the area of exposure. Absorption through the skin may be harmful.

Eyes

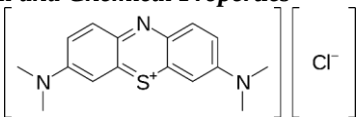
There may be pain and redness. The vision may become blurred. The eyes may water profusely. Absorption through the eye may cause effects similar to skin contact and/or ingestion.

Additional Information

Exposure may cause irritaiton of eyes, mucous membranes, upper respiratory tract and skin. To the best of our knowledge, the chemical, physical and toxicological properties have not been fully investigated

2. Methylthioninium chloride (Urelene blue, Provayblue, Proveblue)

2.1. Physical and Chemical Properties



IUPAC Name: 3,7-bis(dimethylamino)-5λ^4-phenothiazin-5-ylium chloride

Molecular weight: 319.85

Methylthioninium chloride (*Methylene blue*) is an investigational drug being developed by the University of Aberdeen and TauRx Therapeutics that inhibition of Tau protein aggregation has been shown in early clinical trials. The drug is of potential interest for the treatment of patients with Alzheimer's disease.

2.2. Clinical study information

Methylene blue (MB), a thionine dye, is a potent inhibitor of monoamine oxidase (MAO)-A. This property may at least in part, mediate its antidepressant effects in humans and animals. The MB's central inhibition of MAO-A has also been linked to serotonin toxicity (ST) which araises when it is combined with serotonergic drugs. Azure B, a Structural analogue and the principal metabolite of MB, has also been reported to inhibit the MAO enzymes, specifically for the MAO-A isoform. The structure-activity relationships (SARs) of MAO inhibition by MB analogues described by *Delport A et al* **(30)** investigates five MB analogues: neutral red, Nile blue, new methylene blue, cresyl violet and 1,9-dimethyl methylene blue inhibiting the human MAO.

These analogues are also Similar to MB, exhibiting higher potency for inhibition compared to MB (IC50=0.07μM) i.e MAO-A inhibitors with cresyl violet (IC50=0.0037μM), Nile blue (IC50=0.0077μM) and 1,9-dimethyl methylene blue (IC50=0.018μM). Non-thionine MB analogues (e.g., cresyl violet and Nile blue) also exhibit a potent MAO inhibition, a property which is to be considered during pharmacological studies. Benzophenoxazines (cresyl violet and Nile blue) are, similar to phenothiazines (e.g. MB), representing a high potency and selectivity for MAO-A inhibition with a potential risk of ST.[2]

2.3. Pharmacokinetics

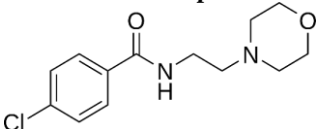
Methylene blue has a Volume of distribution of 10mg/Kg in rats and was reported to bind strongly to rabbit plasma (71–77% of bound drug). Following distribution into tissues, the drug was rapidly reduced to leukomethylene blue (leucomethylthioninium chloride). Metabolism of leucomethylene blue is less efficient in neonates than in older individuals **(17)**. The drug was mainly Excreted in urine and bile. About 75% of an oral dose excreted in urine, primarily as stabilized colourless leukomethylene blue. The half-life of the drug was found to be 5–6.5 hours (after IV dose) and clearance was found to be 3.0 ± 0.7 L/min

2.4. Toxicity Information

LD50 = 1180 mg/kg (Rat)

3.Moclobemide (Aurorix, Manerix, Moclamine) (FDA Approved)

3.1. Physical and Chemical Properties



IUPAC Name: 4-chloro-N-[2-(morpholin-4-yl) ethyl] benzamide,

Molecular weight: 268.739

A reversible monoamine oxidase inhibitor (MAOI) selective for isoform A (RIMA) is used to manage major depressive disorder. Most meta-analyses indicate that in the acute depression management, moclobemide is more effective than placebo and is as efficacious as tricyclic antidepressants (TCA) or selective serotonin reuptake inhibitors (SSRIs). Due to the exhibition of negligible anticholinergic and antihistaminic actions, moclobemide is better tolerated than tri- or heterocyclic antidepressants.[3] It is Commercially prescribed available in Canada, USA and many countries as 100mg, 150mg, 300mg and 600mg dosed tablets.

3.2. Clinical study information

Moclobemide has been extensively evaluated in the management of a wide spectrum of depressive disorders

and evaluated less extensively in anxiety disorders. The growing evidence that moclobemide being not inferior to other antidepressants in the treatment of subtypes of depression, such as dysthymia, endogenous (unipolar and bipolar), reactive, atypical, agitated, and retarded depression. With other antidepressants, evidence suggests that long-term efficacy of moclobemide is limited. More controlled studies addressing this issue are needed. In patients with bipolar depression, the risk of developing mania seems to be lesser with moclobemide than with other antidepressants. The effective therapeutic dose ranged from 300 to 600 mg, divided in 2 to 3 doses for moclobemide in most acute phase trials. While one controlled trial and one long-term open-label study indicates moclobemide being efficacious in social phobia, three controlled trials reveals either no effect or less robust effects with the tendency of higher doses (600 - 900 mg/d) being more efficacious.

Two comparative trials demonstrated moclobemide is as efficacious as fluoxetine or clomipramine in patients suffering from panic disorder.[33] Placebo-controlled trials in this indication are, however, still less available. A plasma concentration relationship of moclobemide and its therapeutic efficacy is not apparent but a positive correlation with adverse events is found. Dizziness, nausea and insomnia occurred more frequently with moclobemide than on placebo. Due to negligible anticholinergic and antihistaminic actions, moclobemide is better tolerated than tri- or heterocyclic antidepressants. Gastrointestinal adverse events and, sexual dysfunction was much less frequent with moclobemide than with SSRIs. Moclobemide has a very low tendency induce hypertensive crisis after ingestion of tyramine-rich food ("cheese-reaction"). Therefore, dietary restrictions are not compulsory but with doses above 900 mg/d the risk of interaction with ingested tyramine becomes clinically relevant. During multiple dosing the oral bioavailability of moclobemide reaches almost 100% and at therapeutic doses, moclobemide lacks significant negative effects on psychomotor performance, cognitive function or cardiovascular system. Moclobemide is particularly attractive in the treatment of elderly patients due to the relative freedom from these side effects. Moclobemide is a CYP2C19 substrate.[3]

Although it shows inhibition of CYP1A2, CYP2C19, and CYP2D6, relatively few clinically important drug interactions have been reported thus Meclobemide is relatively safe even in overdose. The drug shows a short plasma elimination half-life that allows to switch to an alternative agent within 24 h. Therapeutic doses can often be reached rapidly upon onset of treatment, since it is well tolerated. Following dose adjustment, steady-state plasma levels are reached approximately at one week. Patients with renal dysfunction require no dose reduction in contrast to patients with severe hepatic impairment who require dose correction. With a combination of moclobemide with other antidepressants cases of refractory depression might improve, such as clomipramine or a SSRI. It requires lower entry doses, a slower dose titration and a more careful monitoring of patients since this combination has rarely been associated with a potentially lethal serotonin syndrome. Although no serious adverse events have been published with therapeutic doses of moclobemide to date combination therapy with moclobemide and other serotonergic agents, or opioids, should be undertaken with caution. Animal data suggests the combined use of moclobemide with pethidine or dextropropoxyphene should be avoided. Evidences are lacking that moclobemide would increase body weight or produce seizures. Some preclinical data shows anticonvulsant property of moclobemide.[3]

3.3. Pharmacokinetics

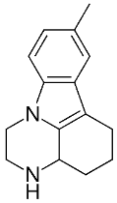
The drug is well absorbed from the gastrointestinal tract (> 95%). The presence of food reduces the absorption rate but not the extent of absorption. Hepatic first-pass metabolism reduces bioavailability to about 56% following administration of one dose, but increases to 90% with steady-state dosing as a result of saturation of the first pass effect. Peak plasma concentrations are reached within 0.3 - 1 hours following oral administration with a terminal half-life of 1.6 hours. The drug has a volume of distribution of 1-1.5 L/Kg and Approximately 50% protein bound (primarily to albumin). Moclobemide is metabolized in the liver by Cytochrome P450 2C19 and 2D6. Moclobemide is a CYP2C19 substrate. Although it acts as an inhibitor of CYP1A2, CYP2C19, and CYP2D6. Moclobemide is almost completely renally excreted with 1-2 hours of half-life period (4 hours in cirrhotic patients) and has a Clearance of 30-78 L/h, mainly excreted in urine.[31]

3.4. Toxicological information

Lethal Dose 50 in mouse is 730mg/kg and LD50 in rat is 1,300mg/kg. Toxicity signs include hypertension, drowsiness, dizziness, confusion, tremors, headache, agitation, muscle rigidity and seizures. The effects of moclobemide alone in overdose are negligible, even with high volume ingestion. Severe serotonin toxicity can occur with Moclobemide overdose combination with a serotonergic agent (even in small, therapeutic doses). At overdoses, the elimination half-life is prolonged by two to four times, compared with that found in healthy volunteers who are given therapeutic doses.[32]

4.Pirlindole (Pirazidol) (available in Russia)

4.1. Physical and Chemical Properties



IUPAC Name: 12-methyl-1,4-diazatetracyclo[7.6.1.0^{5},^{16}.0^{10},^{15}]hexadeca-9(16),10,12,14- tetraene

Molecular weight: 226.323

It was developed and is currently used as an antidepressant in Russia. Its chemical structure is similar to metralindole, and it also shares pharmacological properties with this drug.

Pirlindole is a selective, reversible inhibitor of monoamine oxidase (MAO) subtype A (MAO-A) that is approved in several European and non-European countries for the management of major depression. Supported by many years of clinical experience in the treatment of depression, the antidepressant efficacy and safety of pirlindole have been demonstrated in numerous studies and Pirlindole's efficacy and safety have also been shown in the treatment of fibromyalgia.[4]

4.2. Clinical study information

Debilitating chronic conditions such as depression and fibromyalgia syndrome impose a significant burden on individuals, families and society. Both disorders have many overlapping symptoms. Antidepressants of several classes are among recommended treatment options for patients with fibromyalgia syndrome. The drug's efficacy and safety have also been demonstrated, more recently, in the treatment of fibromyalgia syndrome. Pirlindole has a very good tolerability profile, with no deleterious effect on cardiovascular dynamics. The action of pirlindole on sensorimotor performance relevant to driving a motor vehicle was similar to that of placebo, as pirlindole has an activating rather than a sedating antidepressant profile. No tyramine or 'cheese' effect is likely after short- or long-term administration because of its specific and reversible inhibition of MAO-A and relatively short elimination half-life. The available evidence enhances pirlindole as a safe and effective treatment regimen for the management of depression and fibromyalgia syndrome.[4]

4.3. Pharmacokinetics

The drug is well absorbed with a bioavailability of 90%. Plasma proteins confines 97% binding of the drug. The drug is metabolized through the hepatic system. dogs and rat studies of Pirlindole has a bioavailability of between 20 and 30% due to the hepatic first-pass effect.[34]

The rats have shown elimination of mainly unconjugated drug while the dog elimination shows of mostly conjugated drug. Excretion is through renal route, with 0.4-0.5% being excreted in the urine as unchanged drug in healthy males. with 0.7±0.3 hours of half-life in one study of healthy volunteers. Plasma clearance observed with the drug was high (450–1000 l/h).[34]

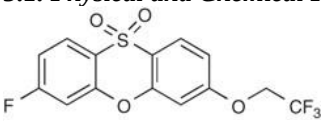
4.4. Toxicity Information

Pirlindole, a short-acting selective and reversible monoamine oxidase A inhibitors, is commonly well-tolerated and benign during an overdose.

During interactions with tyramine-rich foods, tricyclic antidepressants (TCAs), or sympathomimetic drugs, and selective serotonin reuptake inhibitors (SSRIs), deaths from an overdose of this medication have more commonly observed. The common adverse effects from clinical conditions includes agitation, extreme tremor, followed by seizures and hyperthermia. After intractable seizure and/or hyperthermia and its sequelae, such as disseminated intravascular coagulation (DIC) and multi-organ failure, deaths occurred 3-16 hours after ingestion of the drugs.[35]

5. CX157 (Tyrima)

5.1. Physical and Chemical Properties



IUPAC Name: 3-fluoro-7-(2,2,2-trifluoroethoxy) phenoxathiine 10,10-dioxide
Molecular weight: 348.27 g/mol

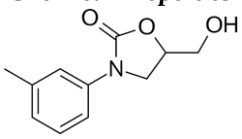
CX157,3-fluoro-7-(2,2,2, - trifluoroethoxy) phenoxathiin-10,10-dioxide, is a reversible, selective inhibitor of MAO-A crafted to have improved oral bioavailability and reduced clearance compared to previous MAO-A inhibitors of this class.

5.2. Clinical study information

CX157, a specific RIMA A in a phase 1, single-center, double-blind, placebo-controlled, three-period study assessed cardiovascular safety, following the oral administration of tyramine. The sensitivity of each subject to orally administered tyramine was established in Period 1, by determining the dose of tyramine that elevates SBP ≥30 mmHg on ≥3 consecutive occasions (i.e., TYR303). In Period 2, twelve subjects qualified for randomization during which an oral CX157 Modified Release Tablet of 125 mg [N = 10] or placebo (N = 2) were administered twice per day for 6 days to reach steady state. CX157 and placebo were administered with oral tyramine in fed state in Period 3 with daily increase in the tyramine dose of 20, 40, and 80 mg in an attempt to achieve the TYR303. CX157 Modified Release Tablet, 125 mg administered twice per day with 250 mg daily dose, was not associated with a tyramine reaction i.e., TYR303. It is generally agreed that a high tyramine meal would contain up to 40 mg of dietary tyramine. The data obtained with CX157 provides an adequate information on safety with respect to tyramine interaction and suggests that future studies can be conducted without the need for dietary tyramine restrictions.[5] Further data available on the Tyrima are under the clinical study pipeline for discovery which cannot be concluded.

6. TOLOXATONE

6.1. Physical and Chemical Properties



IUPAC Name: *5-(hydroxymethyl)-3-(3-methylphenyl)-1,3-oxazolidin-2-one*

Molecular Weight: *207.229*

Toloxatone is an antidepressant medication, the first ever use of which was at France in 1984. It acts as a selective and reversible inhibitor of monoamine oxidase-A (MOA)

6.2. Clinical study information

Second-generation antidepressive origin molecule: Toloxatone, a specific and reversible MAO A inhibitor was administered to one hundred and one depressed inpatients. All 101 patients with depressive illness did not score higher than 20 on Hamilton's Scale upon admission, and did not score lower than 4 on Fischer, Fernández Labriola and Rodríguez Casanova's Endogeneity Test. Biological profiles such as Phenyl-ethylamine, NA, and MHPG were available on 57 subjects. At the beginning of the experiment the following were ensured:
(a) No subject was taking antidepressive,
(b) Patients' age averaged 46;
(c) The 6-week experiment was a double-blind vs. placebo type.

Toloxatone dose was standardized to a 400 mg intake daily. Significant modifications were detected in 51 subjects. 37 achieved either "excellent" or "good" outcomes among the 59 subjects that were administered with Toloxatone. A better response to Toloxatone was pointed out by biological markers namely, patients with a lower noradrenergic activity. Anxiety-free depression and inhibited depressions are a choice for administering Toloxatone by the psychiatrist.[18]

6.3. Pharmacokinetics

The drug follows hepatic excretion and 1% of drug is excreted unchanged in the urine and has 1-3 hours of half-life.[36]

6.4. Toxicity Information

In rare cases, toloxatone toxicity may cause sudden onset of hepatitis. More common adverse events of the drug include dysuria, nausea, constipation, vertigo, and insomnia. Administration of toloxatone with selective serotonin reuptake inhibitors (SSRI), and tricyclic antidepressants can lead to an increased risk of serotonin syndrome. Increased blood pressure can occur with sympathomimetic medication coadministration. One study showed that elevated doses of toloxatone may contribute to elevated blood pressure in healthy subjects when combined with a meal. This interaction could be explained by enhanced tyramine bioavailability in the presence of toloxatone. After long-term administration of the drug at therapeutic dosages this tyramine in meals and toloxatone is unlikely to occur in patients.[37]

DISCUSSION AND CONCLUSION

On observing the various pharmacokinetic data available, the drugs *Moclobemide* and *Pirlindone* shows better absorption pattern but studies indicate that bioavailability is delayed by the first-pass metabolism in contrast of their low tendency to produce “Cheese Reactions”.

Bifemelane shows a very low creatinine-clearance indicating a drug suitable for longer MAO-A inhibition bound with albumin and ά-1-acid glycoprotein.

The investigational drug *CX157* also seems to be a potent MAOAI but its pharmacokinetic and toxicological profile are yet to be explored. Adverse events to the drug are linked to vomiting, chest pain, palpitations, upper abdominal pain and abnormal spermatozoa progressive motility. *Methythionium blue* and its structural analogues can also be considered as drug of choice but further clinical studies are required to indicate its efficacy and safety profile. This review on different treatment options available in MAOA Inhibitors as of now can be a milestone in providing alternative antidepressants which is to be explored in future.

On evaluating the pharmacokinetic data, the comparative absorption pattern of these drugs are presented in figure 2. The drug moclobemide shows highest absorption of 95% of the drug being absorbed after oral administration followed by pirlindole with 90% but absorption pattern of both are delayed by the hepatic first-pass metabolism.

Table 2 summarises the available pharmacokinetic data on the newer drugs. The newer drugs provide valid data on selective MAO-A inhibition with less tendency to produce “Cheese Reactions”. Even though these drugs are under investigation and require more studies focussing on their safety and efficacy, they find themselves potentially essential in some countries for treatment of depression, neurological and psychiatric disorders.

Figure3 compares the plasma half-life of the drugs indicating methylene blue having the longest half-life (5-6.5 hours) making it a potential drug for pro-longed MAO-A inhibition. Pirlindole shows a short half-life with 0.4-1hour followed by Toloxatone (0.96-1.81 hours) and moclobemide (1.6 hours) indicating a good drug of choice for selective MAO-A inhibition as they allow for to switch to an alternative antidepressant within 24 hours in the event of any adverse reactions.

Figure: 4 depicts the data available on the percentage Plasma binding of the newer drugs enabling their ease of distribution. The drug Pirlindole having high affinity towards the plasma proteins shows 97% binding to plasma proteins followed by the drug Methylthionium Blue showing 71%-77% of the drug bound to plasma protiens. Moclobemide and Toloxatone shows 50% of the drug bound to plasma protein albumin. There was no

data available for CX157 and Bifemelane regarding their plasma binding.

Conflicts of Interest: Nil.

Table 1: Classification of MAOIs.

Group	Class	Compound	MAO selectivity	Application
First generation MAOIs (non-selective)	Hydrazines	Iproniazid	A and B	Antidepressant
	Hydrazines	Isoniazid	A and B	Antidepressant
	Hydrazines	Octamoxin	A and B	Antidepressant
	Nitrofuran	Furazolidone	A and B	Antidepressant
	Curcuminoids	Curcumin	A and B	Antidepressant
	Flavonoid glycosides	Myricetin	A and B	Anti-Alzheimer
	Quinolinamine	Echinopsidine	A and B	Antidepressant
Second generation MAOIs (selective-irreversible)	Propargylamines	Selegiline	B	Anti-Parkinson
	Propargylamines	Rasagiline	B	Anti-Parkinson
	Propargylamines	Clorgyline	A	Antidepressant
Third generation MAOIs (selective-reversible)	Piperidylbenzofurans	Brofaromine	A	Antidepressant
	Morpholinobenzamide	Moclobemide	A	Antidepressant
	Indole derivative	Prilindole	A	Antidepressant

Table 2: Comparative toxicity and Pharmacokinetic profiles of the selected drugs.

DRUG	PHARMACOKINETIC PARAMETER	VALUE OBSERVED
Bifemelane[19]	Cmax	13.41-3.21ng/ml
	absorption	delayed by first-pass metabolism
	CLcr	102.5-52.9ml/min
	Tmax	11.25-2.67ng/ml
	Plasma concentration	9.18-3.11ng/ml
	excretion	urine
	distribution	albumin and ά1acid glycoprotein
MethyThionium blue	Vd	10mg/kg
	plasma binding	71-77%
	excretion	urine and bile
	Thalf	5-6.5h
	CLcr	2.3-3.7l/min
Moclobemide	absorption	>95%. Delayed by first-pass metabolism.
	Tmax	0.3-1h
	Thalf	1.6h
	Vd	1-1.5l/kg
	plasma binding	50%
	metabolism	liver
	excretion	urine
	CLcr	30-78l/hr
Pirlindole	absorption	90%; Delayed by first pass metabolism
	plasma binding	97%
	metabolism	liver
	excretion	urine
	Thalf	0.4-1h
	CLcr	450-1000l/h
Toloxatone [20]	Cmax	0.384 to 0.640 mg/l
	Tmax	0.53 and 1.00 h
	Thalf	0.96-1.81 h
	Vd	1.09 - 1.64 l/kg
	plasma binding	protein50% albumin
	absorption	50%-62%

Vd- Volume of Distribution; Clcr- Creatinine clearance; Tmax-Time taken to reach maximum concentration; Thalf-Half life; Cmax- Maximum Concentration.

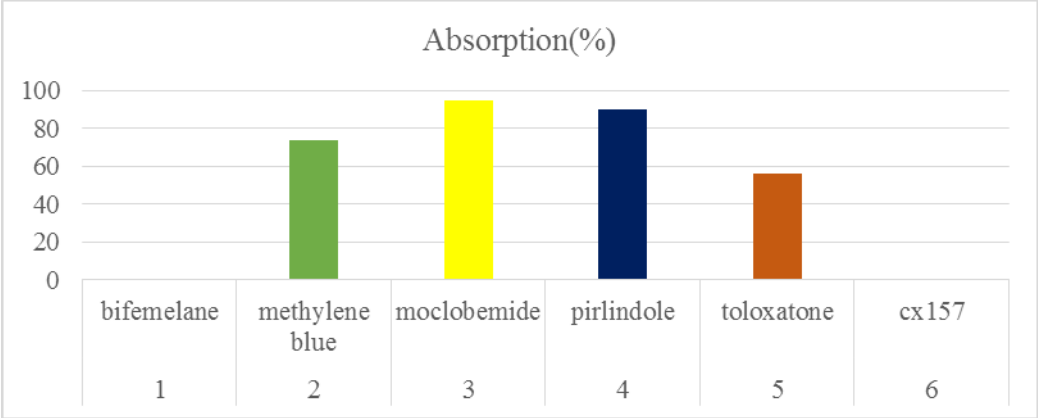


Figure 2: Comparative Absorption on oral administration of the drug (Bifemelane and CX157 are under Investigational New Drug [IND] application hence the data is not globally disclosed).

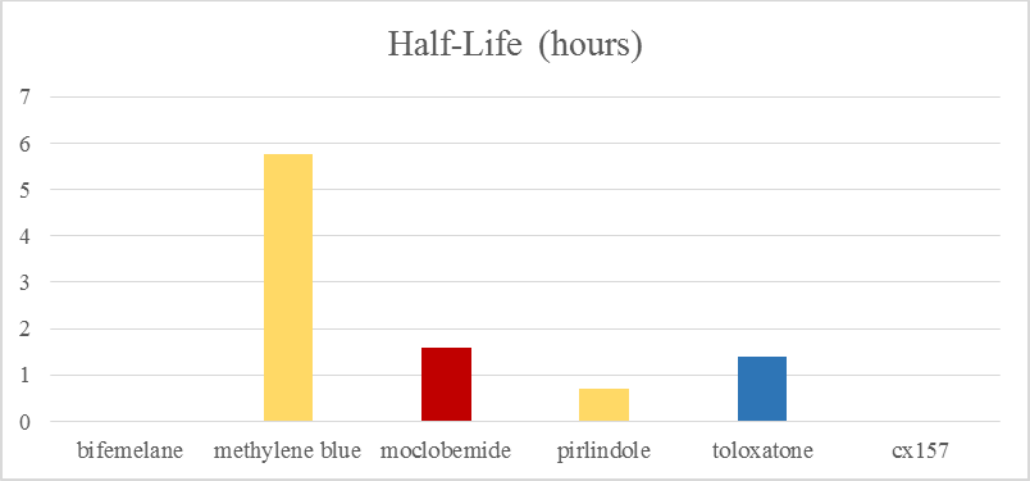


Figure 3: Comparison on Half-life (Bifemelane and CX157 are under IND application hence the data is not globally disclosed).

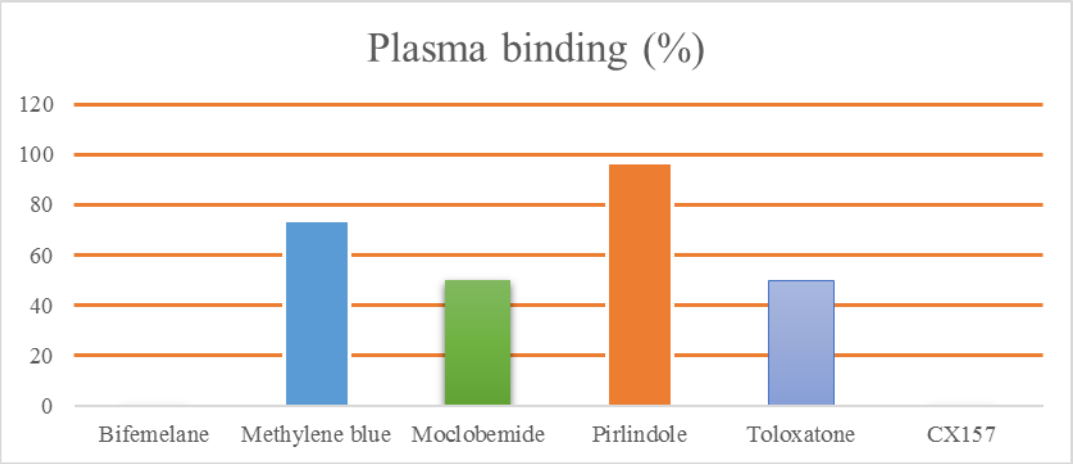


Figure 4: Comparative Plasma Binding, (Bifemelane and CX157 are under IND application hence the data is not globally disclosed).

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