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Anti Leishmanial Activities of Some Antidepressant Drugs

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Review Article

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ABSTRACT

Leishmaniasis is a complex vector-borne disease caused by different species of Leishmania. It affects at least 12 million people worldwide. Leishmaniasis is commonly associated with poor economic conditions and immune compromised situations like HIV co infection. There is increasing in drug resistance to commonly used therapeutics as well as lack of vaccine program. This leads to a perpetual search for a new drug for leishmaniasis. This review fundamentally deals with some antidepressant drugs showing the anti leishmanial activities. These antidepressant drugs are Imipramine, Sertraline, Ketanserin and Mianserin. Imipramine being a Tri Cyclic Antidepressant (TCA) drug kills *Leishmania donovani* elevating IL-12/IL-10 ratio. Sertraline belonging to the selective serotonin reuptake inhibitor (SSRI) drugs, removes parasite loads from spleen and liver probably by declining cytoplasmic ATP consumption. Ketanserin is a serotonin receptor (5-HT2A/2C) antagonist that kills both amastigotes and promastigotes probably due to inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR). Mianserin belonging to the TCA group of drug, kills both promastigote and amastigote parasites also probably due to the inhibition of HMGR. The present review will give the summarized information about putting some old antidepressant drugs for the treatment of another disease like Leishmania.

INTRODUCTION

Leishmaniasis is one of the most diverse and complex vector-borne metazoonosis diseases[1]. The causing agent is at least 17 species[2] of obligate intracellular protozoan parasites that belong to the genus Leishmania[3]. It is transmitted to human by the bite of phlebotomine female sand flies of the genera Phlebotomus and Lutzomyia in the old and new worlds respectively[4]. The species are in widespread tropical and subtropical continents except Antarctica[5]. The disease is endemic in 88 countries of Indian subcontinent, Southern Europe and Western Asia to America including rural and peri urban areas[6]. Leishmaniasis shows a disease burden of 12 million affected people with an annual estimation of 2-4 million new cases globally of which 60% cases occur in India alone[7].

Leishmaniasis is traditionally classified in three different clinical forms: Visceral Leishmaniasis (VL), Cutaneous Leishmaniasis (CL) and Mucocutaneous Leishmaniasis (MCL). This ranges from simple cutaneous ulcers to huge destruction in CL and subcutaneous tissues in ML. Other cutaneous manifestations are Diffuse Cutaneous (DCL), Recidivans (RL) and Post Kala-Azar Dermal (PKDL) Leishmaniasis. However, VL is the most complicated form of Leishmaniasis that can cause death if remain untreated.

Leishmaniasis is a disease of poor mainly living in tropical regions of developing world. It is more seen in immunocompromised health conditions like HIV co-infection[8, 9]. Increasing drug resistance to commonly used drugs [sodium stibogluconate (SSG), Amphotericin B, Pentamidine or Miltefosine][10-14], lack of effective vaccine programme[15] and difficulties in sustaining treatment procedure sharply demands for newer cost-effective orally used drugs. Perhaps, the search for a new drug is a perpetual process.

This review deals with encouraging antileishmanial activities of some antidepressant drugs.

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Leishmaniasis and its Immunology

Leishmania parasites were independently described by William Leishman and Charles Donovan in 1903[16].

Leishmania shows a dimorphic life cycle of two stages: extracellular promastigote form and intracellular amastigote form. Parasites multiply in the gastric tract of the haemophagus vectors as extracellular promastigotes that are long, elongated and flagellated. Parasites are engulfed within the phagocytic vacuoles of macrophages in mammalian hosts as intracellular amastigotes where they multiply with spherical shape and internalized flagellum. Amastigotes survive to the innate immune stress conditions and then lyse macrophages followed by another phagocytosis by new macrophages[17,18]. They also can reside into the phagosomes of other phagocytic cells like dendritic cells and neutrophils[19]. Amastigotes are resistant to proteolysis and degradation in the phagosome.

Leishmania must evade both innate and adaptive immune responses of the host in order to develop a successful parasitic relationship with it. The most potent immune opsonin C3b, part of component system, first binds to the special surface glycoproteinn gp63 of Leishmania and gets converted into iC3b[20]. This results in uptake of the amastigote parasites into the macrophage and favors phagocytic clearance rather than lytic clearance. Parasite faces oxidative bursts that include superoxides, hydroxyl radicals within the macrophage as the regulation of primary host defense[21]. Eventually, Leishmania resist the acidic enzyme attack through a proton pump present on its surface that retains the intra cellular pH close to neutral[22].

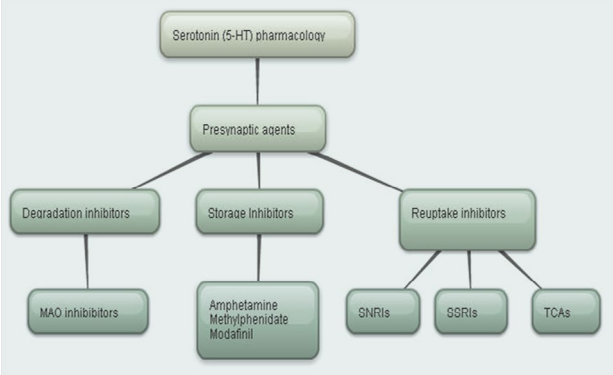
Leishmania infection usually shows anti-leishmanial antibodies in the sera of the infected patients. Antibodies are found in low concentration in CL[23] whereas strong titers are documented in VL[24,25]. In L. braziliensis infection, antibody titers are critically monitored for the purpose of diagnosis and disease prognosis[26-30]. Leishmania antigen specific immunoglobulin (Ig) isotopes, IgM, IgE, IgG and its subclasses are elevated during the disease[31-36]. Whether these high titers indicate host protection or pathogenesis, is still unclear.

Immunity towards Leishmaniasis is predominantly mediated by T lymphocytes. T helper 1(Th1) and T helper 2 (Th2) cells are usually recognized by their cytokines secretion. Th1 cells secrete Interferon - gamma (IFN-γ) that activates the cell mediated immunity. Th2 cells secrete Interleukin -4 (IL-4) that promotes antibody responses. T-cell differentiation either to Th1 or Th2 is dependent on this cytokine priming during differentiation[37]. Th1 type of cell responses to the parasite infection are promoted by IL-12. Tumor Necrosis Factor - alpha (TNF-α) also promotes Th1 response like IL-12 but to a lesser extent. IL-12 thus activates the macrophages via IFN-γ secretion by the Th1 subsets. This in turn, promotes macrophages to produce nitrogen species for killing the parasites in both CL and VL[38,39].

On the other hand, Th2 cytokine IL-10 is the main macrophage-deactivating cytokine along with Treg cells in *Leishmania major*[40]. Abrogating the overall phagocytic activity of macrophages, IL-10 allows the persistent of skin lesions in CL by inhibiting IFN-γ production[41]. Likewise, Th2 cytokines IL-4 and IL-6 are elevated after infection to establish the disease progression. IL-6 level is more increased in case of drug resistant strains[42].

Classification of Antidepressant drugs

Classification of antidepressant drugs are based on their pharmacological action and/or structural configurations. Antidepressant drugs act as pre synaptic agents to target different neurotransmitter receptors, mainly serotonin receptors. **Figure 1** shows broad classification of three fundamental types of antidepressant drugs; degradation inhibitors, storage inhibitors and reuptake inhibitors[43, 44]. The list of commonly prescribed antidepressant drugs are shown in the **Table-1** of which four antidepressant drugs are showing encouraging results against Leishmaniasis[43-49]. These antidepressant drugs are Imipramine, Sertraline, Ketanserin and Mianserin.



There are three major kinds of presynaptic agent's acts as antidepressant drugs; degradation inhibitors, storage inhibitors and reuptake inhibitors.

Figure 1. Major groups of antidepressant drugs.

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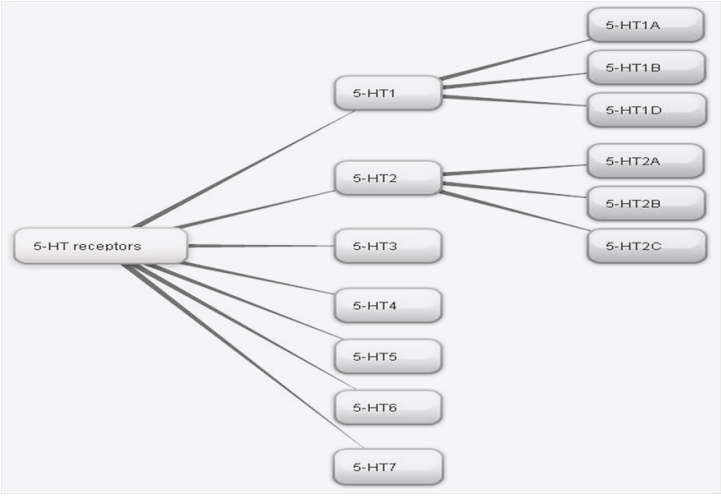
Table 1. Major Groups of antidepressant drugs with examples of marketed compounds.

Name of Antidepressant drug groups	Name of Antidepressant drugs
Selective Serotonin Reuptake Inhibitor (SSRI*)	Citalopram, Paroxetine, Escitalopram, Fluoxetine, Fluvoxamine, Sertraline
Serotonin-nonepinephric reuptake inhibitor (SNRI*)	Desvenlafaxine, Duloxetine, Levomilnacipran, Milnacipran, Venlafaxine
Serotonin antagonistic and reuptake inhibitor (SARI*)	Etoperidone, Lubazodone, Nefazodone, Trazodone,
Norepinephrine reuptake inhibitor (NRI*)	Atomoxitine, Reboxetine, Viloxazine
Norpinephrine-dopamine reuptake inhibitor (NDRI*)	Bupropion
TAAR1* agonist	Amphetamine,Dextroamphetamine, Dextromethamphetamine, Lisdexamfitamine
Tricyclic antidepressant (TCA*)	Amitriptyline, Butriptynine, Clomipramine, Desipramine, Dosulepin, Doxepin, Imipramine,Iprindole, Lofepramine, Melitracen, Nortriptyline, Opipramol, Protrityline, Trimipramine
Tetracyclic antidepressant (TeCA*)	Amoxapine, Maprotiline, Mianserin, Mirtazapine
Monoamine oxidase inhibitors (MAOI*)	Irriverssible: Isocarboxazid, Phenelzine, Selegiline, Tranylcypromine Reverssible: Moclobemide, Pirlindole
Noradrenergic and specific serotonergic antidepressant (NaSSA*)	Mianserin, Mirtazapine
Serotonin Modulator and Stimulator (SMS*)	Vilazodone, Vortioxetine
Serotonin antagonist*	Clozapine, Ketanserin

Knowledge about serotonin receptor classes is needed to understand the underlying mechanism of actions of these antidepressant drugs. There are seven general serotonin receptor classes that include a total of fourteen known receptors[43]. A brief account about serotonin receptors are shown in **Figure 2**[44]. They are categorized in the **Table-2** along with their subtypes, mode of action, functions, distribution[45,46].



5-HT receptors: serotonin receptor family; 5-HT1-7: serotonin receptor subtypes; 5-HT1A-1D : 5-HT1 receptors subtypes; 5-HT2A-2C : 5-HT2 receptor subtypes.

Figure 2. Classification of serotonin receptors.

Table 2. Types of serotonin receptors, signaling pathway, distribution and functions.

Serotonin Receptors	Subtypes	Major Signaling pathways	Potential	Major distributions and functions of the Serotonin Receptors
5-HT_1	5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1E}, 5-ht_{1F}	cAMP↓	inhibitory	Blood vessels, CNS
5-HT_2	5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}	IP_3↑	Excitatory	Blood vessels, CNS, PNS, Gastrointestinal tract, Platelets, smooth muscle
5-HT_3	5-HT_{3A}, 5-HT_{3B}	Ion Channel	Excitatory	Gastrointestinal tract, CNS (area postrema related to vomiting), PNS
5-HT_4		cAMP↑	Excitatory	Gastrointestinal tract,CNS, PNS
5-HT_5	5-HT_{5A}, 5-HT_{5B}	cAMP?	Inhibitory	CNS
5-HT_6		cAMP↑	Excitatory	CNS (mainly throughout limbic system)
5-HT_7		cAMP↑	Excitatory	CNS (mainly throughout limbic system), blood vessels, gastrointestinal tract

Legend:
cAMP: cyclic adenosine monophosphate
IP_3: Inositol phosphate 3
CNS: Central Nervous System
PNS: Peripheral Nervous System
$5\text{-}HT_{1\text{-}7}$: 5-Hydroxy Tryptamine / Serotonin receptor subtypes

Monoamine oxidase inhibitors (MAO) are the enzyme responsible for serotonin, dopamine, norepinephrine inactivation that prevents excess neurotransmitters to diffuse from pre synaptic end to synaptic space[47-49]. These inhibitors actually interfere in storage of monoamines in vesicles at presynaptic terminals. However, reuptake inhibitor drugs block neurotransmitters reuptake (mainly serotonin but also nor epinephrine and dopamine) at pre synaptic ends in a concentration dependent manner. This results in accumulation of neurotransmitters in the synaptic cleft that enhances postsynaptic neural activity[47-49]. On the other hand, TCAs inhibit reuptake of 5-HT (5-hydrxytryptamine or serotonin) and nor epinephrine from synaptic cleft by blocking their transporters. Likewise, they help to enhance postsynaptic response[47-49].

Antileishmanial Activities of the Antidepressant Drugs:

Imipramine

Imipramine [N-(γ-dimethylaminopropyl)-iminodibenzyl HCL] is a TCA group of antidepressant drug and belongs to the broad class of cationic amphiphilic drugs. Imipramine is Food and Drug Administration (FDA) approved drug, generally used for treatment of depression and paediatric nocturnal enuresis[50]. It is also often used to treat chronic pain in combination therapy with other pain medications[50,51]. Mukherjee et al. [52] had chosen Imipramine for the therapy of experimental VL on the basis of the following previous observations:

i) The proton motive force of membrane of *Leishmania donovani* (LD) gets altered by the drug[53].

ii) The enzyme trypanothione reductase is upregulated in SSG resistant LD and Imipramine can inhibit this enzyme[54].

iii) TNF α is an important cytokine for antileishmanial defense and Imipramine can act as effective immune modulator by inducing its production[55].

iv) Cationic property of Imipramine helps in the absorption by phagocytic cells and accumulation in phagolysosomes[56].

v) Desipramine being the metabolite of Imipramine also effective against LD promastigotes[57].

Mukherjee et al. [52] reported that imipramine induced 60% apoptosis of LD parasites in comparison to Miltefosine which causes only 5.5% apoptosis. The decrease in mitochondrial trans membrane potential of Sodium Stibogluconate sensitive (SSG-S) and resistant (SSG-R) LD promastigotes corroborates previous reports [58, 59]. LD infection is associated with increased membrane fluidity[60] which is restored after successive doses of Imipramine that improved antigen presentation ability. The workers further reported that the TNF-α, IFN-γ and iNOS activities were increased with concomitant decrease in IL-10 and Transforming Growth Factor-β (TGF-β) level in the Imipramine treated LD infected hamsters[52].

The mechanism of action of the drug Imipramine on Kala-azar patients infected with antimony-resistant *Leishmania donovani* [Sb(R) LD] has also been postulated[61]. The workers observed that Imipramine inhibits IL-10 production from Sb(R) LD-infected macrophages [Sb(R)LD-Mφs] and helps to accumulate surrogate antimonials. IL-10 driven nuclear translocation of c-Fos/c-Jun is inhibited which is critical for enhanced multidrug resistance protein (MDR-1) expression. Histone deacetylase 11 inhibits acetylation of IL-10 promoter[62]. Imipramine up regulates Histone deacetylase 11 that leads to decrease in IL-10 production from Sb(R)LD-Mφs. They observed that Histone deacetylase 11 does not interfere in IL-12 promoter activity but Imipramine induced decreased IL-10 level which in turn, allows optimal IL-12 production in Sb(R)LDMφs resulting in increased IL-12/IL-10 ratio. This skewing in Th1/Th2 ambience is crucial for halting disease progression.

Sertraline

Sertaline belongs to selective serotonin reuptake inhibitor (SSRI) class of antidepressant. It is widely used for treating major depressive disorder (MDD), obsessive compulsive disorder (ODD), body dysmorphic disorder (BDD), post-traumatic stress disorder (PTSD), premenstrual dystrophy disorder (PMDD), panic disorder and social anxiety disorder[63].

Sertraline shows encouraging antifungal activities[64], antimicrobial[65], spermicidal and antitrichomonas[66], anticancer activities[67]. It has also been observed that, Sertraline killed L.donovani promastigotes and amastigotes with IC50 value of 2.2 mg/L and 2.3 mg/L respectively[68]. Sertraline was also effective in removing parasite loads from spleen (72%) and liver (70%) in LD infected BALB/c mice[68]. This drug induced decline in cytoplasmic ATP levels and oxygen consumption rate in promastigotes indicates that promastigotes were killed by apoptosis[68].

Ketanserin

Ketanserin is clinically used for the treatment of arterial hypertension and vasopastic disorders[69]. It lowers blood pressure in essential hypertension as well as inhibits platelet aggregation particularly effective in older patients[70]. Ketanserin is a 5-HT2A/2C

receptor antagonist with weak adrenergic receptor blocking properties [44,70-71]. Ketanserin shows some affinity for alpha-1 receptors[71] which contributes to its antihypertensive effect.

On the other hand, in receptor binding assays and autoradiography Ketanserin radioactively labeled with tritium (3H) is used as radio ligand for serotonin 5-HT2A receptor[72]. This radio labeling, in tern, assists in the study of the serotonin 5-HT2A receptor distribution in the brain[73].

Singh et al. (2014) observed that Ketanserin killed both promastigotes and amastigotes with an IC50 value of 37 μM and 28 μM respectively in a dose dependent manner[74]. They also reported that Ketanserin was found to inhibit L. donovani recombinant 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) enzyme activity i.e. the first rate limiting enzyme of the sterol biosynthetic pathway. HMGR-overexpreesing parasite model (promastigote transfected with an episomal pspα hygroα-HMGR contruct) was used to study the effect which showed two fold resistance to Ketanserin. The lethal effect of Ketanserin to the parasite was due to inhibition of HMGR. Hence, Ketanserin might be a useful choice for Kala-Azar therapy.

Mianserin

Mianserin belongs to the TCA therapeutic family but classified as a noradrenergic and specific serotonergic antidepressant (NaSSA). This drug acts as antidepressant, anxiolytic, hypnotic, antiemetic, orexigenic and antihistaminic effects [69]. Mianserin has been tried against treatment-resistant depression[75] and schizophrenia successfully reducing negative and cognitive symptoms[76-78].

Dinesh et al.[79] observed that Mianserin killed both promastigotes and amastigotes with an IC50 value of 21 μM and 46 μM respectively in a dose dependent manner. According to them, Mianserin inhibits the recombinant L. donovani HMGR enzyme at IC50 value of 19.8 μM with competitive inhibition kinetics. Ergosterol levels of promastigotes were depleted after Mianserin treatment which was reversed after Ergosterol supplementation though it was refractory to cholesterol supplementation.

CONCLUSION

Visceral Leishmaniasis (VL) or Indian Kala-azar is one of the neglected tropical diseases that show mortality worldwide. Current drugs are showing treatment failure due to unresponsiveness of the parasites for the prevailing drugs. The disease control strategy has become further complicated due to the complicated epidemiological picture i.e. involvement of other species (L. tropica)[80-82] or even other genus (Leptomonas)[83] with the disease. The drug suitable for L. donovani may not kill L. tropica or Leptomonas sp. HIV co infection also makes the picture further bleak[84-85]. Thus, present status of disease control strategy demands new promising drugs of cheaper prices which may combat both the responsive and unresponsive cases of VL.

Current trend in chemo therapeutic drug discovery is aimed to search of some new purpose of putting an old drug for the treatment of another disease. Many drugs well used for other diseases, like Miltefosine for cancer and Amphotericin B for fungal infection, were successfully used against Leishmaniasis. Four antidepessant drugs showed some promise in controlling experimental Leishmaniasis. This could be extrapolated to higher rank of study involving clinical trials. Present antileishmanial drug search indicates a future evolution of promising antidepressant drug groups effective against Leishmania sp.

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