WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 8, 113-120. Research Article ISSN 2277– 7105

# QUANTUM ANALYSIS OF THE INTERACTION OF VORTIOXETINE VS. NEUROTRANSMITTERS.

**Bernardo Ojeda-Lara[1], Jesús Francisco Mondragón-Jiménez[1], Carlos Arturo Brito-Pérez[1], Adrián Alvarez-Aguilar[1], Francisco José Rosales-Hernández[1] and Manuel González Pérez*[2,3]**

[1]Universidad Juárez Autónoma de Tabasco (UJAT)-División Académica de Ciencias de la Salud (DACS).

[2]Universidad Popular Autónoma del Estado de Puebla (UPAEP). A.C. Centro Interdisciplinario de Posgrados (CIP). Posgrado en Ciencias de la Ingeniería Biomédica.

[3]Sistema Nacional de Investigadores. Nivel I.

Article Received on
30 May 2017,
Revised on 20 June 2017,
Accepted on 10 July 2017
DOI: 10.20959/wjpr20178-9020

***Corresponding Author**
**Dr. Manuel González Pérez**
Universidad Popular Autónoma del Estado de Puebla (UPAEP). A.C. Centro Interdisciplinario de Posgrados (CIP). Posgrado en Ciencias de la Ingeniería Biomédica.

## ABSTRACT

Vortioxetine (Vx) is a drug recently approved by the Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD) which is a disease that mainly affects the emotional state of people. The main objective of this work is to determine the interaction between Vx and the neurotransmitters (NT) using the semi-empirical quantum method Parametrical Method 3 (SE-PM3). Researchers use Hyperchem to analyze the Electron Transfer Coefficient (ETC) of compounds and to identify possible interactions between compounds. As results we obtained by the quantum method that the interaction between Vx and adrenalin (AD) had the lowest ETC while the interaction between Vx and noradrenaline (NE) had the highest ETC. Therefore, we conclude that Vx is a good antioxidant agent for AD because there is a high electron transfer from Vx to AD and Vx is not a good antioxidant agent for NE because there is a low Transfer of electrons from the Vx to NE.

**KEYWORDS:** Vortioxetine, Adrenalin, Quantum method, Hyperchem, SE-PM3.

## INTRODUCTION

MDD is a disease that affects the emotional state of people causing persistent feelings of sadness and loss of interest in personal activities.[1-3] The FDA approved Vx a structurally new drug for the treatment of MDD on September 30, 2013.[1, 4] Vx exhibits both an antidepressant and anxiolytic effect. Vx has an effect that can not only be effective in the treatment of depressive disorders but also anxiety.[5] Vx was studied in 11 randomized, double-blind, placebo-controlled trials of 6/8 weeks duration of treatment evaluating its efficacy and safety.[6,7] Vx in the United Kingdom is a cost-effective treatment option at a threshold of £ 20,000 / QALY vs escitalopram, citalopram, sertraline and was associated with more health benefits, less costs (was dominant) versus comparators Relevant third-line drugs such as venlafaxine and duloxetine.[8] Vx significantly improves cognition, independent of depressive symptoms and is an important treatment for MDD-related cognitive dysfunction.[9, 10]

In patients with MDD the recommended dose range is 5-20 mg / day.[11] Scientists have found that Vx 5-20 mg over 6/8 weeks improves the overall functioning of patients with MDD.[12] Vx is targeted at serotonin receptors(5-HT) and transporters.[13] Vx inhibits serotonin reuptake, in addition it is a 5-HT 1D, 5-HT 3, 5-HT 7 receptor antagonist, a 5-HT 1B receptor agonist and a 5-HT 1A receptor agonist.[14-17] Vx increases serotonergic, noradrenergic, dopaminergic, cholinergic, histaminergic and glutamatergic neurotransmission in brain structures associated with MDD.[21]

The Japanese Takamine and Uenaka settled in New York on August 5, 1900, crystallizing AD by a different procedure to that used.[20] AD is an active hormone and NT secreted by the adrenal medulla. AD activates the alpha and beta adrenergic receptors, mainly causing heart stimulation, systemic vasoconstriction, gastrointestinal relaxation and dilation of bronchi and cerebral vessels.[18, 19]

Hyperchem is a molecular modeling program. Hyperchem's graphical interface allows researchers to perform chemical simulations that facilitate multiple data entry.[22-25]

The main objective of this work is to determine by the quantum method SE-PM3 the interaction between Vx and NT.

## MATERIAL AND METHODS

### Software and Simulation

It used Hyperchem molecular simulator for Windows Serial # 12-800-1501800080 SE-PM3 to extracting the molecules.

### General Setting

SE-PM3 a total load of around 0. Multiplicity1. Pairing turns the RHF. State under the Convergent limit of 0.01. 50. Limit iteration accelerates convergence Yes. Polarizability. Geometry Optimization: Algorithms Polak-Ribiere (conjugate gradient). RMS termination condition gradient 0.1 kcal / Amol. Algorithm Polak-Ribiere (conjugate gradient), the termination condition or 1000 cycles Maximum. Algorithm Polak-Ribiere (conjugate gradient).

### Hardware

Hardware ATA ST500DM002 IDB14SCSI. 6.1.7600.16385.

### ETC Theory.

When comparing the interaction of two substances by this theory, there is a range between the ETC of a substance A and an ETC of substance B. Therefore; there are 3 zones in which the ETC value of its cross bands can fall. One in range and two out of range (Figure 1). The area of greatest electronic interaction is I. In this zone I a chemical reaction has a very high probability of being carried out. Zone II is of medium probability; While Zone III is the very low likelihood of interaction between these two substances.

**Table 1. Parameters used for quantum computing molecular orbitals - HOMO and LUMO.** [25]

| Parameter | Value | Parameter | Value |
|---|---|---|---|
| **Total charge** | 0 | Polarizability | Not |
| **Spin Multiplicity** | 1 | Geometry Optimization algorithm | Polak-Ribiere (conjugate Gradient) |
| **Spin Pairing** | RHF | Termination condition RMS gradient of | 0.1 Kcal/Amol |
| **State Lowest Convergent Limit** | 0.01 | Termination condition or | 195 maximum cycles |
| **Interation Limit** | 50 | Termination condition or | In vacuo |
| **Accelerate Convergence** | Yes | Screen refresh period | 1 cycle |

| Table 2. Parameters used to visualize the map of the electrostatic potential of the molecules. [25] | | | |
|---|---|---|---|
| **Parameter** | **value** | **Parameter** | **Value** |
| **Molecular Property** | Property Electrostatie Potential | Contour Grid increment | 0.05 |
| **Representation** | 3D Mapped Isosurface | Mapped Function Options | Default |
| **Isosurface Grid: Grid Mesh Size** | Coarse | Transparency level | A criteria |
| **Isosurface Grid: Grid Layout** | Default | Isosurface Rendering: Total charge density contour value | 0.015 |
| **Contour Grid: Starting Value** | Default | Rendering Wire Mesh | |

## RESULTS AND DISCUSSION

In table 3 it is observed that Vx and AD have the lowest ETC, so the specificity of Vx by AD is very high. It is also observed that Vx has high specificity for dopamine by having the second lowest ETC in the table. Vx and NE have the highest ETC, so the specificity of Vx by NE is very low. It should be mentioned that the 3 NT belong to the catecholamines group.

**Table 3. Interaction of Vx vs. NT**

CHEMICAL REACTIVITY TABLE OF COMPOUNDS

| Reducing agent | Oxidizing agent | HOMO | LUMO | BG | E- | E+ | EP | ETC |
|---|---|---|---|---|---|---|---|---|
| VORTIOXETINE | VORTIOXETINE | -8.203136 | -0.3179295 | 7.8852065 | -0.119 | 0.125 | 0.244 | 32.31642 |
| **VORTIOXETINE** | **ADRENALIN** | **-8.203136** | **0.09176242** | **8.2948984** | **-0.119** | **0.198** | **0.317** | **26.166872** |
| VORTIOXETINE | SEROTONIN | -8.203136 | -0.1294475 | 8.0736885 | -0.119 | 0.141 | 0.26 | 31.052648 |
| **VORTIOXETINE** | **DOPAMINE** | **-8.203136** | **0.1988791** | **8.4020151** | **-0.119** | **0.189** | **0.308** | **27.27927** |
| VORTIOXETINE | GABA | -8.203136 | 0.9385893 | 9.1417253 | -0.119 | 0.18 | 0.299 | 30.574332 |
| VORTIOXETINE | GLYCINE | -8.203136 | 0.8744405 | 9.0775765 | -0.119 | 0.188 | 0.307 | 29.568653 |
| VORTIOXETINE | ASPARTY ACID | -8.203136 | 0.5161864 | 8.7193224 | -0.119 | 0.198 | 0.317 | 27.505749 |
| VORTIOXETINE | GLUTAMIC ACID | -8.203136 | 0.5371279 | 8.7402639 | -0.119 | 0.197 | 0.316 | 27.659063 |
| **VORTIOXETINE** | **NORADRENALINE** | **-8.203136** | **-0.00427538** | **8.1988606** | **-0.119** | **-0.222** | **0.103** | **79.600589** |
| VORTIOXETINE | ACETYCHOLINE | -8.203136 | 1.034277 | 9.237413 | -0.119 | 0.105 | 0.224 | 41.238451 |

The figure 1 shows that Vx-AD has a quantum well located in an area of high probability of interaction. AD-Vx have a quantum well that is in an area of low or zero probability. The blue and orange lines represent the pure ETCs of the Vx and AD.

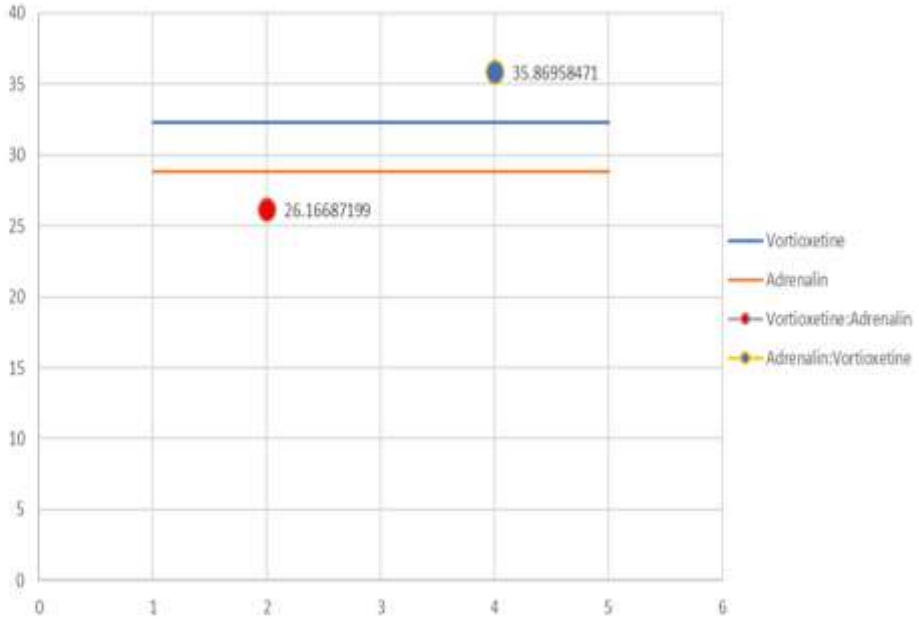


**Figure 1. Quantum wells of the interaction between Vx-AD and AD-Vx**

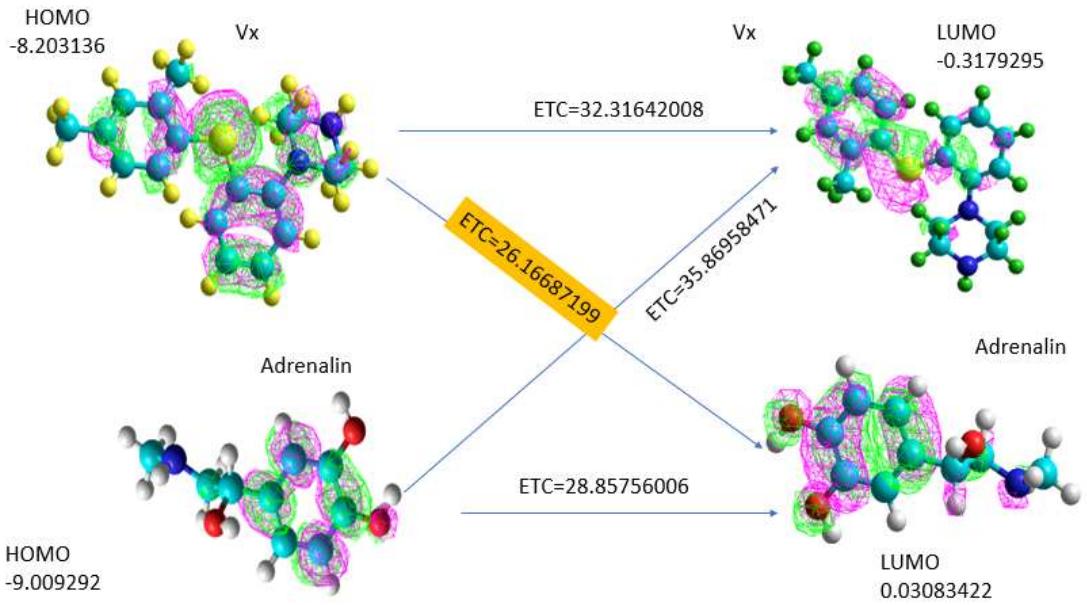


**Figure 2. Graphic representation of cross bands between Vx and AD.**

## CONCLUSION

Based on calculations and quantum methods we compared the interaction of Vx with the following NT: AD, serotonin, dopamine, GABA, glycine, aspartic acid, glutamic acid, NE and acetycholine and let the interaction between Vx and AD had a lower ETC of 26.166872, the affinity of Vx for AD is very high and therefore there is a significant electron transfer from Vx to AD. On the other hand, it was found that Vx also has a high affinity for

dopamine, another NT belonging to the catecholamines group. Vx and NE had the highest ETC of 79.6005885, the affinity of Vx for NE is the lowest and therefore the electron transfer from Vx to NE is very low.

**ACKNOWLEDGEMENTS**

We thank the UJAT-DACS for the support provided during the Summer of Scientific Research carried out in the city of Puebla and the UPAEP especially to the Interdisciplinary Center of Postgraduate for the support with its facilities for the of this article.

**REFERENCES**

1. D'Agostino, A., English, C. D., & Rey, J. A. (2015). Vortioxetine (Brintellix): a new serotonergic antidepressant. Pharmacy and Therapeutics, 40(1): 36.
2. Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M.,... & Schatzberg, A. F. (2016). Major depressive disorder. Nature reviews. Disease primers, 2: 16065-16065. 2.
3. Ye, M., Qing, P., Zhang, K., & Liu, G. (2016). Altered network efficiency in major depressive disorder. BMC psychiatry, 16(1): 450.
4. Connolly KR, Thase ME. Expert Opin Pharmacother. 2016; 17(3): 421-31.
5. Sowa-Kućma, M., Pańczyszyn-Trzewik, P., Misztak, P., Jaeschke, R. R., Sendek, K., Styczeń, K., ... & Koperny, M. (2017). Vortioxetine: A review of the pharmacology and clinical profile of the novel antidepressant. Pharmacological reports: PR, 69(4): 595.4
6. Thase ME, Mahableshwarkar AR, Dragheim M, Loft H, Vieta E.Eur Neuropsychopharmacol. 2016 Jun; 26(6): 979-93. Epub 2016 Mar 25.
7. Baldwin DS, Chrones L, Florea I, Nielsen R, Nomikos GG, Palo W, Reines E.J Psychopharmacol. 2016 Mar; 30(3): 242-52. Epub 2016 Feb 9.
8. Young, A. H., Evitt, L., Brignone, M., Diamand, F., Atsou, K., Campbell, R., ... & Danchenko, N. (2017). Cost-utility evaluation of vortioxetine in patients with Major Depressive Disorder experiencing inadequate response to alternative antidepressants in the United Kingdom. Journal of Affective Disorders, 218: 291-298.
9. McIntyre RS, Harrison J, Loft H, Jacobson W, Olsen CK. Int J Neuropsychopharmacol. 2016 Aug 24; Epub 2016 Aug 24.
10. McIntyre, R. S., Florea, I., Tonnoir, B., Loft, H., Lam, R. W., & Christensen, M. C. (2017). Efficacy of Vortioxetine on Cognitive Functioning in Working Patients With Major Depressive Disorder. The Journal of clinical psychiatry, 78(1): 115-121.

11. Findling, R. L., Robb, A. S., DelBello, M., Huss, M., McNamara, N., Sarkis, E., ... & Areberg, J. (2017). Pharmacokinetics and Safety of Vortioxetine in Pediatric Patients. Journal of Child and Adolescent Psychopharmacology.
12. Florea, I., Loft, H., Danchenko, N., Rive, B., Brignone, M., Merikle, E., ... & Sheehan, D. V. (2017). The effect of vortioxetine on overall patient functioning in patients with major depressive disorder. Brain and behavior, 7(3).
13. Tritschler L, Felice D, Colle R, Guilloux JP, Corruble E, Gardier AM, David DJ. Expert Rev Clin Pharmacol. 2014 Nov; 7(6): 731-45. Epub 2014 Aug 28. 3.
14. David DJ, Tritschler L, Guilloux JP, Gardier AM, Sanchez C, Gaillard R.Encephale. 2016 Feb; 42(1 Suppl 1): 1S12-23.
15. Smith, J., Browning, M., Conen, S., Smallman, R., Buchbjerg, J., Larsen, K. G., ... & Hawkins, P. (2017). Vortioxetine reduces BOLD signal during performance of the N-back working memory task: a randomised neuroimaging trial in remitted depressed patients and healthy controls. Molecular Psychiatry.
16. Basgiouraki, E., Papazisis, G., Apostolidis, A., & Goulas, A. (2017). Pharmacodynamic and pharmacokinetic properties of the novel antidepressant vortioxetine. Aristotle University Medical Journal, 43(3): 25-28.
17. Orsolini, L., Tomasetti, C., Valchera, A., Iasevoli, F., Buonaguro, E. F., Fornaro, M., ... & Vecchiotti, R. (2017). Current and future perspectives on the major depressive disorder: focus on the new multimodal antidepressant Vortioxetine. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders), 16(1): 65-92.
18. Verma, I. P., Garg, P., Karnawat, B. S., Jain, A., Verma, P., & Kumawat, R. (2017). Study of therapeutic effects of nebulized adrenaline alone, nebulized adrenaline plus injectable dexamethasone (in combination) and nebulized 3% hypertonic saline alone in clinically diagnosed cases of bronchiolitis. International Journal of Contemporary Pediatrics, 4(4): 1414-1419.
19. Kleine, B., & Rossmanith, W. G. (2016). Hormones Derived by Amino Acid Conversion. In Hormones and the Endocrine System (pp. 237-245). Springer International Publishing.
20. Yamashima, T. (2017). Adrenaline/Epinephrine Hunters: Past, Present and Future at 1900. Emerg Med Inves.
21. Sanchez, C., Asin, K. E., & Artigas, F. (2015). Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. Pharmacology & therapeutics, 145: 43-57.

22. González-Perez, M., Pacheco-Bautista, D., Ramirez-Reyes-Montaño, H. A., Medel-Rojas, A., González-Murueta, J. W., & Sánchez, C. (2017). ANALYSIS OF THE INTERACTIONS OF N-(L-A-ASPARTIL)-L-PHENYLALANINE, 1-METIL ESTER (ASPARTAME) AND THE NITROGEN BASES OF DNA AND RNA USING QUANTUM METHODS.
23. González-Pérez, M., Briteño-Vázquez, M., García-Barrera, F. A., Ham-Tirado, A. K., López-Oglesby, J. M., Salazar-Amador, M. R., & Pacheco-García, P. F. (2016). Molecular Interactions of Nicotine and the Nitrogenous Bases of DNA and RNA Calculated by Quantum Methods. World Journal of Pharmaceutical Research, 5(3): 1778-1792.
24. González-Pérez, M. (2015). Applied quantum chemistry. Analysis of the rules of Markovnikov and anti-Markovnikov. International Journal of Science and Advanced Technology, 5(5).
25. Perez, M. G., Barrera, F. A. G., Diaz, J. F. M., Torres, M. G., & Oglesby, J. M. L. (2014). Theoretical calculation of electron transfer coefficient for predicting the flow of electrons by PM3, using 20 amino acids and nicotine. European Scientific Journal, ESJ, 10(27): ISO 690.