AtreMorine (E-PodoFavalin-15999™): A Biotechnological/Nutraceutical product for Prevention and Treatment of Parkinson's disease

AtreMorine is a novel biopharmaceutical compound obtained by means of non-denaturing biotechnological procedures from the structural components of the *Vicia faba* L. plant, for the prevention and treatment of Parkinson´s disease (PD) and related disorders. E-PodoFavalin-15999 extract is the structural base of AtreMorine and a natural source of L-DOPA, with an average concentration of 25 mg per gram of AtreMorine; it also contains a plethora of other bioactive substances as vegetal proteins, unsaturated fatty acids, minerals and vitamins, vegetal fibre, starch, vegetal pigments (carotenes), and vegetal sterols (phytosterols).

The *in vitro* studies revealed that AtreMorine is a powerful neuroprotectant in

(i) cell cultures of human neuroblastoma SH-SY5Y cells
(ii) hippocampal slices in conditions of oxygen and glucose deprivation
(iii) striatal slices under conditions of neurotoxicity induced by 6-OHDA

AtreMorine displays neuroprotective and anti-inflammatory effects in different *in vitro* models, suggesting that this novel bioproduct can be of utility to protect neurons against neurodegenerative processes, especially dopaminergic neurons associated with PD pathogenesis.

The *in vivo* studies showed that AtreMorine:

(i) protects against 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)-induced dopaminergic neurodegeneration
(ii) inhibits MPTP-induced microglia activation and neurotoxicity in substantia nigra
(iii) improves motor function in mice with MPTP-induced neurodegeneration

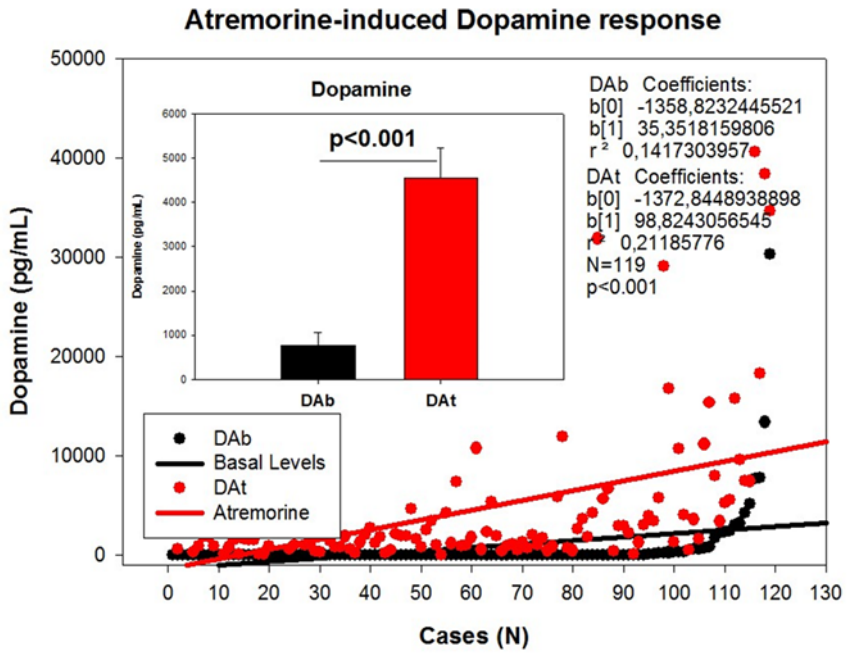
The clinical studies showed that AtreMorine is a potent enhancer of dopaminergic neurotransmission, increasing plasma dopamine levels by 200- to 500-fold in patients with PD and related movement disorders. AtreMorine is effective in untreated patients who receive AtreMorine for the first time (never treated before with antiparkinsonian drugs) and in patients chronically treated with L-DOPA or other antiparkinsonian drugs.

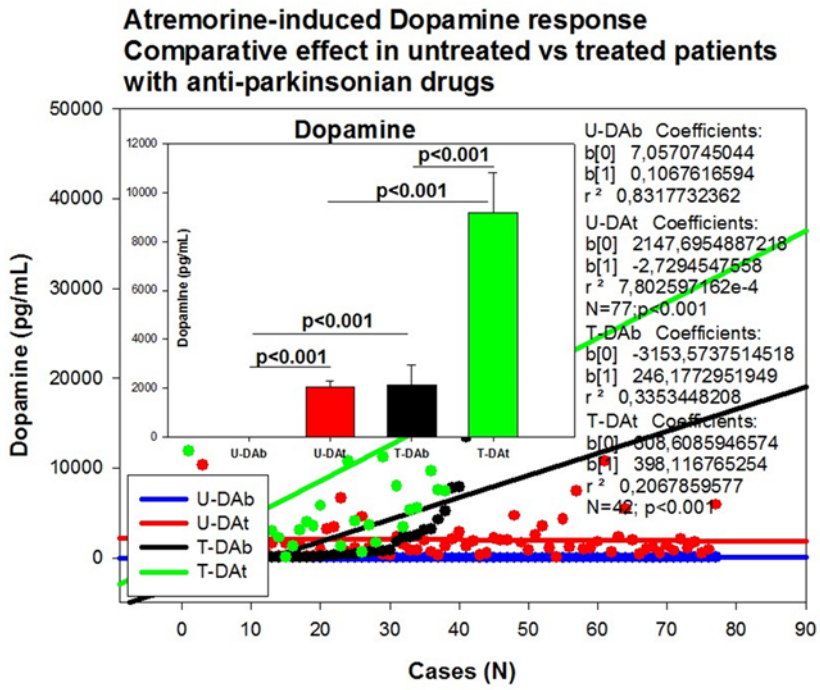
AtreMorine is an optimal option to reduce and minimize the potential side effects of conventional antiparkinsonian drugs, as the ''wearing-off'' phenomenon, motor fluctuations and dyskinesia, systemic complications (gastrointestinal disorders, cardiovascular problems, hormonal dysregulation), and neuropsychiatric disorders (depression, anxiety, toxic psychosis).

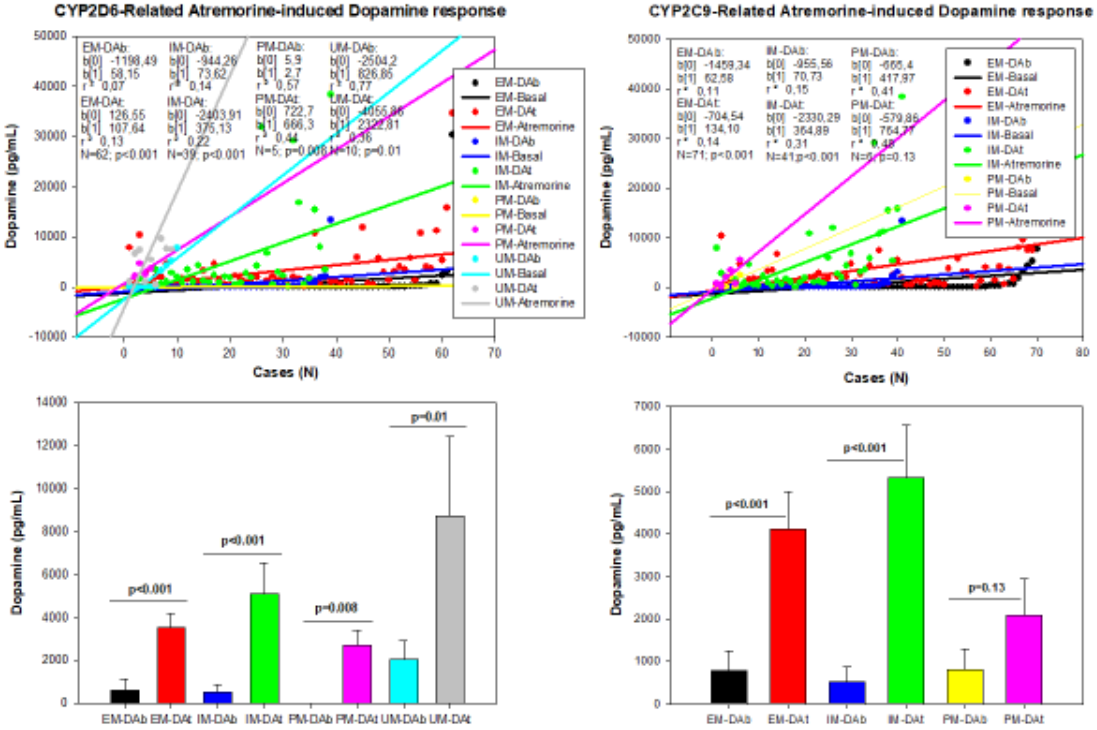
The coadministration of AtreMorine with other antiparkinsonian drugs allows a dose reduction of conventional drugs by 25%–50%, with enhancement of clinical benefits, reduction of short- and long-term adverse drug reactions, and extending the therapeutic effect of conventional antiparkinsonian drugs.

AtreMorine induces an increase in plasma levels of noradrenaline and adrenaline in PD patients, with no changes in serotonin. This effect may explain, in part, its clinical and biochemical benefits. AtreMorine also induces a significant decrease in prolactin, GH, and cortisol levels. The prolactin and GH response to AtreMorine can be directly attributed to the effect of L-DOPA on dopamine and noradrenaline synthesis and release, with the consequent increase in central and peripheral dopamine and noradrenaline levels. In contrast, the effect on cortisol might be primarily influenced by a direct effect of dopamine, noradrenaline, and adrenaline on the adrenal gland, and secondarily by pituitary and/or hypothalamic regulation of ACTH, which in plasma did not show any significant changes.

The pharmacodynamic and pharmacokinetic properties of Atremorine are highly influenced by genetic and pharmacogenetic factors. Genetic variants in pathogenic (LRRK2), metabolic (CYP2D5, CYP2C9, CYP2C19, CYP3A5, NAT2), transporter (ABCB1), pleiotropic (APOE) and detoxifying genes (CYP1B1, GSTT1, GSTP1, GSTM1, SOD2) affect the dopamine response to Atremorine.




Atremorine-induced Dopamine response
Comparative effect in untreated vs treated patients with anti-parkinsonian drugs
Dopamine
Dopamine (pg/mL)
p<0.001
p<0.001
p<0.001
U-DAb
U-DAt
T-DAb
T-DAt
U-DAb Coefficients:
b[0] 7,0570745044
b[1] 0,1067616594
r ² 0,8317732362
U-DAt Coefficients:
b[0] 2147,6954887218
b[1] -2,7294547558
r ² 7,802597162e-4
N=77;p<0.001
T-DAb Coefficients:
b[0] -3153,5737514518
b[1] 246,1772951949
r ² 0,3353448208
T-DAt Coefficients:
b[0] 808,6085946574
b[1] 398,116765254
r ² 0,2067859577
N=42; p<0.001
Dopamine (pg/mL)
Cases (N)


CYP2D6-Related Atremorine-induced Dopamine response
CYP2C9-Related Atremorine-induced Dopamine response
Dopamine (pg/mL)
Cases (N)
p<0.001
p<0.001
p=0.008
p=0.01
p<0.001
p<0.001
p=0.13
EM-DAb EM-DAt IM-DAb IM-DAt PM-DAb PM-DAt UM-DAb UM-DAt

References

Cacabelos R, Fernández-Novoa L, Alejo R, Corzo L, Alcaraz M, Nebril L, Cacabelos P, Fraile C, Carrera I, Carril JC. E-PodoFavalin-15999 (Atremorine®)-induced dopamine response in Parkinson's Disease: Pharmacogenetics-related effects. J Genomic Med Pharmacogenomics 2016; 1:1-26.

Cacabelos R, Fernández-Novoa L, Alejo R, Corzo L, Rodríguez S, Alcaraz M, Nebril L, Cacabelos P, Fraile C, Carrera I, Carril JC. E-PodoFavalin-15999 (Atremorine®)-induced neurotransmiiter and hormonal response in Parkinson's Disease. J Explor Res Pharmacol 2016; 1:1-12. DOI: 10.14218/JERP.2016.00031.

Cacabelos R. Parkinson's disease: From pathogenesis to pharmacogenomics. Int. J. Mol.Sci., 2017; 2017; 18:551. Doi:10.3390/ijms18030551.

Carrera I, Fernández-Novoa L, Sampedro C, Cacabelos R. Neuroprotective effect of atremorine in an experimental model of Parkinson's Disease. Current Pharmaceutical Design 2017; 23:1-12.

Romero A, Parada E, González-Lafuente, Farré-Alins, Ramos E, Cacabelos R, Egea J. Neuroprotective effects of E-PodoFavalin-15999 (Atremroine®). CNS Neurosci Ther 2017; DOI: 10.111/cns.12693.

Cacabelos R. Pharmacogenomics of Alzheimer's and Parkinson's diseases. Neurosci Lett. 2018 Sep 17. pii: S0304-3940(18)30624-4. doi: 10.1016/j.neulet.2018.09.018.

Carrera I, Fernandez-Novoa L, Sampedro C, Tarasov VV, Aliev G, Cacabelos R. Dopaminergic neuroprotection with Atremorine in Parkinson's disease. Current Medicinal Chemistry 2018; 25:5372-5388.

Carrera I, Cacabelos R. Current Drugs and Potential Future Neuroprotective Compounds for Parkinson's Disease. Curr Neuropharmacol. 2019;17(3):295-306. doi: 10.2174/1570159X17666181127125704.

Cacabelos R, Carrera I, Alejo R, Fernández-Novoa L, Cacabelos P, Corzo L, Rodríguez S, Alcaraz M, Tellado I, Cacabelos N, Pego R, Carril JC. Pharmacogenetics of Atremorine-induced neuroprotection and dopamine response in Parkinson's disease. Planta Medica 2019; DOI https:// doi.org/10-1055/a-1013-7686.