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DRUGS REPURPOSED FOR DEPRESSION AND THEIR IN-SILICO STUDIES AGAINST P2X7 RECEPTOR

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ABSTRACT:

Depression is a typical mental illness that results in a constant feeling of low mood and loss of interest. The major cause of disability in the today's world is depression which also significantly contributes to the overall burden of illness on the population. Drug repurposing is a powerful method for reutilizing the existing medications outside the parameters of their original use and speeding up the development of novel treatment alternatives. The research suggests that drug repurposing is crucial for the quicker and economical development of anti-depressants agents. In this article, reviewed various approved drugs of different classes that can be repurposed as anti-depressants. Also, we conducted in-silico docking studies of various compounds against P2X7 receptor which is now widely being researched for depression for the evaluation of the efficacy of the drugs.

IndexTerms: Depression, Repurposing, Anti-depressants, Docking, P2X7 receptor

INTRODUCTION:

Depression is a disorder that comes with stress and trauma resulting in ruined physical and mental health. Depression being one of the leading disorders lately has become a sensitive topic for the researches to study upon. It is reported in the studies that more of women are affected than men due to depression [1].

Stress is proved to be a major cause of depression. One's mental health brain functioning is definitely affected along with the physical health if a person is under stress for a long time. Melancholia, clinical depression or major, depression are the terms used to explain the deteriorated mental illness due to depression accompanied by mood disorders [2]. The female to male ratio of depression is reported to be 5:2.major symptoms of the disorder includes low mood, disinterested, feelings of guilt , sleepless nights, suicidal thoughts, etc. In fact, a survey says that approximately 15% depressed patients commit suicide. The treatment of depression, i.e,

antidepressants are recommended depending on the severity of symptoms. Major depression gives reduced response towards pharmacotherapy [3].

Depression can be managed upto an extent by certain modifications in our lifestyles that indicates to self management .As per the mental health foundation, "self management includes the processes and tacts that are wisely incorporated in lives to get rid of specific disease or to meet the objective set before"[4].

The class of drugs used extensively against depression are called antidepressants [5] . As far as all the clinical practices guidelines(CPGs) are concerned, they recommended serotonin selective reuptake inhibitors(SSRIs) as first line treatment against depression. Alternatively, agomeltine, milnacipran, and mianserin are also considered as first line treating options. Also the factors for selecting the first line treatment includes the situation of individual patient, availability, financial reasons, etc [6].

Antidepressants; mirtazpine in 1996,citalopram in 1998,fluvoxamine in 2000 and escitalopram in 2002 are the drugs approved by US Food and Drug Administration against depression. [7] It is surveyed that 20% of the patients consuming amitryptyline , imipramine or doxepin (frist generation antidepressants) came up with four or more prescriptions in upcoming 6 months whereas this percentage for the patients treated with nortryptyline, desipramine, trazodone and fluoxetine(newer antidepressants) is seen as 34%. [8]

In spite of action against stress and depression ,antidepressants are also effective against several pains including;migraine pain, head pain, neurogenic pain, arthritis pain, and may be many hgmore of them.[9] Antidepressants including benzodiazepines and cognitive behavioural psychotherapies are effective in panic disorder. On the other hand, generalized anxiety disorder(gad) is recommended with treatments including buspirone , benzodiazepines , cognitive behavioural therapies and relaxation techniques.[10]

DRUG REPURPOSING:

Repurposing of drugs is a strategy to find new indications for already approved medications.[12] The main aim of repurposing strategy is to save time and finance upto an extent by skipping some of the steps of drug discovery process. It is all about studying the new uses of already marketed drugs that lowers the years of time and billions of cost for marketing a single drug.[13]

Types of repurposing-

Different terms studied under repurposing are; Drug repositioning, drug reformulation and drug combination.[14]

1.Drug Repositioning- It involve finding new indication for drugs already approved for some other indications. Example- Antiprogesterone drug mifepristone, approved for abortion was later found experimentally effective in depression.[15]

2. Drug Reformulation- This is the strategy to change the dosage form of a medication with or without changing its route of administration. Example- Reformulation of ketamine as intranasal and sublingual routes administration.[16]

3. Drug Combination- The idea of using two or more medications together in order to enhance safety and efficacy of treatment. Example- Antidepressants combined with anti-inflammatory drugs results in improved activity against depression.[17]

Drugs that can be repurposed for depression-

Depression has been known among one of the most prevalent disorders and affects about 264 million individuals all around the world.[14] Drug repurposing for depression can be a useful aspect to save time and cost and make treatment effective. Several drug

classes are evaluated for their antidepressant activity including;anti-diabetic,anti-inflammatory,anti-hyperlipidaemic,and so on.[18] Some of the marketed drugs that are reported to be used against depression are mentioned in the article.

Ketamine, a drug used as an anaesthetic and for pain management can be a good choice for repurposing it as an antidepressant.[19] Ketamine has an action of blocking GluN2B-selective extra-synaptic N-methyl-D-aspartate(NMDA) receptor and also it activates a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor. These mechanisms results in antidepressant action of ketamine.[20] Minocycline is a tetracycline antibiotic of second-generation that can be used as an antidepressant for its neuroprotective and anti-inflammatory properties.[21] One of the most efficient epileptic drug valproic acid regulates ionic currents and facilitates GABAergic transmission.[22] Antidepressant action of valproic acid is due to its action of activating phosphatidylinositol 3-kinase (PI3K)/mTOR/Akt pathway.[23] Quetiapine Inhibits D2 dopaminergic receptor treating parkinson's disease and its mechanism of enhancing glucocerebrosidase level prevents neurodegenerative diseases that helps in depression treatment.[24] Anti-hyperlipidaemic drugs can be proved to be good antidepressants. One such drug is lovastatin that acts as HMG-CoA inhibitor giving anti-hyperlipidaemic activity.[25] Anti-oxidant,anti-inflammatory and anti-hyperlipidaemic effects of lovastatin makes it a good treating option for depression.[26]

Dextromethorphan ,a well known anti-tussive from several years can also be repurposed as an antidepressant. [27] The mechanism of dextromethorphan giving acions at b,a-2 and serotonin receptors contributes in combating bipolar, psychotic disorders, depressive disorders.[28] Anti-inflammatories are well studied to be correlated in reducing depression by reduction in level of inflammation cytokines. Celecoxib is a COX-2 blocker reducing inflammation and its mediators namely intraleukin-4, intraleukin-5, intraleukin-6 and intraleukin-10 which in turn prevents depressive disorders.[29] Another marketed drug under the category of thiazolidinediones that is approved as an anti-diabetic is pioglitazone that has its action upon PPARs and treats the patients of type 2 diabetes.[30] Ligands acting on PPAR regulates inflammation and have neuroprotective action, thus giving an antidepressant effect.[31] Calcium channel blockers are way effective in neurodegenerative diseases. Nimodipine is among calcium channel blockers that inhibits monoamine oxidase-b enzyme preventing CNS disorders including depression.[32] Another studied drug in repurposing of depression is zileuton known as lipooxegenase blocker and can be repurposed as an antidepressant on its capability of activating NRF2 and based on its anti-inflammatory properties.[33]

Table1- Drugs Repurposed as Antidepressants

S.NO	DRUG	PHARMACOLOGICAL ACTION	REPURPOSED AS ANTIDEPRESSANT	REFERENCES
1	KETAMINE	Anaesthetic	NMDA receptor inhibition.	19,20
2	MINOCYCLINE	Antibiotic	Neuroprotective and anti-inflammatory.	21
3	VALPROIC ACID	Antiepilectic	PI3K and mTOR activation.	22,23
4	QUETIAPINE	Inhibition of D2 Dopaminergic receptor	Modulates glucocerebrosidase (GCase) level in CNS	24

5.	LOVASTATIN	Anti-hyperlipidaemic	anti-inflammatory, antioxidant and lipid lowering properties	25,26
6.	DEXTROMETHORPHAN	Antitussive	Action on NMDA, sigma-1, calcium channel,alpha2, serotonin 1b/d receptors.	27,28
7.	CELECOXIB	COX –II inhibitor	Dysregulation of HPA axis is prevented, with increase in cortisol.	29
8.	PIOGLITAZONE	Anti-diabetic	Anti-inflammatory	30,31
9.	NIMODIPINE	Calcium channel blocker	MAO inhibitor	32
10.	ZILEUTON	Lipooxygenase inhibitor	Activates Nrf2 modulator and anti-inflammatory	33

In-silico studies of repurposed drugs against P2X7 receptor-

P2X7 receptor is an ATP-gated channel mainly studied for inflammation. The receptor is responsible for regulating inflammatory cytokines and calcium and sodium ions.[34] Blocking P2X7 receptor is evaluated to be beneficial for depression treatment. Inhibition of P2X7 gives anti-inflammatory activity and also it manages release and uptake of neurotransmitters involved in depressive conditions that are;glutamate, noradrenaline and 5-hydroxytryptamine.[35] Thus P2X7 receptor family is widely being studied under depression. Molecular docking of repurposed drugs mentioned above is performed against P2X7 receptor.

Table 2- Molecular Docking of Repurposed Drugs Against P2X7 receptor

S. No.	Compounds	Binding Affinity against P2X7 receptor
1.	Celecoxib	-13.1
2.	Minocycline	-14.9
3.	Dextromethorphan	-11.1
4.	Ketamine	-9.4
5.	Lovastatin	-13.7
6.	Pioglitazone	-12.0
7.	Valproic acid	-6.8
8.	Nimodipine	-11.9
9.	Zileuton	-8.9
10.	Quetiapine	-12.4

CONCLUSION:

The article presented the idea of repurposing the marketed drugs for depression. Drugs from various classes are reviewed as antidepressants and mentioned in this study are; celecoxib, minocycline ,dextromethorphan, ketamine, lovastatin,pioglitazone,valproic acid, nimodipine, zileuton and quetiapine. Molecular docking for these drugs have been performed against P2X7 receptor which gave three best results-minocycline, lovastatin and celecoxib with their binding affinities;-14.9, -13.7 and -13.1 respectively.

DECLARATIONS:

Ethical approval

N/A

Competing interests

N/A

Authors' contribution

Komalpreet Kaur prepared the main manuscript.

Anita singh and Amrita Verma Pargaein prepared the figures and tables.

Komalpreet Kaur and Sakshi Gupta performed the in-silico studies.

All the authors reviewed the manuscript

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REFERENCES:

1. Grover, S., Dutt, A., & Avasthi, A. (2010). An overview of Indian research in depression. *Indian journal of psychiatry*, *52*(Suppl 1), S178–S188. https://doi.org/10.4103/0019-5545.69231s
2. Wang, H., Tian, X., Wang, X., & Wang, Y. (2021). Evolution and Emerging Trends in Depression Research From 2004 to 2019: A Literature Visualization Analysis. *Frontiers in psychiatry*, *12*, 705749. https://doi.org/10.3389/fpsyt.2021.705749
3. Duval, F., Lebowitz, B. D., & Macher, J. P. (2006). Treatments in depression. *Dialogues in clinical neuroscience*, *8*(2), 191–206. https://doi.org/10.31887/DCNS.2006.8.2/fduval
4. A Patient Perspective on the Self-Management of Chronic Anxiety and Depression: A Mixed-Methods Study. Int J Depress Anxiety 5:029. doi.org/10.23937/2643-4059/1710029

5. Duval, F., Lebowitz, B. D., & Macher, J. P. (2006). Treatments in depression. *Dialogues in clinical neuroscience*, *8*(2), 191–206. https://doi.org/10.31887/DCNS.2006.8.2/fduval
6. Avasthi, A., Grover, S., & Aggarwal, M. (2010). Research on antidepressants in India. *Indian journal of psychiatry*, *52*(Suppl 1), S341–S354. https://doi.org/10.4103/0019-5545.69263
7. Gabriel, F. C., de Melo, D. O., Fráguas, R., Leite-Santos, N. C., Mantovani da Silva, R. A., & Ribeiro, E. (2020). Pharmacological treatment of depression: A systematic review comparing clinical practice guideline recommendations. *PLoS one*, *15*(4), e0231700.
8. Olfson, M., & Marcus, S. C. (2009). National patterns in antidepressant medication treatment. *Archives of general psychiatry*, *66*(8), 848-856.
9. Katon, W., Von Korff, M., Lin, E., Bush, T., & Ormel, J. (1992). Adequacy and duration of antidepressant treatment in primary care. *Medical care*, 67-76.
10. Magni, G. (1991). The use of antidepressants in the treatment of chronic pain. *Drugs*, *42*(5), 730-748.
11. Young, A. S., Klap, R., Sherbourne, C. D., & Wells, K. B. (2001). The quality of care for depressive and anxiety disorders in the United States. *Archives of general psychiatry*, *58*(1), 55-61.
12. Pushpakom, S. (2022). Introduction and historical overview of drug repurposing opportunities, 1-13.
13. Schuler, J., Falls, Z., Mangione, W., Hudson, M. L., Bruggemann, L., & Samudrala, R. (2022). Evaluating the performance of drug-repurposing technologies. *Drug Discovery Today*, *27*(1), 49-64.
14. Mohammad Sadeghi, H., Adeli, I., Mousavi, T., Daniali, M., Nikfar, S., & Abdollahi, M. (2021). Drug Repurposing for the Management of Depression: Where Do We Stand Currently?. *Life*, *11*(8), 774.
15. Xue, H., Li, J., Xie, H., & Wang, Y. (2018). Review of Drug Repositioning Approaches and Resources. *International journal of biological sciences*, *14*(10), 1232–1244. https://doi.org/10.7150/ijbs.24612
16. Murteira, S., Millier, A., Ghezaiel, Z., & Lamure, M. (2014). Drug reformulations and repositioning in the pharmaceutical industry and their impact on market access: regulatory implications. *Journal of market access & health policy*, *2*, 10.3402/jmahp.v2.22813. https://doi.org/10.3402/jmahp.v2.22813
17. Jia, J., Zhu, F., Ma, X., Cao, Z., Cao, Z. W., Li, Y., Li, Y. X., & Chen, Y. Z. (2009). Mechanisms of drug combinations: interaction and network perspectives. *Nature reviews. Drug discovery*, *8*(2), 111–128. https://doi.org/10.1038/nrd2683
18. Ebada, M. E. (2017). Drug repurposing may generate novel approaches to treating depression. *Journal of Pharmacy and Pharmacology*, *69*(11), 1428-1436.
19. Morgan, C. J., Curran, H. V., & Independent Scientific Committee on Drugs (ISCD). (2012). Ketamine use: a review. *Addiction*, *107*(1), 27-38.
20. Zanos, P., & Gould, T. (2018). Mechanisms of ketamine action as an antidepressant. *Molecular psychiatry*, *23*(4), 801-811.
21. Miyaoka, T., Wake, R., Furuya, M., Liaury, K., Ieda, M., Kawakami, K., ... & Horiguchi, J. (2012). Minocycline as adjunctive therapy for patients with unipolar psychotic depression: an open-label study. *Progress in neuro-psychopharmacology and Biological Psychiatry*, *37*(2), 222-226.
22. Romoli, M., Mazzocchetti, P., D'Alonzo, R., Siliquini, S., Rinaldi, V. E., Verrotti, A., ... & Costa, C. (2019). Valproic acid and epilepsy: from molecular mechanisms to clinical evidences. *Current neuropharmacology*, *17*(10), 926-946.
23. de Assis Lima, I. V., Almeida-Santos, A. F., Ferreira-Vieira, T. H., Aguiar, D. C., Ribeiro, F. M., Campos, A. C., & de Oliveira, A. C. P. (2017). Antidepressant-like effect of valproic acid—Possible involvement of PI3K/Akt/mTOR pathway. *Behavioural brain research*, *329*, 166-171.
24. Burbulla, L. F., Zheng, J., Song, P., Jiang, W., Johnson, M. E., Brundin, P., & Krainc, D. (2021). Direct targeting of wild-type glucocerebrosidase by antipsychotic quetiapine improves pathogenic phenotypes in Parkinson's disease models. *JCI insight*, *6*(19).

25. Henwood, J. M., & Heel, R. C. (1988). Lovastatin: a preliminary review of its pharmacodynamic properties and therapeutic use in hyperlipidaemia. *Drugs*, *36*, 429-454.
26. Köhler-Forsberg, O., Otte, C., Gold, S. M., & Østergaard, S. D. (2020). Statins in the treatment of depression: hype or hope?. *Pharmacology & Therapeutics*, *215*, 107625.
27. Taylor, C. P., Traynelis, S. F., Siffert, J., Pope, L. E., & Matsumoto, R. R. (2016). Pharmacology of dextromethorphan: Relevance to dextromethorphan/quinidine (Nuedexta®) clinical use. *Pharmacology & therapeutics*, *164*, 170-182.
28. Lauterbach, E. C. (2011). Dextromethorphan as a potential rapid-acting antidepressant. *Medical hypotheses*, *76*(5), 717-719.
29. Mueller, N. (2010). COX-2 inhibitors as antidepressants and antipsychotics: clinical evidence. *Curr Opin Investig Drugs*, *11*(1), 31-42.
30. Smith, U. (2001). Pioglitazone: mechanism of action. *International journal of clinical practice. Supplement*, (121), 13-18.
31. Zhao, Q., Wu, X., Yan, S., Xie, X., Fan, Y., Zhang, J., ... & You, Z. (2016). The antidepressant-like effects of pioglitazone in a chronic mild stress mouse model are associated with PPARγ-mediated alteration of microglial activation phenotypes. *Journal of neuroinflammation*, *13*, 1-17.
32. Rolim, H. M. L., Freitas, R. M., & Santos-Magalhães, N. S. (2016). Antidepressant-like activity of liposomal formulation containing nimodipine treatment in the tail suspension test, forced swim test and MAOB activity in mice. *Brain Research*, *1646*, 235-240.
33. Kubick, N., Pajares, M., Enache, I., Manda, G., & Mickael, M. E. (2020). Repurposing zileuton as a depression drug using an AI and in vitro approach. *Molecules*, *25*(9), 2155.
34. Skaper, S. D., Debetto, P., & Giusti, P. (2010). The P2X7 purinergic receptor: from physiology to neurological disorders. *The FASEB Journal*, *24*(2), 337-345.
35. Ribeiro, D. E., Roncalho, A. L., Glaser, T., Ulrich, H., Wegener, G., & Joca, S. (2019). P2X7 receptor signaling in stress and depression. *International Journal of Molecular Sciences*, *20*(11), 2778.