An Overview of Depression and Two Antidepressants

--Selegiline and Fluoxetine

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Abstract

In response to depression, several types of drugs have already been invented by scientists and drug companies, and two of most well-known drugs are monoamine oxidase inhibitors (MAOIs), and selective serotonin reuptake inhibitors (SSRIs). Two drugs, selegiline and fluoxetine, are selected from these two categories, respectively, to be discussed here. This brief review will include an introduction of depression as a disease, two categories of antidepressants, selegiline (EMSAM™) and fluoxetine (Prozac™)’s chemical structure, pharmacology, syntheses pathways, and pharmacoeconomic. In the pharmacology part, the receptors of the drugs, the inhibition mechanism, delivery of drugs, pharmacokinetics will be discussed. Finally, a comparison of side effects of these two drugs is discussed, and an overview of recent development in antidepressants is provided. This overview reviews selegiline and fluoxetine in the background of antidepressants development and stresses their serious side effects, and it points out the limitedness of research horizon of antidepressants, which mainly focused on monoamine neurotransmitters, in the 20th century. These can encourage more antidepressants development in reducing side effects as well as promoting new mechanisms in the future.

Keywords
Antidepressants; Monoamine Oxidase Inhibitors (MAOIs); Selective Serotonin Reuptake Inhibitors (SSRIs); Selegiline; Fluoxetine.

1. Introduction

Depression, also known as depressive disorders, indicates a group of mental problems including sadness, dullness, guiltiness, insomnia, cibophobia, tiredness and lack of concentration according to World Health Organization (WHO). [1] Some other behaviors, including irritability, social withdrawal and crying spells are also used to study depression symptoms. [2]

Estimated in 2015, there were more than 300 million people globally living with depression, accounting for approximately 4.4% of overall population, while in China, there were altogether 54,815,739 cases (about 4.2%). Such situation of depression led to many people died of suicide, 788000 as was estimated in 2015, adding it into the top 20 leading cause of death. Suicide stood for around 1.5% death worldwide, and it is adequate to show the importance of anti-depressive efforts. [1]

Several types of anti-depressive agents have already been developed, including tricyclic antidepressants (TCA)[3], Bupropion [4], trazodone [5]. However, all of them exhibit some disadvantages like confusion [6], insomnia [7] and cardiac abnormality [8], and there are only a few mechanisms of antidepressants to be well understood now. Two classes of anti-depressive drugs to be mainly discussed in this overview are Monoamine Oxidase Inhibitors (MAOIs) and Selective Serotonin Reuptake Inhibitors (SSRIs).
In this work, selegiline (EMSAM™) and fluoxetine (Prozac™), as two representatives of these categories’, respectively, will be discussed in chemical structure, pharmacology, syntheses pathways, and pharmacoeconomic. In the pharmacology part, the receptors of the drugs, the inhibition mechanism, delivery of drugs, pharmacokinetics will be discussed. Finally, side effects and an overview of recent development is provided. This report highlights the limitedness of research horizon of antidepressants in the 20th century as well as drawbacks of widely used antidepressants today, demonstrating antidepressants’ worth of research.

2. Monoamine Oxidase Inhibitors (MAOIs) and Selective Serotonin Reuptake Inhibitors (SSRIs)

A description of chemical synapse structure in brain can roughly describe how inhibition of specific protein by these two categories of antidepressants can help treat depression.

2.1 Synapse

Fig. 1: Synapse [9]
It’s essential here to introduce chemical synapse as an important part of the brain neurotransmission system. Fig. 0 shows the basic structure of a chemical synapse, which mainly functions through neurotransmitters. When the neuron attains its “firing” potential, the presynaptic cell can give out neurotransmitters as chemical messengers to bind to their cognate receptors on the receiving neuron. After binding, the receptors make the ion channels open, letting the positive ions in the synaptic cleft to create a potential in the postsynaptic cell. [9]

There is also a need of inactivating the neurotransmitters that are already binding to a receptor. Neurotransmitters can be metabolized by a neurotransmitter degrading enzyme, or they can be recycled through neurotransmitter reuptakes on the membrane of the presynaptic cell. In other words, the inhibition of these two ways of inactivation can enhance the overall monoamine neurotransmission strength, and this is roughly the mechanism of function of some antidepressants, including monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs).

The next part will mainly focus on their development, and detailed mechanisms will be included again in selegiline and fluoxetine part respectively.

2.2 Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase inhibitors can be regarded as the first antidepressants. The age of antidepressants began when isoniazid, isonicotinyl hydrazine, was discovered to elevate mood. Later on, iproniazid, another member of the hydrazine class, was found by E. A. Zeller to inhibit monoamine oxidase (MAO) enzyme, and in the 1950s N. S. Kline discovered the drug’s ability to treat depression through an experiment where 70% of the patients improved their conditions. As a result, iproniazid soon became the first modern antidepressants through clinical practice. [9,10,11]

Though this brand-new way to treat depression was successful at first, soon serious side effects was discovered, including hypertension and hepatic necrosis, which finally drew several kinds of MAOIs out of the market. [10] Currently, SSRIs and SNRIs (serotonin norepinephrine reuptake inhibitor, here norepinephrine is another monoamine neurotransmitter) are the first choice of drugs for depression treatment, while some MAOIs, like selegiline (EMSAM™), are still used in specific cases to inhibit MAO-B in small doses. [9,11]

2.3 Selective Serotonin Reuptake Inhibitors (SSRIs)

As scientists begin to rationalize the process of drug development through considering the specific receptors, zimeldine was developed by Dr. Arvid Carlsson as the first SSRI, though it was later found to produce Guillain-Barre syndrome and removed from the market. [11,12] In 1970, the first SSRI that was widely used was discovered by B. B. Malloy’s team, who found the phenoxy propylamine class to be effective in the inhibition of serotonin reuptake pumps. [9]

The side effects of such inhibitors are headache, nausea, sexual dysfunction, tremors and serotonin syndrome, which is life-threatening. [11] However, they are still safer than TCAs especially at large doses when TCAs can cause dangerous cardiac death. [9,13] One of the most well-known SSRIs is fluoxetine (Prozac™).

3. Selegiline (Emsam™)

3.1 Chemical Structure of Selegiline
Selegiline has its chemical formula of C$_{13}$H$_{17}$N, and it’s molar mass is 187.281 g/mol. Selegiline, also known as L-deprenyl, has its systematic nomenclature of (R)-(–)-N-methyl-N-2-propynylamphetamine, (R)-(–)-N,$\alpha$-Dimethyl-N-2-propynylphenethylamine, and (R)-(–)-N-2-propynylmethamphetamine. It is a member of the amphetamine group, and it has an additional methyl group and propargyl group on the nitrogen atom.

3.2 Drug Pharmacology

3.2.1. Monoamine Oxidase (MAO)

MAO is exactly a kind of neurotransmitter degrading enzyme in human brain, and it is also a flavin adenine dinucleotide (FAD) containing flavoprotein. There are two kinds of MAO, MAO-A and MAO-B, that exist in human body. Though they are coded from different genes, these two flavoproteins share 70% amino acid identity, and they both have a covalently-bound FAD co-factor to their identical cysteine on a specific sequence of amino acids, Ser-Gly-Gly-Cys-Tyr. [14]

Fig. 3 Four possible mechanisms for MAO activity [16]
MAO can oxidize a range of biogenic amine substrates. In human brains, MAO mainly serve to oxidize nitro groups of certain amines, especially neurotransmitters, to imines, which can be further hydrolyzed to ketones or aldehydes[15]. MAO A metabolizes serotonin (5-hydroxytryptamine), dopamine, and norepinephrine, while MAO B tends to oxidize dopamine more quickly. [16]

Unlike D-amino acid oxidase, whose mechanism was supported to be a hydride transfer mechanism, [16] as we have learned from our class, MAO’s specific mechanism is still under discussion. In 2011, H. Gaweska proposed four possible mechanisms of the oxidation: Single Electron Transfer Mechanism, Hydrogen Atom Transfer Mechanism, Nucleophilic Mechanism, as well as Hydride Transfer Mechanism. Accumulation of structural and computational evidence were supporting the Hydride Transfer Mechanism for MAO-B, while it could be a different thing for MAO-A[16,17].

3.2.2. Selegiline’s Inhibition of MAO-B

Fig .4 (a) Structure of human MAO-B. The FAD structure is shown in ball-and-stick representation colored of yellow. (b) pargline binding site. (c) the activity capavity of MAO-B is shown in red surface and selegiline structure is shown in black [15,18]
In 2002, C. Binda’s team first explored the crystal structure of MAO-B (Fig. 3(a)) and its interaction with certain inhibitors. They found that that an analog of selegiline, pargyline, could bind to N5 atom of FAD, thus inhibiting the enzyme (Fig. 3(b))[15]. Later on in 2005, l. De Colibus reported the crystal structure of MAO’s inhibition by selegiline, suggesting a bond formation between the N5 atom and terminal acetylenic carbon atom. [18]

Based on these discoveries, R. Borštnar in 2011 made a computational study about several possible mechanisms involved in selegiline’s inhibition of MAO B, and he found that the mechanism which involved deprotonation at the terminal acetylene carbon had a calculated activation energy of 23.7 kcal/mol, and this was in good agreement with experimentally determined value, 21.3 kcal/mol. [19]

After the deprotonation, the inhibitor can act as a nucleophile to attack N5 atom, forming a bond between these two atoms. The carbanion can be well stabilized through resonance. Such a structure prevents FAD’s business end from further reacting with a hydride from monoamine. This can be the most possible mechanism of selegiline’s inhibition of MAO-B now.

Fig 5 Left: 7 possible mechanisms examined in Borštnar’s report; Right: the energy level of different statuses through the 3f (proposed) mechanism. All values are in kcal/mol [19]

3.2.3. Delivery of Selegiline

Selegiline can be delivered through transdermal patch. EMSAM (selegiline transdermal system) was first approved by the US government as a treatment to major depressive disorder. It should be applied to dry, intact skin on the upper torso, upper thigh or the outer surface of the upper arm once a day. [20]

There are three dosage strength of EMSAM: 6 mg per 24 hours, 9 mg per 24 hours and 12 mg per 24 hours, which are administered depending on age, period of treatment and clinical judgments. [20]

It is noteworthy that tyramine-rich food and beverage consumption during treatment should be avoided according the different doses, as such consumption may cause hypertensive crisis, known as “cheese reaction”. [20]

3.2.4. Pharmacokinetics of Selegiline Transdermal System

In human, selegiline can rapidly penetrate the blood-brain barrier, and it is approximately 90% bound to plasma protein over a 2 to 500 ng per mL concentration range. [20]

After the application of EMSAM, 25% to 30% of the selegiline content on average is delivered systemically over 24 hours. This delivery way can ensure the existence of stable concentration of selegiline in plasma for 24 hours, comparing with taking the drug orally. The reason is that while selegiline are not metabolized in human skin, the orally administered selegiline can experience extensive metabolism. In human liver microsomes, selegiline is metabolized through N-dealkylation or N-depropargylation to form N-desmethylselegiline or R(-)-methamphetamine, respectively. Both of these metabolites can be further metabolized to R(-)-amphetamine. [20,21]

Approximately 10% and 2% of radiolabeled selegiline applied through EMSAM was recovered in urine and feces respectively, while at least 63% of the dose remains unabsorbed. As is recovered from
urine, unchanged selegiline accounts for 0.1% of the applied dose, and the rest of the dose are metabolites. [20]

3.3 Synthesis of Selegiline

Though there are rarely anyways of biosynthesis of selegiline, several paths of chemical synthesis have already been discovered. One of the most popular ways is through the alkylation of (−)-methamphetamine using propargyl bromide. This pathway is likely to take a bimolecular nucleophilic substitution, as the secondary amine is a good nucleophile that can attack the carbon attached to bromide. Another possible pathway is through Mannich reaction, which mostly requires formaldehyde, a compound with a reactive hydrogen, and an amine.

The cuprous catalysts were reported by I. N. Azerbaev in 1964 to make 2-methyl-3-butyn-2-ol, which is used in the reaction, as a reactive hydrogen compound, enabling the Mannich reaction. The secondary amine, as a nucleophile, first attacks the formaldehyde, forming an imine after elimination. Afterwards, the 2-methyl-3-butyn-2-ol is deprotonated by a base, and the alkynyl anion nucleophilic attack the imine to form the protected selegiline. Acetylenic carbinols can undergo KOH-catalyzed decomposition to the acetylene and carbonyl compound, as the reverse reaction for acetylenic carbanion’s nucleophilic attack, and it helps form selegiline. [22] The protection of acetone in this reaction prevents ethyne to react with two molecules of imine to increase the conversion rate.

![Fig. 6 Synthesis of Selegiline through Mannich Reaction. [22]](image)

3.4 Pharmacoeconomies of Selegiline (EMSAM™)

Since a generic version of EMSAM to treat depression is not yet available, EMSAM is relatively expensive as a brand name drug, selling around $627.1 for 30 a box of patches for all strengths (12 mg/24hr, 9mg/24hr and 6mg/24hr). [23]

4. Fluoxetine (Prozac™)

4.1 Chemical Structure of Fluoxetine

![Fig. 7 Fluoxetine](image)

The chemical name of fluoxetine is N-Methyl-γ-[4-(trifluoromethyl)phenoxy] benzenepropanamine, and the molecular formula is C_{17}H_{18}F_{3}NO. In this structure, an inductive electron-withdrawing group, trifluoromethyl group, is attached to one of the benzene rings, while the alkoxy chain at the para site of the -CF₃ can be electron-donating through resonance. A methyl group is attached to the
nitrogen. It is often prescribed as C_{17}H_{18}F_{3}NO\cdot HCl, fluoxetine hydrochloride. Both (R)-fluoxetine and (S)-fluoxetine are potent, so fluoxetine is often prescribed as a racemate. [24]

4.2 Drug Pharmacology

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a kind of monoamine neurotransmitter. It can regulate aggression, mood, sleep, body temperature etc. Its deficiency can contribute to symptoms including depression and anxiety. [9] As a monoamine, it can be metabolized by MAOs, and therefore, the interactions of MAOIs can help increase serotonin’s concentration in the synaptic cleft. Another way to achieve this is to block specific neurotransmitter reuptake pump, serotonin transporter (SERT). [25]

4.2.1. Serotonin Transporter (SERT)

Serotonin transporter (SERT) is a kind of monoamine transporter protein to reuptake serotonin from the synaptic cleft to presynaptic cell for recycling, directly controlling the concentration of the neurotransmitter. [9,25]

SERT is a member of neurotransmitter sodium symporter, which means that when transporting these biogenic amines, they need to co-transport a Na\(^+\) and a Cl\(^-\) as well. [26] In this specific case of transporting serotonin, the mechanism of transportation is shown below:

![Mechanism of serotonin transport. Coupling to sodium, chloride and potassium gradients](image)
Counter-clockwise from the lower left, the transporter is shown binding external Na\(^+\), 5-HT (S) and Cl\(^-\) to form a combination of the three. After deformation of the protein, the binding sites are accessible from the cytoplasm. This represents the transport process. Following dissociation of Na\(^+\), 5-HT and Cl\(^-\), the transporter binds internal K\(^-\) (upper left) and converts to release K\(^-\) to the external medium (left side) to return to the starting point. [27]

4.2.2. Fluoxetine inhibition of Neurotransmitter Transporter

In 1974, D. T. Wang first discovered that fluoxetine was a selective inhibitor of serotonin transmitter through experiment in rats, and he proposed its prospect in treating depression. [28] At that time, many scientists, organized by Eli Lilly Co., were just researching drugs to inhibit monoamine reuptakes. Soon in 1976, Phase I clinical safety studies of fluoxetine were completed successfully. Following the beginning of Phase II studies testing the effectiveness in treating depressive patients in 1978, in 1979, first indication of fluoxetine’s antidepressant effect came out. After Phase III trials were completed, fluoxetine was approved and launched as Prozac in 1987 (United States) as the first SSRI marketed there to treat depression. It turned out to be a really successful way to treat depression compared with earlier SSRIs including zimelidine[29].

Though fluoxetine’s efficacy was discovered around 50 years ago, its binding mechanism was only understood in recent years due to the lack of SERT structural studies. Some researches discussing that fluoxetine binding is chloride-dependent and highly sensitive toward mutation of SERT Ile172 to Met are already shedding light on the possible mechanism that fluoxetine binding site is in the central part of the SERT. [30,31] J. Anderson proposed in 2014 that fluoxetine binds within the S1 pocket of SERT through computational and experimental evidence. [32]

![Fig. 10: Location of SERT’s S1 site (left), S2 site (middle), and the putative fluoxetine binding site (right) shown on a homology model of SERT. [32]](image)

4.2.3. Delivery of Fluoxetine

Fluoxetine is delivered orally, and there are mainly two ways:

1. Take conventional pills or solution once a day (in the morning) or twice a day (better in the morning and at noon) regardless of meals.
2. Take delayed-release capsules once a week without regard to meals. [33]

4.2.4. Pharmacokinetics of Fluoxetine

After oral administration of the medicine, fluoxetine is well absorbed from the gastrointestinal tract. The mean peak plasma concentration of fluoxetine appears in 6 to 8 hours after administration, and fluoxetine is reported to bind extensively to plasma proteins (around 94.5% of fluoxetine was protein bound in pooled plasma of normal subjects). [34,35]

Fluoxetine can be metabolized in liver to form its only metabolite, norfluoxetine, or N-desmethyl fluoxetine, through demethylation. It is found that both optical isomers are potent in serotonin uptake...
inhibition, while (R)-norfluoxetine is less effective than (R)-fluoxetine, and (S)-norfluoxetine is almost equipotent as (S)-fluoxetine in animal model tests. [36] One feature of fluoxetine and norfluoxetine is its long elimination process. Elimination half-life of fluoxetine after a single dose changes from 1 to 4 days. As for norfluoxetine, its half-life can be between 7 and 15 days. [35]

After a dose of 30mg oral dose of radiolabelled fluoxetine, about 60% was recovered in urine in 35 days and 16% in feces was recovered in 28 days, showing the long existence of the drug in human body after a single dose. Meanwhile, only 2.5% of the urine-recovered activity were from unmetabolized fluoxetine, which indicated the extensive metabolizing process. [35]

4.3 Synthesis of Fluoxetine

The original synthesis pathway adapted by Eli Lilly Co. was reported in 1982 by Molloy and Schmiegel. [37]

![Fig. 11: the original pathway of fluoxetine synthesis](image)

In the first step, a Mannich reaction is adapted. The formaldehyde first reacts with dimethylamine to form an imine with a positive formal charge on the nitrogen. As a reactive hydrogen donor, acetophenone’s α-carbon can act as a nucleophile to attack imine, pushing the π electrons towards the nitrogen to form 3. Diborane is used to reduce the carbonyl group to a hydroxy group, and thionyl chloride is used to substitute the hydroxyl with chloride. A first nucleophilic substitution on the thionyl group by the hydroxy, gives out a chloride anion to nucleophilic attack the hydroxy, which has already been converted into a good leaving group by the thionyl. This reaction makes a good leaving group for phenolox’s attack, which further forms 7. A von Braun reaction happens from 7 to 8. The tertiary amine first nucleophilic attack the C atom of CNBr, breaking the C-Br bond. Then, the bromide anion act as a nucleophile to attack one of the carbons previously attached to the nitrogen, breaking a C-C bond and forming the product. [39]

Therefore, one of 7’s N-methyl group is substituted with a cyano to form 8. 8 then experiences basic hydrolysis to form racemic fluoxetine. [38]

Later on, Eli Lilly was trying to synthesis individual enantiomers, and they prompted D. W. Robertson to lead this research. Robertson’s synthesis pathway of (S)-fluoxetine is shown below[40]:

In the first step from 9 to 10, (+)-diisopinocampheylchloroborane ((+)-DIP-Cl) is applied to reduce the carbonyl group with enantioselectivity. Diisopinocampheylchloroborane is a remarkably efficient chiral reducing agent for aromatic ketone’s reduction. [41] Next, a Finkelstein reaction is employed to change chloride into a better leaving group, iodide, and this enables the nucleophilic substitution by methylamine. After the deprotonation by NaH in DMAC, the oxide anion can be a good nucleophile to attack 1-fluoro-4-(trifluoromethyl)benzene, which can be a proper reagent for SnAr substitution due to the p-trifluoromethyl group. This attack finally produces (S)-fluoxetine, while (R)-fluoxetine can be obtained through diastereomeric recrystallisation. [38]
Fig. 12: Original pathway of (S)-fluoxetine synthesis and (R)-fluoxetine’s structure[38]

4.4 Pharmacoeconomics of Fluoxetine

Fluoxetine sells in different ways: Prozac 20mg/5mL solution 120mL Bottle sells $266.51; Prozac weekly 90 mg capsule sells $34.5; Prozac 40 mg capsule sells $13.89. [42]

Fluoxetine is a compound with the best overall profile. Even Wong’s team, who first reported fluoxetine, did not foresee that their pale-green and light-yellow capsule would appear on the cover of Newsweek (26 March 1990), where it was described as “A breakthrough drug for depression”. Nine years later, Fortune magazine regarded it as one of the “Pharmaceutical Products of the Century” (22 November 1999). Its annual sales reached $1 billion, $2 billion in 1992, 1995, respectively, and it now has annual sales of over $3 billion. [9, 29]

5. Side effects of Selegiline (EMSAM\textsuperscript{TM}) and Fluoxetine (Prozac\textsuperscript{TM})

While selegiline and fluoxetine are both effective as antidepressants, what differentiates them is the side effects.

5.1 Serotonin Syndrome

Serotonin syndrome can be a potential life-threatening side effect. Its symptoms include mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities. It can be caused by the use of two or more serotonergic drugs, while many antidepressants’ function may affect the serotonin level, especially SSRIs and SNRIs. Meanwhile, TCAs and MAOIs, which functions by inhibiting MAOs, can also play a role in causing the serotonin syndrome. [43]

Therefore, fluoxetine, as a SSRI, can cause serious side effects when overdosed. Meanwhile, as is previously mentioned, fluoxetine has a long half-life, which may account the phenomenon that serotonin syndrome can be caused by another serotonergic agent within five weeks of fluoxetine therapy. [43] Fluoxetine has a high possibility to cause this syndrome when applied with nonselective MAOIs, which should be avoided.

Selegiline, when properly assigned, is an inhibitor of MAO-B, which cannot oxidize serotonin to affect its concentration. [44] However, at higher doses, the main target of selegiline can switch to MAO-A, which serves to oxidize serotonin. [9] Thus, under normal doses, selegiline, unlike other nonselective MAO inhibitors and fluoxetine, has less possibility to cause serotonin syndrome, and it can help support the safety of using EMSAM as a controlled delivery of selegiline. However, it should be noted that concomitant use of selegiline with fluoxetine should also be avoided, since it can cause mania, chills, and hypertension. [44]

But, after all, instead of being an idiopathic drug reaction, serotonin syndrome is in fact a predictable consequence of excess serotonergic agonism of central nerve system. [43] Therefore, it can be
avoided under right doses, and extensive studies have already been carried out on this topic. In addition, many cases of serotonin syndrome are actually barely perceptible. Hence, though serotonin can be life-threatening, actually there is little need to consider it as a fatal drawback of SSRIs.

5.2 Hypertension

Hypertension refers to a high blood pressure, and it is a risk factor of several serious cardiovascular disease, including stroke, heart attack.

EMSAM inhibits the metabolism of some of the dietary amines, including tyramine, and has the potential to produce a hypertensive crisis after the ingestion of tyramine-rich foods or beverages, including aged cheese, most soybean products and sausages. It includes many of daily eaten food. In addition, the use of selegiline with some other drugs, including adrenergic drugs can also increase blood pressure. [45] As many people may have a limited understanding of such drug interactions, it may be a potential threat to EMSAM users.

On the other hand, fluoxetine is not reported to cause hypertension, and it can even be applied as a part of subscription to treat hypertension. [46]

Fluoxetine and selegiline may also exhibit some other side effects, including sexual dysfunction. [47] However, comparing these two drugs, while fluoxetine’s main drawback, serotonin syndrome, can be avoided through medical instructions of dosage and drug taking, sometimes there can be a greater possibility for a selegiline taker to forget some drug interactions of selegiline and suffer from hypertension. Therefore, it is easy to conclude that fluoxetine can be a safer drug than selegiline, which is just the same improvement from MAOIs and TCAs to SSRIs and SNRIs. However, due to the existing side effects, fluoxetine cannot be considered as a magic bullet for depression, and further researches are going on.

6. A Historical View and Recent Advancements

To review the history of antidepressants through these 70 years since the birth of isoniazid, we may classify the drugs into three generations: the first generation symbolized by MAOIs and TCAs, the second generation symbolized by extensive serotonin reuptake studying, which gave birth to SSRIs and SNRIs, and the third generation which studied variable mechanisms of anti-depressive functions.

As a reminder of the first generation, MAOIs, including selegiline, is actually sparsely used today partly due to various drug interaction problems, while SSRIs, including fluoxetine, and SNRIs are of the first choice to many antidepression treatment thanks to their remarkable improvement in safety issues from TCAs and MAOIs as well as the lack of epochal achievements in the third generation.

In the third generation of antidepressants, some more researches on monoamine-neurotransmitter-related antidepressants have also been made. A possibility on triple antidepressants, which inhibit all the three monoamine neurotransmitter (serotonin, norepinephrine, and dopamine) reuptakes is in research, and new norepinephrine reuptake inhibitors, including reboxetine, are studied for their potential to substitute fluoxetine as a possible antidepressant. [48,49,50]

In fact, what is remarkable for the third generation is a broader range of possible mechanisms being researched. In addition, B. E. Murphy in 1993 first introduced the use of glucocorticoids receptor (GR) antagonists’ use in antidepression, and he also reported mifepristone as a possible antidepressant in the future. [51] Later, two reports by J. K. Belanoff supported the use of mifepristone as a GR-II receptor antagonist, as the side effects were mild. [52,53] Belanoff also found that a higher dose of mifepristone (600mg or 1200mg) can be more effective than low dose (50mg). It was later available in the United States, and GR antagonists were having good prospect in antidepressant researching in the third generation.

In 2000, ketamine, a N-methyl-D-aspartate receptor (NMDAR) antagonist, was discovered to exhibit rapid-acting antidepressant effects. [54] This rapid onset (within hours or a few days) was quite unique comparing with previous antidepressants which may take weeks or months to function. [55] However, it took a long time for this drug to be admitted in clinical use, while it was limitedly used
partially due to abuse liability and psychosis-like side effects. [48] One focus of recent antidepressant development was the rapid onset of action as well as NMDAR antagonists’ applications in antidepressants. However, NMDAR antagonist’s applications in antidepressants are doubted due to some failures of members other than ketamine in showing the potency [56], and the reason can be inadequate dose [57] or special α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activity of ketamine [58]. Whichever the reason is, the understanding of this question will be an advance in antidepressants development.

7. Conclusion

Due to the threat of depression, possible antidepressants developments are worth researching. The review can help a comprehensive understanding of the two drugs, selegiline and fluoxetine. A review of mechanisms of function may provide inspirations for developing similar but more effective drugs; understanding delivery and pharmacokinetics can help researchers develop new delivery strategies to reduce side effects as well as enhance absorbance; syntheses pathways may also help syntheses of similar drugs. This review also highlights serious adverse reactions of commonly used antidepressants as well as the limitedness of researching horizon in the 20th century, pointing out possible researching directions in the future, including to reduce the side effects through new strategies, including augmentation mechanisms, or similar drugs as well as new mechanisms of antidepressants are also essential, as they may have the potential to avoid previously common adverse reactions or to be more effective in treating depression. There can be systems other than monoamine neurotransmission system in our brain to regulate mood.

From MAOIs in the 1950s, SSRIIs in the 1970s, to ketamine in the 2000s, generations of antidepressants, promoted by generations of scientists, keep developing to enhance the efficacy, to reduce adverse reactions, and to accelerate the onset of action. Owing to the enhanced understanding in human brain, more drug targets are being selected for antidepressants design; more antidepressants are being invented rationally; precise dosage and treatment are assigned to avoid relevant adverse reactions; creative strategies are applied either to increase the efficacy of the first antidepressant or to treat residual symptoms. These efforts are really helpful to humans’ battle against depression, and who knows one day, when a new drug, advanced SSRI, new NMDAR antagonist, or a discovery of a brand-new mechanism, is designed to open the fourth generation of antidepressants.

References


