Desipramine
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I. Compound Information

Common name: Desipramine

Structure:

![Desipramine Structure](image)

Pubchem ID: 2995  Mol. Formula: \(\text{C}_{18}\text{H}_{22}\text{N}_2\)  FW: 266.38

CASRN: 50-47-5  Polar surface area: 15.3  logP: 4.13

IUPAC name: 3-(5,6-Dihydrobenzo[b][1]benzazepin-11-yl)-N-methyl-propan-1-amine

Other names: 10,11-Dihydro-5-[3-(methylamino)propyl]-5H-dibenz[b,f]azepine; Norpramin®

Drug class: Tricyclic dibenzazepine antidepressant

Medicinal chemistry development potential: High
II. Rationale

IIa. Scientific Rationale / Mechanism

Desipramine is a classical tricyclic antidepressant with a relatively selective mechanism of action. The primary action of desipramine in the CNS is selective inhibition of the norepinephrine transporter (NET), thus preventing norepinephrine reuptake. While much of our current focus in addressing Parkinson’s disease is driven by the depletion of dopaminergic neurons and replacement therapy with L-DOPA, the noradrenergic projections of the locus coeruleus are actually depleted earlier in disease onset. These projections are thought to play a significant role in the protection of dopamine neurons and the abnormal involuntary movements (AIMs) induced by long-term L-DOPA treatment are improved by drugs which increase noradrenergic activity.¹

There are several potential mechanisms of noradrenergic impact on the dopamine-based symptoms of Parkinson’s disease and the side-effects of dopaminergic therapy. The first, and simplest, mechanism relates to the inhibition of NET by desipramine which results in a greater availability of the catecholamine precursors for uptake by the dopaminergic neurons, thus providing greater activity of the dopaminergic pathways. Secondary to this mechanism, there is some data to suggest that desipramine inhibition of NET, resulting in an increased extracellular norepinephrine, can reduce the striatal levels of α-synuclein. This effect, however, has only been supported in the Kyoto Wistar rat (a rodent model of depression) and not in the “wild-type” Wistar rat.²

An interesting additional element in the consideration of potential neuroprotective applications of desipramine is that a large proportion of Parkinson’s patients develop a characteristic depression. This depression is often successfully treated clinically with desipramine, although there seems to be no evidence collected, as yet, on whether the administration of desipramine for depression also attenuates the onset of Parkinsonian symptoms.

IIb. Consistency

n/a
III. Efficacy (Animal Models of Parkinson's Disease)

IIla. Animal Models: Rodent

There are no published reports of the efficacy of desipramine in rodent models of Parkinson’s Disease. Fulceri et al (2007) have demonstrated that the noradrenergic system is a pivotal part of the protection of the dopamine system in 6-OHDA-induced loss of catecholaminic neurons. Bilateral ablation of the noradrenergic system in the locus coeruleus anticipated the onset and worsened the severity of L-DOPA-induced contralateral abnormal involuntary movements in hemiparkinsonian rats.¹

In a less direct model of Parkinson’s pathology, Jeannotte et al (2009) have demonstrated that in the Kyoto Wistar rat (a rodent model of depression), but not the Wistar rat, chronic desipramine treatment decreases NET expression in the frontal cortex and decreases the levels of α-synuclein in the striatum.² Given the complex role for α-synuclein in the pathophysiology of Parkinson’s disease, it seems highly relevant that desipramine can reduce the levels of this protein.


n/a
IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical Studies

No clinical efficacy studies of anti-Parkinsonian activity have been published with desipramine in Parkinson's disease. Desipramine is, however, a well established antidepressant for use in both Parkinsonian and non-Parkinsonian patients at a dose of around 25-50 mg (marketed by Sanofi-Aventis as Norpramin, 25 mg).\(^3\) Norpramin was approved in 1964 and, as the active metabolite of imipramine, it is a widely used tricyclic antidepressant with a well understood side effect profile (Section VIIa) and metabolic clearance by CYP P450 isozymes (Section V1a).

IVb. Epidemiological Evidence

n/a
V. Relevance to Other Neurodegenerative Diseases

n/a
VI. Pharmacokinetics

VIa. General ADME
The general pharmacokinetics of desipramine have recently been reported by Boni et al. as part of a drug-drug interaction study with chemotherapeutic agents. Since desipramine has been in clinical use since 1964, little of the original pharmacokinetics data is readily accessible, and the analytical techniques of the time were considerably limited. Using modern techniques, Boni et al have described a human oral pharmacokinetic profile for desipramine (50 mg dose; 22 subjects) with a 24.7 hour half life, a Cmax of 19.6 ng/mL and an AUCT of 602 ng h/mL and a Tmax at 8 hours. CL/F (clearance) was 123 L/h and the volume of distribution (Vz/F) 2,974 L – suggesting significant compartmentalization of the drug out of the body water/plasma.

VIb. CNS Penetration
Desipramine has an intended target of the NET in the CNS. CNS penetration of this compound is good enough to produce clinical efficacy at safe, well-tolerated dose levels (50 mg orally).

VIc. Calculated log([brain]/[blood])
0.54 (Clark model)
VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

Desipramine has been in clinical use as an antidepressant since the Sanofi-Aventis approval for Norpramin in 1964. There is substantial information about the clinical tolerability, toxicity and potential drug-drug interaction with desipramine. Clinical side-effects of desipramine treatment that have been reported are: nausea, drowsiness, weakness or tiredness, nightmares, dry mouth, sensitivity to sunlight, changes in appetite or weight, constipation, difficulty urinating, frequent urination, blurred vision, changes in sex drive or ability, excessive sweating, jaw, neck, and back muscle spasms, slow or difficult speech, shuffling walk, uncontrollable shaking or movement of a part of the body, fever, difficulty breathing or swallowing, severe rash, yellowing of the skin or eyes, irregular heartbeat, sore throat, fever, and other signs of infection. Symptoms of overdose include: irregular heartbeat, seizures, coma, confusion, hallucination, pupil dilation, drowsiness, agitation, fever, low body temperature, stiff muscles, and vomiting.

These signs are also supported in a recent study by Boni et al. in which desipramine treated control subjects reported accidental injury, chills, headache, pain, nausea and pharyngitis. Further to the clinical side effects and symptoms of overdose, the interactions of desipramine with CYP P450 isozymes such as 2D6, 2C9 and 2C19 can adversely affect the metabolism of other drugs, such as phenytoin through 2C19.

VIIb. Drug Interaction Potential

As discussed above, the interactions of desipramine with CYP P450 isozymes can modify the metabolism rates of other compounds and result in altered toxicity or efficacy of other drugs. Further to this, the differences in basal CYP isozyme expression between individuals is thought to produce marked differences in the effectiveness of desipramine as well as other highly metabolized drugs that might be co-administered with the tricyclic antidepressants, such as chemotherapeutic agents.
VIII. Bibliography


