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Review on Novel Monoamine Oxidase Inhibitors: A Clinician's Guide

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Mini Review

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Abstract

The purpose of this review is to provide information on the mechanisms of action, pharmacokinetics, therapeutic effectiveness, safety, and tolerability of four novel antidepressants: pirlindole, safinamide, selegiline, and toloxatone. In spite of the initial pharmacological interest, monoamine oxidase (MAO) inhibitors are used in clinics for their antidepressant effects and in the treatment of Parkinson's syndrome due to proven neuroprotective effects. Patients with a lack of efficacy or tolerability for some monoamine oxidase inhibitors may benefit from the option of a new one monoamine oxidase inhibitors with various mechanism of actions. In the selection of newer monoamine oxidase inhibitors, these drugs may be an alternative. The simple deficiency of serotonin in the brain does not cause depression, but rather a complex interplay of different neurotransmitters, including some regions of the brain include serotonin, norepinephrine, dopamine and histamine. The novel monoamine oxidase inhibitors described above exert their therapeutic advantages by acting on multiple neurotransmitters. When formulating a plan of treatment, the ambiguity of the underlying neurobiological process should be considered.

Keywords: Depression; Monoamine Oxidase Inhibitors; Pirlindol; Safinamide; Selegiline; Toloxatone

Introduction and Background

Major Depressive Disorder (MDD) may be a major public health concern with significant impairment in psychological, occupational, and social functioning. The prevalence rates for depression are estimated to be around 3.2% in patients without concurrent physical illnesses and 9.3% to 23.0% in patients with chronic conditions. It is the fourth explanation for disability around the world and is estimated to be the second leading explanation for disability in 2020. It affects around 300 million individuals no matter gender, ethnicity, geographical location, and socio economic status, contributing to the general global burden of disease [1].

Early antidepressant medications e.g. all the synthesized analogs at a portion of 20 mg/kg IP showed anticonvulsant activity. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are compelling because they upgrade either noradrenergic or serotonergic systems, or both. Shockingly, these derivatives block cholinergic, histaminergic, and alpha-1-adrenergic receptors sites, communicate with various different prescriptions and realize various unfortunate reactions. There has been significant debate about the use of MAO inhibitors, first because of the periodic hypertensive crises associated with their use, and second because many have questioned their effectiveness as opposed to the tricyclic antidepressants (TCAs) [2]. Clinical theory indicates that MAO inhibitors can be used refractory to other types of treatment in depressed Patients [3].

All these more up to date mixes are the consequences of balanced formative methodologies. Most as of now presented antidepressants are monoamine based and tweaking monoamine activity. It must be emphasized, however, that these newer antidepressants are far from the ideal ones, also

resulting in undesirable side effects and requiring 2-6 weeks of treatment to produce a therapeutic effect. Furthermore, approximately 30% of the population does not respond to current therapies. A significant new improvement has been the development of potential novel systems of activity past the monoaminergic neural connection. The results of recent novel developmental approaches have suggested that modulation of N-methyl-D-aspartate (NMDA), neuropeptide (substance P and corticotrophin-releasing factor) receptors and the intracellular messenger system may provide entirely new set of potential therapeutic targets. Thus, chemically new classes of antidepressants must be explored in order to treat such patients. Monoamine oxidase (MAO) inhibitors, notwithstanding the preliminary pharmacological interest are used in medical institution for their antidepressant impact and in the management of parkinson symptoms, due to the mounted neuroprotective action. Efficacy and tolerability of these agents is emerged from large-scale and randomized scientific trials [4,5].

Historically, MAOIs had been categorized either by means of chemical structure (e.g., hydrazine versus non-hydrazine [tranylcypromine]), or via receptor type selectivity (MAO-A, MAO-B, or both), or properly as their reversibility (reversible or irreversible). It used to be later shown that selective blockade of MAO-A alone also offered comparable therapeutic benefits in contrast to inhibition of each MAO-A and MAO-B [2]. Adrenaline, noradrenaline, and serotonin are deaminated through MAO-A receptors, whereas benzylamine and B-phenylethylamine are substrates for MAO-B receptors. Dopamine and tyramine use both isoforms. This encouraged the rummage around for each reversible and selective MAO-A inhibitor for depression and MAO-B for Parkinson's disease. There are few more up to date treatment choices including, pirindole,, safinamide toloxatone furthermore, selegiline with stimulant activities through various neurochemical activities [6]. This review article may guide the clinicians about the clinical components including the system of activity, pharmacokinetics, clinical viability, and wellbeing and bearableness. The creators additionally give a rundown of proof based examinations with respect to the fresher antidepressants. The randomized controlled trials (RCTs) and open-label trials are the main basis of this review article.

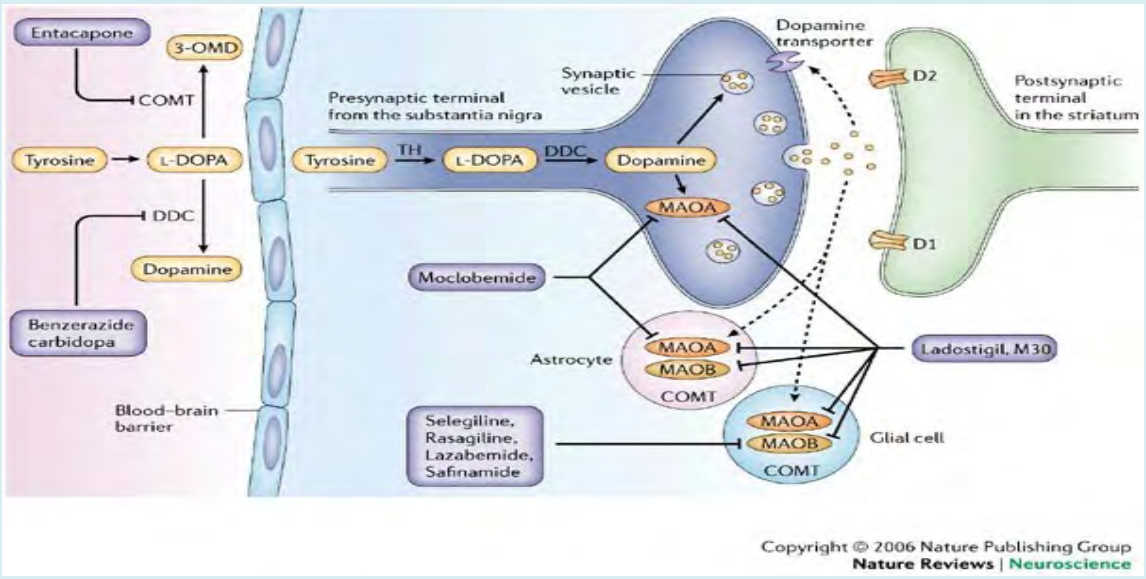

Figure 1: Synthesis and metabolism of Dopamine by MAO A and MAO B: The tyrosine hydroxylase (TH) catalyzes the conversion of tyrosine to levodopa (l-DOPA), which is then decarboxylated by dopa decarboxylase (DDC) to release dopamine. Intraneuronal monoamine oxidase A (MAOA), as well as glial and astrocyte MAOA and MAOB, metabolize dopamine. Selective MAOA and MAOB antagonists (selegiline, rasagiline, and safinamide, for example) have little impact on steady-state striatal dopamine levels, but prolonged therapy with these medications improves dopamine production, probably due to enhanced endogenous brain amines or receptor regulation [7].

Pirindole

Pirlindole hydrochloride (2,3,3a,4,5,6-hexahydro-8-methyl-1H-pyrazino [3,2,1-jk]-carbazole HCl) is a tetracyclic compound that was synthesized in the late 1960s [8]. It is a monoamine oxidase A (RIMA) reversible inhibitor which has been developed and is widely used as an antidepressant in Russia. Metralindole is structurally and pharmacologically related to it [9].

Structure

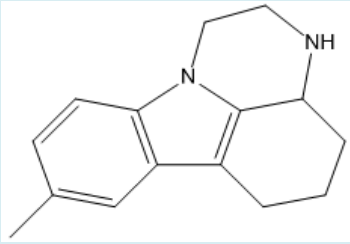

Figure 2: Pirlindole.

Mechanism of Action

Mechanism of action of pirlindole consists of inhibiting monoamine oxidase A selectively and reversibly. It also exerts an inhibitory effect on reuptake of noradrenaline and 5-hydroxytrypt-amine. It has no effect in the dopaminergic and cholinergic systems. It has only a slight potential for amplifying the pressure effect of tyramine and noradrenaline, which makes one expect that it would not be based on a 'cheese effect [10].

Dosage and Administration

Pirlindole is used in doses of 150–450 mg/day, with 225 mg/day being the most common dose (given as 75mg three times daily) and it is administered by oral route [11].

Pharmacokinetics

Pirlindole was almost fully absorbed, with approximately 90 percent relative bioavailability. The presumption of rapid biotransformation of pirlindole was confirmed by the high apparent plasma clearance (450–1000 1/h). The primary course of removal of the metabolites in man was renal excretion. After repeated dosing of 75 mg pirlindole t.i.d. at intervals of at least 6 hrs over 8 days, the kinetic parameters of the plasma levels did not account for accumulation or enzyme induction by the unchanged compound. The binding to human plasma proteins was 95–97% [12].

Clinical use

The efficacy of pirlindole for MDD was established in 9 RCTs in adults at a dose range of 75-300 mg. Pirlindole appears as a safe medication relative to tricyclic antidepressants and nonselective MAO inhibitors due to its relatively low degree of activity with the cardiovascular system and low ability to amplify the effects of tyramine and noradrenaline strain. This double-blind randomized placebo-controlled study clearly shows the effectiveness and safety of pirlindole in the treatment of major depression [13]. In comparison to critical depressive symptoms in the pirlindole group, cognitive depressive factors predominate in the amitriptyline group in addition to core symptoms [14,15]. No specific and statistically meaningful differences were identified with regard to the therapeutic efficacy in depressive syndromes of a nosologically different classification, either in comparison with amitripytline versus pirlindole or in comparison with imipramine and pirlindole [16]. This clinical trial confirms the potential for the treatment of unipolar (single or chronic episodes) and bipolar disorder with RIMAs, such as moclobemide and pirlindole [17]. This four week, double-blind, placebo controlled study indicates that pirindole (75 b.i.d) could be well tolerated and beneficial treatment for fibromyalgia syndrome [18]. In an open-label trial of 52 weeks, short-and long-term administration of pirlindole did not alter platelet and plasma MAO-B activity, indicating a lack of inhibition of MAO-B Table 1 summarizes the features of these trials including the participants sample size, duration, doses, and age ranges [19,10].

Studies	Design	Groups (n)	Duration	Age (years)	Dose range (mg)
Schwarz A, Schwarz H, et al. [13]	RCT	Pirindole (50 mg/day)=5 (75 mg/day)= 10 (375 mg/day)= 1(Flex)	21 days	25-65	100-375
Lehmann E, Kinzler E, et al. (1985) [14]	RCT	Pirindole (75 mg 3 times / day) =52 Desipramine (2x 25 mg/day -3 x 50/ day)=59	3 wks	>18	Pir = 225 Des = 50-150
Schapperle O, Eckmann F, et al. (1985) [17]	RCT	1.Pirindole (a.m.:150 mg and Noon:75mg) =40 Amitriptyline (a.m.:100 mg and noon:50mg) =40	1) 6 wks	1.Pir: 27-67 (F) 21-49 (M)	1. Pir = 75-150 AMT= 50-100
		2. Pirindole (50 mg t.i.d/day) = 40 Imipramine (75 mg t.i.d/day) = 40	2) 3 wks	2. Pir: 20-60 IMP: 18-56	2.Pir = 50 IMP = 75

Renfordt Ernst [16]	RCT	Pirindole 300 mg /day =10	28 days		Pir 300
		Amitriptyline 200 mg/day =10			AMT 200
De Wilde JE, Geerts S, et al. (1996) [15]	RCT	Pirindole (300 mg/day)=49	42 days	44-57	75-300
		Placebo=49			
Tanghe' A, gee S, JS, et al. (1996) [18]	RCT	Pir (150-300 mg / day) = 52	42 days	18-65	Pir = 150-300
		Moc (300-600 mg / day)=59			Moc = 300-600
Ginsberg F, Joos E, et al. (1998) [19]	RCT	Pirindole (75 mg b.i.d)= 45	4 wks	39.8± 8.8	75-150
		Placebo =44 [SA]			
		Pirindole (75 mg b.i.d)= 33			
		Placebo =28 [EA]			
Bruhwyler et al. (1997) [10]	OLT	Pir (150-500 mg/day)=1330	32 months	-	150-500
		PMS			

Table 1: Summary of demographic characteristics, dose ranges, and duration of studies of Pirlindole.
AMT: Amitriptyline, Des: Desipramine, EA: Efficacy analysis Flex: Flexible dose, IMP: imipramine MDD: Major Depressive Disorder, Moc: Moclobemide, OLT: Open-label trial, Pir: Pirlindole, PMS: Post marketing survey, RCT: Randomized controlled trial, RIMA: Reversible inhibitor monoamine oxidase A, SA: Safety Analysis.

Studies	Clinical outcomes
Schwarz JA, Schwarz H, et al. (1975) [13]	Pirlindole appears as a safe medication relative to tricyclic antidepressants and non-selective MAO inhibitors
Lehmann E, Kinzler E, et al. (1985) [14]	Pirlindole appears as a safe medication relative to tricyclic antidepressants and non-selective MAO inhibitors
Schapperle O, Eckmann F, et al. (1985) [17]	In both trials, pirlindole, amitriptyline or imipramine showed no phenomena of intolerance, no significant side effects or irregular laboratory parameters.
De Wilde JE, Geerts S, et al. (1996) [15]	The higher efficacy of pirlindole was apparent and statistically important relative to placebo. The tolerability of pirlindole was nice and did not vary substantially from placebo.
Tanghe A, Gee SJ, et al. (1997) [18]	No difference in the care outcomes in any of the assessment methodsused (HDRS, HARS and MADRS) in the pirindole and moclobemide groups.
Bruhwyler J, Monseu MJ, et al. (1997) [10]	Long-term administration substantially decreased plasma norepinephrine and serotonin uptake concentrations and improved [3H]-yohimbine binding site expression.
Ginsberg F, Joos E, et al. (1998)[19]	Pirindole (75 b.i.d) could be a fibromyalgia syndrome treatment that is well tolerated and beneficial.

Table 2: Summary of clinical outcomes of studies of Pirlindole.
MAOIs: Monoamine oxidase inhibitors, HDRS: Hamilton Depression Rating Scale, HARS: Hamilton Anxiety Rating Scale, MADRS: Montgomery-Asberg Depression Rating Scale.

Safety and Tolerability

A number of placebo and active comparator controlled trials have shown the antidepressant effectiveness and protection of pirlindole are supported by several years of clinical experience of depression care. It has also been seen recently in the treatment of fibromyalgia syndrome with no deleterious effects on cardiovascular dynamics. Pirlindole has a favourable tolerability profile. The effect of pirlindole is close to that of placebo on sensorimotor output related to driving a motor vehicle, as pirlindole tends to have an activating profile rather than a sedating antidepressant profile. No tyramine or 'cheese' effect is likely after short or long-term administration due to its unique and reversible MAOA inhibition and relatively short removal half-life. Pirlindole is validated by available evidence as a safe and

successful therapeutic choice for the management of depression and fibromyalgia syndrome [20].

Pregnancy

There is little research on the use of pirlindole in pregnancy and lactation, and pirlindole administration in these cases is not recommended. Also, pirlindole is not recommended for the care of children < 12 years of age [20].

Safinamide

Safinamide (INN; brand name Xadago) is a drug used during 'off' episodes as an add-on treatment for Parkinson's disease; it has several modes of action, including monoamine oxidase B inhibition. It was approved in Europe in February 2015, in March 2017, in the United States and in January 2019 in Canada [21].

Structure:

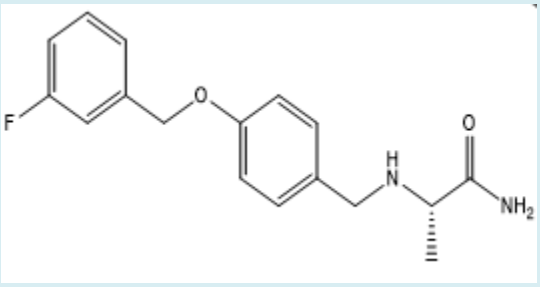

Figure 3: Safinamide.

Mechanism of Action

The antiparkinson mechanism of safinamide is via reversible inhibition of selective MAO-B, as a mesylate salt, thus it reduces the degradation of dopamine. It blocks the release of glutamate and the brain's dopamine reuptake. Safinamide also blocks channels of sodium and calcium, but the clinical relevance of this for PD is unclear [22].

Dosage and Administration

Begin with 50 mg orally administered once daily at the same time of day; the dose may be increased to 100 mg once daily after two weeks, depending on individual need and tolerability. Hepatic impairment: in patients with mild hepatic impairment, not exceeding 50 mg once daily; contraindicate in patients with extreme hepatic impairment [21].

Pharmacokinetics

Safinamide is absorbed easily, with a bioavailability of 95%, and a demonstrated time to maximum plasma concentration of 1.8–2.8 hours. It has extensive extravascular distribution with a volume of distribution of approximately 165 L. Safinamide does not undergo extensive first-pass metabolism and is regulated by amidase enzymes producing safinamide acid and other metabolites. Safinamide is mediated by cytochrome P450 (CYP) 3A4 isoenzymes. Safinamide acid, while not clinically significant, also binds to OAT3 (Organic Anion Transporter 3). It is 88 % to 90% bound to plasma protein and is mainly removed in the form of its metabolites by the kidneys (about 76%), with a half-life of 20 to 30 hours of removal. About 1.5% of safinamide is considered to be excreted in faeces. After oral administration of 50 mg to 300 mg, safinamide exhibits linear pharmacokinetics [22].

Clinical Use

Five placebo controlled RCTs have been reviewed for the safety and efficacy of safinamide. The addition of safinamide may provide an alternative approach to raising the dose of DA, thereby reducing the risk of side effects associated with DA, such as ICDs. The key clinical benefits of safinamide at 24 weeks were an improvement of approximately 30 to 60 minutes a day in 'ontime' without affecting dyskinesia (involuntary movements) and a comparable decrease in 'off time' relative to placebo [23]. This effect was still observed in a follow-up period of 2 years [24-26]. In levodopa treated patients, safinamide was a safe and effective first adjunct therapy. It strengthened 4/5 cardiac symptoms of PD, thus supporting moderate and non-mild fluctuators and patients undergoing other concomitant dopaminergic therapies [27]. In an open-label, randomized, two-period, two-sequence cross-over study, safinamide can be administered along with powerful inhibitors of CYP3A4 without dose modification requirement [28]. Findings of open label trials, clearly support the clinical utility of safinamide as an efficient levodopa adjunctive therapy of 50 and 100 mg / day once daily in patients with fluctuating PD [29]. Table 3 summarises the features of these trials including the participants sample size, duration, doses, and age ranges. Table 4 summarises the clinical finding s of those studies.

Studies	Design	Groups (n)	Duration	Age (years)	Dose range (mg)
Fabrizio S, et al. (2011) [23]	RCT	Safinamide 100 mg/day=90 Safinamide 200 mg/day=89 vs placebo = 90	24 wks	30-80	100-200
Borgohain, et al. 2014a (study 016) [24]	RCT	Safinamide 50 mg or 100 mg daily vs placebo. n=669	24 wks	30-80	50-100
Borgohain, et al. 2014b (study 018) [25]	RCT	Safinamide 50 mg or 100 mg daily vs placebo. n=669	18 months	30-80	50-100
Jost, Wolfgang H Kenney, et al. (2016) (SETTLE study) [26]	RCT	Safinamide 50 mg or 100 mg daily= 274 Vs placebo = 275 n=549	24 wks	61.9	50-100
Cattneo, et al. (2016) (SETTLE study) [27]	RCT	Safinamide 50 mg or 100 mg daily= 487 vs placebo = 484, Adjunct with levodopa 100 mg/day =43 vs Placebo = 46	24 wks	30-80	50-100
Sonja Krosser, et al. (2007) [28]	OLT	Safinamide 100 mg daily= 14 Ketconazole 200mg (b.i.d.)	6 days	18-45	Saf=100 Keto=200-400
Tsuboi Y, Hattori N, Yamamoto A, et al. (2020) [29]	OLT	safinamide 50 mg /day.=227	52 wks	>30	50

Table 3: Summary of demographic characteristics, dose ranges, and duration of studies of Safinamide.
CYP3A4: cytochrome 450 3A4; DA: dopamine ICDs: impulse control disorders; Keto: Ketoconazole; PD: Parkinson's disease; OLT: Open-label trial; RCT: Randomized controlled trial; Saf: safinamide.

Studies	Clinical outcomes
Fabrizio S, et al. (2011)[23]	Adding safinamide to a safe DA dose enhances motor symptoms at an early stage of PD and needs further study.
Borgohain, et al. (2014) (study 016)[24]	Mean daily change from baseline to week 24 without troublesome dyskinesia on time. (recorded in patient's diary)
Borgohain, et al. 2014b (study 018) [25]	Alteration of the mean total DRS score over time.
Jost, Wolfgang H Kenney, et al. (2016)	Mean daily change from baseline to week 24 without troublesome dyskinesia on time. (recorded in patient's diary)
(SETTLE study) [26]	
Cattneo, et al. (2016)	Safinamide was a safe and effective first adjunct therapy in patients treated with levodopa and strengthened 4/5 of the cardinal symptoms of PD thus supporting moderate and nonmild fluctuators and other concomitant dopaminergic therapy patients.
(SETTLE study)[27]	
Sonja Krosser, et al. (2012)[28]	Therapeutic steady state concentrations of the potent ketoconazole inhibitor CYP3A4 do not alter the characteristics of safinamide exposure.
Tsuboi Y, Hattori N, Yamamoto A, et al. (2020) [29]	Safinamide was safe, well tolerated, and effective in improving ON-time and other symptoms of PD at 52 weeks as an adjunctive treatment for levodopa.

Table 4: Summary of clinical outcomes of studies of safinamide.
DA: Dopamine; DRS: Dyskinesia Rating Scale; PD: Parkinson's disease; RCT: Randomised Controlled Trial.

Safety and Tolerability

Randomized, double-blind, placebo-controlled trials have identified the safety and efficacy of safinamide as an alternative for the treatment of motor symptoms of PD. The change in symptoms was substantial and lasted for at least two years without the worsening of dyskinesia. For patients who are not receptive to other pharmacotherapy choices for PD, safinamide is worthy of formal consideration. Unlike the MAO-B inhibitors selegiline and rasagiline, which show dyskinesia as a secondary effect. Dyskinesia, falls, and nausea are the most common adverse effects recorded in clinical trials of safinamide 100 mg at a rate of 2 % or higher versus placebo [22]. Hypertensionindigestion, hypersensitivity reactions, drowsiness, insomnia, anxiety and hallucinati-ons are some side effects [21].

Pregnancy

The advantages and risks of the drug in pregnant women or women of childbearing age are due to the lack of human evidence testing foetal risk when safinamide is used. Prior to commencing treatment, this demographic must be weighed. Likewise, the occurrence and effect of safinamide in breast milk on breastfed infants is uncertain [22].

Selegiline

Deprenyl/Selegiline (DEP), developed by Joseph Knoll in the 1960s, registered as the first selective inhibitor of B-type monoamine oxidase (MAO-B) in more than 60 countries to treat Parkinson's disease. Alzheimer's disease is a major depressive disorder; and used as an anti-aging drug [29]. Selegiline is the first irreversible, highly potent inhibitor of MA0 without 'cheese effect' [30].

Structure

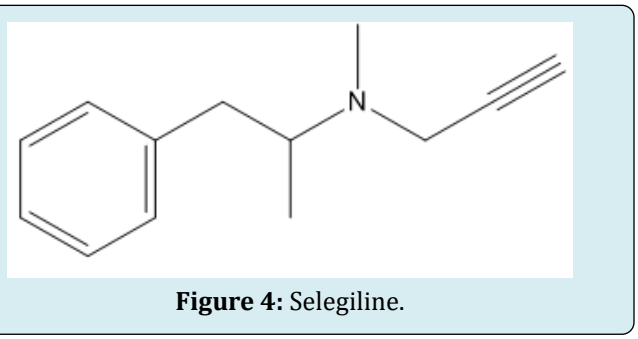

Figure 4: Selegiline.

Mechanism of Action

Selegiline is an irreversible monoamine oxidase inhibitor (MAO), an enzyme which catabolizes norepinephrine, serotonin and dopamine. Blocking enzyme prevents the reuptake of these neurotransmitters in the CNS, resulting in increased levels at the synaptic cleft of the biologically active monoamines. Selegiline shows selective B-type monoamine oxidase (MAO-B) inhibition at lower doses. The cause of Parkinson's disease is the loss of dopamine containing neurons in the midbrain substantia nigra and the resulting deficiency of dopamine throughout the striatum. The selective inhibition of MAO is therefore required for the treatment of Parkinson's disease, because MAO-B mainly metabolizes dopamine [31]. In comparison, selective inhibition of MAO-B is not the desired result when using selegiline to treat MDD. Inhibition of both MAO-A and MAO-B is used as an effective mechanism, for selegiline when used as a treatment for MDD. The monoamine hypothesis of depression suggests a fundamental physiological basis for depression as a decrease in central nervous system serotonin, nor epinephrine, and dopamine levels [32]. Since elevated levels of these three monoamines are often the intended consequence of treating MDD, non-inhibitory inhibition of both MAO subtypes is preferred. Selegiline Pre-treatment Could protect neurons from various neurotoxins, Tetrahydropyridine, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (MPTP), N-(2-chloroethyl)-N-ethyl- 6-hydroxy dopamine; 2-DSP-4 bromo benzyl amine, methyl-acetoxyethyl-2-Chloroethylamine and 5,6-dihydroxy serotonin (AF64A), which damages to dopaminergic, cholinergic, adrenergic, and sertoninergic neurons, each [33]. Selegiline can also inhibit monoamine oxidase type A (MAO-A) at higher doses, so it can be used for depression treatment.

Dosage and Administration

Selegiline (deprenyl) is a potent inhibitor of type B cerebral monoamine oxidase at the dosage (10mg /day) used in Parkinson's disease patients. Selegiline 5 mg orally twice daily, with breakfast and at noon, is prescribed in care of patients with Parkinson's disease. Higher dosages are no more effective than 10 mg / day, and it may be appropriate to limit all tyramine containing food and indirect sympathomimetic drugs above this dosage [34].

Pharmacokinetics

Selegiline undergoes significant metabolism (presumably due to presystemic clearance in the gut and liver). The major plasma metabolites are N-desmethylselegiline, L-mephetamine and L-meth- amphetamine. Only N-methylselegiline is an active MAO-B inhibitor. There is no known absolute bioavailability of selegiline after oral dose. After a single oral dose of 10 mg, the peak plasma concentrations of these metabolites are 4 to almost 20 times greater than that of normal selegiline plasma concentration [1 ng/mL] [34]. However, single oral dose studies don't predict multiple dose kinetics. The peak plasma level of selegiline

at a steady state is 4-fold which was obtained after a single dose. The concentrations of metabolites increase to a lesser degree, by an average of 2 folds seen after a single dose. When taken with food, the bioavailability of selegiline is increased 3 to 4-fold. The level of systemic selegiline exposure at a given dose varies significantly between individuals. No estimates of systemic selegiline clearance are valid. The mean half-life of selegiline removal after a single oral dose is 2 hours. Under stable conditions the half-life elimination increases to 10 hrs [35].

Clinical use

The efficacy of selegiline for PD has been identified in several adult RCTs and open-label trials. Selegiline provides positive effects at all levels of PD and helps the patient to obtain longer benefitsfrom levodopa treatment [36]. For 6 weeks, transdermal selegiline (20 mg applied once daily via a 20 cm2 patch) was a successful and well-tolerated treatment for adult outpatients with major depressions [37]. The early combination of selegiline and levodopa proved clearly superior to mono- therapy with levodopa in most case of an open label trial, the replacement of orally disintegrating selegiline (ODS) with decreasing doses of dopamine agonist (DAs) significantly reduced excessive daytime sleepiness (EDS), pedal oedema, hallucinations and impulse control disorders(ICDs) without sacrificing effectiveness [38-41]. Selegiline ODT on a long term 2.5 mg /day was successful, healthy and well tolerated in Parkinson's disease patients experiencing episodes off levodopa therapy [42]. Table 5 summarises the features of these trials including the participants sample size, duration, doses, and age ranges. Table 6 summarises the clinical findings of those studies.

Studies	Design	Groups (n)	Duration	Age (years)	Dose range (mg)
Myllya, et al. (1992) [36]	RCT	Selegiline 10 mg/day=27	3 wks	—	10
		Placebo=25	2,4,8,12 months		
Alexander Bodkin J, et al. [37]	RCT	Transdermal Selegiline	6 wks	41-44	20
		20 mg/day in			
		20 cm2 Patch= 89			
		Placebo=88			
Przunztek H, Conrad B, Dichgans J, et al. (1999) [38]	RCT	Selegiline 5 mg= 61 vs Placebo=55,	5 yrs	—	5
		as adjunt to Levodopa=116			
Larsen JP, Boas J, Erdal JE, et al. (1999) [39]	RCT	Selegiline vs Placebo as adjunt to Levodopa	5 yrs	35-75	10
		10 mg/day =163			
		Placebo as adjunt to Levodopa			
Palhagen S, Heinonen EH, Hagglund J, et al. (2006) [40]	RCT	Selegiline 10 mg/day =71	7 yrs	—	10
		Placebo =69			
		As adjunt to Levodopa			
Lyons KE. Friedman JH, etal. (2010) [41]	OLT	Orally disintegrating Selegiline 1.25-2.5 mg/day =60	12 wks	-90	1.25-2.5
Lewa MF, Rajesh pahwab, et al. (2007) [42]	OLT	selegiline ODT 2.5 mg = 254	12 months	—	2.5

Table 5: Summery of demographic characteristic, dose ranges, and duration of studies of Selegiline.
OLT: Open-label trial; RCT: Randomized controlled trial; ODT: Oral disintegrating Selegiline.

Studies	Clinical outcomes
Myllya, et al. (1992) [36]	Sel appears to delay the levodopa therapy's long-term problems and allow parkinsonian patients to maintain the benefits of levodopa therapy longer
Alexander Bodkin J, et al. [37]	The selegiline transdermal system was superior to placebo on all measures of efficacy
Przunztek H, Conrad B, Dichgans J, et al. (1999) [38]	Sel shows symptomatic benefit as adjunct to levodopa. About twice longer time to need for 50% increase in levodopa dose in the selegiline group
Larsen JP, Boas J, Erdal JE, et al. (1999) [39]	Symptomatic benefit as adjunct to madopar and Sel Possible disease-modifying effect. Less deterioration of the disease within the selegiline group after 5 years. After 1 month of washout, benefit was maintained
Palhagen S, Heino- nen EH, Hagglund J, et al. (2006) [40]	Improved motor scores after 5 years in the selegiline group with 19 % lower levodopa dose.
Lyons KE, Friedman JH, et al. (2010) [41]	The addition of ODS permitted a reduction in the mean daily dose of pramipexole from 2.3 to 0.5 mg and ropinirole from 11.2 to 2.9 mg for Immediate release.
Lewa MF, Rajesh pahwab, et al. (2007) [42]	Sel ODT 2.5 mg was effective for in Parkinson's disease patients experiencing episodes off levodopa therapy

Table 6: Summary of clinical outcomes of studies of Selegiline.
Sel: Selegiline; ODT: Oral disintegrating Selegiline.

Safety and Tolerability

Selegiline has been on clinical experience since the 1960s. Overall, the number of patients participating in reported clinical trials investigating the effectiveness and safety of selegiline in Parkinson's disease is more than 4000. Since selegiline is well tolerated as monotherapy in the early phase of the disease, adverse effects are moderate, and mainly dopaminergic. In conjunction with levodopa, selegiline can potentiate the dopaminergic adverse effects (dizziness, dyskinesias, orthostatic hypotension, nausea, hallucination, and insomnia) caused by levodopa, but these adverse effects can typically be controlled by decreasing levodopa dosages. One recent study suggested an increase in mortality associated with the combination of selegiline and levodopa compared to levodopa only therapy, but ten other studies did not support this result. Therefore, it is possible that selegiline does not increase mortality, and the earlier findings were the result of study design problems. In general, when administered in combination with other drugs, selegiline was relatively well tolerated. However, we should avoid the combination of pethidine and selegiline. Caution should be taken when combining SSRIs or TCAs with selegiline, as these combinations have produced some severe adverse effects [43].

Pregnancy

Animal studies failed to disclose evidence of teratogenicity. At high multiples of human doses and Developmental toxicity, reproductive toxicity was observed at doses greater than clinically utilized [44].

Toloxatone

Animal studies failed to disclose evidence of teratogenicity. At high multiples of human doses and Developmental toxicity, reproductive toxicity was observed at doses greater than clinically utilized [44].

Structure

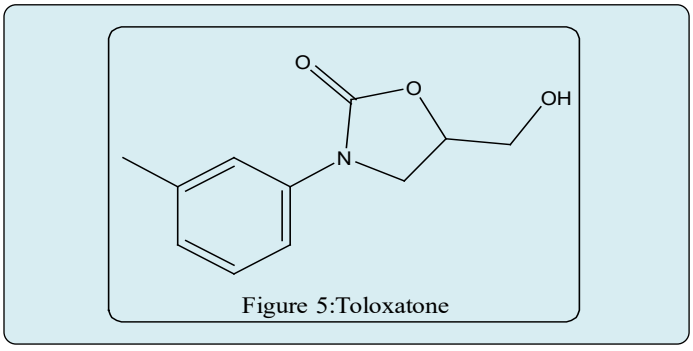

Figure 5:Toloxatone

Mechanism of Action

This drug is a type-A (also known as RIMA) monoamine oxidase reversible inhibitor. In norepinephrinergic and serotonergic neurons, MAO-A can be found and regulates the metabolism of serotonin and catecholamines, allowing the synaptic cleft to increase circulation. Traditional monoamine oxidase inhibitors irreversibly inhibit monoamine oxidase and thus, side effects, medication interactions, and food interactions occur as much as 2-3 weeks after discontinuing toloxatone [46].

Dosage and Administration

The dose of toloxatone was 1000 mg on day 1 (400 mg in the morning, 200 mg in the middle of the day and 400 mg in the evening) by oral administration [45].

Pharmacokinetics

Following oral administration, toloxatone is readily absorbed. The peak plasma levels at 30 min after dosing are also shown to be fast absorption. The fecal elimination (7% of the dose in one subject), may be due to either incomplete absorption or biliary excretion. Toloxatone is metabolized extensively. In human urine, a phenolic derivative of the drug has been found that this metabolite may also be present in the human brain and contribute to the pharmacological effect of the drug [47].

Clinical Use

Both moclobemide and toloxatone inhibit norepinephrine and dopamine deamination significantly. The MAO inhibiting effect of moclobemide is greater than toloxatone. Together with physiologic doses of tyramine, the new reversible and selective MAOA inhibitor toloxatone can be administered without the risk of inducing a substantial rise in systolic blood pressure [45,48]. In patients treated with moclobemide, depressive retardation is signifycantly better than with toloxatone [49]. Most important advantage of moclobemide treatment is improving sleep. The present study has shown that there was only a slight metabolic interaction between amitriptyline and toloxatone, with a marginal increase in the AMT/NT ratio due to an increase in the plasma AMT level [50]. Table 7 summarises the features of these trials including the participants sample size, duration, doses, and age ranges [51]. Table 8 summarises the clinical findings of those studies.

Studies	Design	Groups (n)	Duration	Age (years)	Dose range (mg)
Berlin I, Zimmer R, et al. (1990) [45]	RCT	Toloxatone 1000mg/day=12	1 month	Male= 20-29	Tol =1000
		Moclobemide 150 mg/day=12 Placebo		Female= 59-77	Moc=150
Dingemanse J, Berlin I, Payan C, et al. (1992) [48]	RCT	Toloxatone 1000mg/day=12	1 month	Male= 20-29	Tol =1000
		Moclobemide 150 mg/day=12 Placebo		Female= 59-77	Moc=150
Provost J, Funck- Brentano C, Rovei, et al. (1992) [49]		Toloxatone 600 mg/day			
	RCT	Toloxatone 1200 mg/day	2 wks	_	Tyr=100-800
		Placebo			
		Tyramine100-800 mg/ day			
Lemoine P, Mirabaud C, et al. (1992) [50]	RCT	Toloxatone 1000 mg/day =133	28 days	>18	Tol =1000
		Moclobemide 450 mg/day =135			Moc=450
Vandel S, Bertschy G, et al. (1992)	RCT	Toloxatone 600 mg/day=17	2 wks	24-69	Tol= 600
		Amitriptyline 125 mg/day =17			Amt= 125

Table 7: Summery of demographic characteristic, dose ranges, and duration of studies of Toloxatone.
AMT: Amitriptyline; Moc: Moclobemide; OLT: Open-label trial; RCT: Randomized controlled trial; ODT: Oral disintegrating Toloxatone; Tol: Toloxatone; Tyr: Tyramine.

Studies	Clinical outcomes
Berlin I, Zimmer R, et al. (1990) [45]	Neither moclobemide nor toloxatone altered the subjects' memory function, alertness, subjective emotions or sleep characteristics.
Dingemanse J, Berlin I, Payan C, et al. (1992) [48]	Neither moclobemide nor toloxatone altered the subjects' memory function, alertness, subjective emotions or sleep characteristics
Jean-Claude P, -C Funck Brentano, Christian, et al. (1992) [49]	Together with physiologic doses of tyramine, the new reversible and selective MAOA inhibitor toloxatone can be administered without the risk of inducing a substantial rise in systolic blood pressure.
Lemoine P, Mirabaud C, et al. (1992) [50]	Moclobemide was found to be as effective as toloxatone, but with the benefits of improved sleep patterns and decreased anxiety.
Vandel S, Bertschy G, et al. (1992) [51]	A small pharmacokinetic interaction between toloxatone and amitriptyline (AMT), with a slight increase in plasma AMT / NT (nortriptyline) ratio: 0.68 before and 0.78 after toloxatone.

Table 8: Summary of clinical outcomes of studies of toloxatone.
MAO-A: Monoamine oxidase Inhibitor-A; AMT: Amitriptyline; NT: nortriptyline.

Safety and Tolerability

Toloxatone was well tolerated. Over 80 percent of patients in the community found global tolerance to be good or very good, and this level increased significantly during the course of treatment. Somatic complaints are more common, such as anxiety [52].

Pregnancy

Toloxatone is contraindicated in pregnancy and lactation.

Discussion

In recent years, the incidence of depression has increased due to increased depression awareness. While many effective antidepressants are available, only 30 percent of patients take psychotropic medicines as prescribed due to the prevalence of AEs, the absence of significant therapeutic effects for many weeks, and the lack of response in some patients to conventional antidepressants. SSRI, NRIs, bupropion, and mirtazapine. This paper reviews related papers in order to provide a detailed description of several novel inhibitors of monoamine oxidase, including pirlindol, safinamide, selegiline and toloxatone. The study of MAO-B inhibitors used as agents for the treatment of disease, Alzheimer's disease, and neurological disorders is currently of significant concern, potentially due to the progressive ageing of the population. For the treatment of depression and new psychological conditions, many medications with MAO-An inhibitory activity are used in the first line treatment of MDD. This review helps to represent treatment alternatives from which both clinicians and their patients have difficulties choosing at the present moment. Pirlindole is a tetracyclic compound act as is a monoamine oxidase A (RIMA) reversible inhibitor and confirms the potential for the treatment of unipolar (single or chronic episodes) and bipolar disorder with RIMAs, such as moclobemide and pirlindole. Short-and long-term administration of pirlindole did not alter platelet and plasma MAO-B activity, indicating a lack of inhibition of MAO-B. Safinamide is another drug, its antiparkinson mechanism is via reversible inhibition of selective MAO-B. The addition of safinamide may provide an alternative approach to raising the dose of DA, thereby reducing the risk of side effects associated with DA, such as ICDs. Selegiline is the first irreversible, highly potent Inhibitor of MA0 without 'cheese effect'. Inhibition of both MAO-A and MAO-B is used as an effective mechanism, for selegiline when used as a treatment for MDD. Higher dosages are no more effective than 10 mg / day, and it may be appropriate to limit all tyramine containing food and indirect sympathomimetic drugs above this dosage. The early combination of selegiline and levodopa proved clearly superior to monotherapy with levodopa. Toloxatone is a type-A (also known as RIMA) monoamine oxidase reversible inhibitor. Together with physiologic doses of tyramine, the new reversible and selective MAO-A inhibitor toloxatone can be administered without the risk of inducing a substantial rise in systolic blood pressure.

Conclusion

Clinical theory indicates that MAO inhibitors can be used refractory to other types of treatment in depressed patients. In the selection of newer monoamine oxidase inhibitors, these drugs may be an alternative. The simple deficiency of serotonin in the brain does not cause depression, but rather a complex interplay of different neurotransmitters, including some regions of the brain include serotonin, norepinephrine, dopamine, and histamine. The novel monoamine oxidase

inhibitors described above exert their therapeutic advantages by acting on multiple neurotransmitters. When formulating a plan of treatment, the ambiguity of the underlying neurobiological process should be considered .Research on the use of novel antidepressants in human subjects is limited and further studies are warranted to reveal significant differences and other novel characteristics of these new drugs.

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