International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 15(2): March-April 2025

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Research Article……!!!

Received: 01-12-2024; Revised: 19-02-2025; Accepted: 21-02-2025

REPURPOSING OF CARVEDILOL, A BETA-ANTAGONIST, AGAINST SELECTIVE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS FOR FIBROMYALGIA

Vaishnavi Alloli[1]*, Aparna Kakad[1], Neha Chavan[1], Ankita Dhere[1], Shivtej Devane[1], Ishwari Nimbalkar[2], Babaso Udugade[1]

[1]Department of Pharmaceutical Chemistry, Ashokrao Mane College of Pharmacy, Peth Vadagaon, Affiliated to Shivaji University 416112, Maharashtra, India.

[2]Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth Vadagaon, Affiliated to Shivaji University 416112, Maharashtra, India.

Keywords:

Fibromyalgia, Carvedilol, Drug Repurposing, Molecular Docking, Human Serum Albumin

For Correspondence:

Vaishnavi Alloli

Department of Pharmaceutical Chemistry, Ashokrao Mane College of Pharmacy, Peth Vadagaon, Affiliated to Shivaji University 416112, Maharashtra, India.

E-mail:

vaishnavialloli17@gmail.com

ABSTRACT

Fibromyalgia is a chronic pain condition that brings about widespread musculoskeletal pain, fatigue, and cognitive issues. The current treatments available, like serotonin-norepinephrine reuptake inhibitors (SNRIs) and anticonvulsants, often fall short in effectiveness and can come with unwanted side effects. Drug repurposing offers a smart way to find new treatment options that already have established safety records. This study aims to explore the potential of carvedilol, a non-selective beta-blocker, as a repurposed treatment for fibromyalgia by examining how it interacts with Human Serum Albumin (HSA) and its pharmacokinetic properties. We used a ligand-based screening method to find compounds that are structurally similar to duloxetine, which is an FDA-approved treatment for fibromyalgia. Molecular docking studies were carried out using CB-Dock 2 to evaluate how well these compounds bind to HSA, a crucial protein involved in drug transport and bioavailability. Additionally, we conducted ADME and toxicity analyses to assess carvedilol's pharmacokinetic properties and safety profile. Carvedilol showed a strong binding affinity to HSA, surpassing several other similar compounds. Its docking score and interaction profile indicate it may play a role in modulating neurotransmitter activity, particularly in the serotonin and norepinephrine pathways that are linked to fibromyalgia. Moreover, carvedilol displayed favorable ADME properties, reinforcing its potential as an effective treatment option for fibromyalgia.

1. INTRODUCTION

Fibromyalgia is a long-lasting condition that causes widespread pain in the muscles and joints, along with fatigue, trouble sleeping, and cognitive difficulties often referred to as "fibro fog"[1]. While the exact cause of fibromyalgia remains unclear, it's thought to involve the central nervous system interpreting pain signals abnormally [2]. Many people with this condition report being more sensitive to touch, with their pain levels often more intense than what's experienced by most [3]. Fibromyalgia also tends to occur alongside other issues like depression, anxiety, and irritable bowel syndrome (IBS), which makes managing it even more complicated [4].

Dealing with fibromyalgia can be tough, especially since there's no known cure at the moment [5]. Treatments mainly focus on alleviating symptoms such as pain relief, sleep improvement, and stress reduction [6]. Common medications prescribed include analgesics, antidepressants, and anticonvulsants [7]. Some frequently used options are tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) like duloxetine and milnacipran, as well as medications like pregabalin and gabapentin [8]. Unfortunately, these treatments often provide limited relief, come with significant side effects, and don't always work well for all patients, highlighting the need for new therapeutic approaches [9].

The challenges of current fibromyalgia treatments have sparked interest in exploring alternative therapies [10]. Many existing drugs don't adequately relieve pain or lead to unpleasant side effects, making it a complex and tailored journey to find relief [11]. Patients may respond differently to treatments, adding another layer to the already intricate clinical management [12]. Moreover, side effects from current medications, like weight gain, grogginess, and cognitive issues, can result in patients not sticking with their treatment plans, ultimately impacting their quality of life [13].

Given these hurdles, drug repurposing has come up as an exciting strategy to discover effective fibromyalgia treatments. This approach investigates existing approved medications for new uses, making it a cost-effective and quicker option, especially since there's already safety data available [14]. This can be particularly beneficial for fibromyalgia, where many treatments currently on the market don't quite hit the mark.

One potential candidate for repurposing is carvedilol, a non-selective beta-blocker typically used to treat heart failure, high blood pressure, and ischemic heart disease [15]. It works by blocking certain receptors, leading to lower blood pressure and heart rate. Beyond its heart-related benefits, carvedilol has antioxidant properties and might also help modulate inflammation, which could be relevant to fibromyalgia.

New research suggests that carvedilol might have effects beyond its traditional application, potentially influencing the central nervous system and affecting neurotransmitter systems connected to pain perception, such as serotonin and norepinephrine. These neurotransmitters play essential roles in regulating mood and pain, both of which are disrupted in

fibromyalgia. Therefore, examining carvedilol as a treatment option could be worthwhile [16].

The idea of using carvedilol for fibromyalgia stems from its impact on serotonin and norepinephrine reuptake mechanisms. Since both neurotransmitters are pivotal in mood and pain regulation, SNRIs like duloxetine and milnacipran—which also increase their levels in the brain—are commonly prescribed for fibromyalgia. However, they often come with side effects and vary in effectiveness.

Interestingly, carvedilol might offer a dual benefit by affecting both adrenergic and serotonergic/noradrenergic systems, possibly providing a unique way to relieve fibromyalgia symptoms. By exploring carvedilol's potential, researchers hope to identify a safer, more effective treatment solution that targets both pain and the mood disturbances common in fibromyalgia. This study aims to assess carvedilol's interactions with key receptors, its safety, and its potential benefits for those dealing with this condition [17].

This strategy presents an encouraging way to investigate the repurposing of carvedilol, building on what is already known about its pharmacological properties while addressing the urgent need for more effective fibromyalgia treatments [18].

2. MATERIALS AND METHODS

2.1 Identifying Similar Compounds [19]

To find potential candidates for treating fibromyalgia, we used the Drug Rep website to locate compounds similar in structure to carvedilol. By entering carvedilol's chemical structure, we produced a list of 20 compounds that share similar pharmacological characteristics. We chose these compounds based on their structural likeness to carvedilol, taking into account functional groups, molecular size, and physical-chemical properties. These compounds were then analyzed further through molecular docking to assess their potential as viable drug candidates for fibromyalgia.

2.2 Selecting Target Proteins [20]

For this study, we focused on Human Serum Albumin (HSA) as our target protein due to its essential role in binding and distributing drugs in the body. HSA is a major protein in human blood circulation, responsible for transporting various substances such as medications, hormones, fatty acids, and other metabolites. We selected HSA because it significantly impacts a drug's pharmacokinetics, influencing its bioavailability and overall effectiveness. HSA also binds to various compounds, including beta-blockers like carvedilol, which can modify their pharmacodynamic properties. Because of its broad presence and interaction with numerous drugs, HSA was deemed a relevant target for evaluating the binding potential of carvedilol and similar compounds.

2.3 Repurposing of Compound [21]

1. Disease and Drug Selection:
   Disease: Fibromyalgia
   FDA-approved Drug: Duloxetine (for fibromyalgia treatment)
2. Identifying Similar Compounds:
   We identified 20 compounds similar to duloxetine using a drug repurposing website.

3. Target Protein Identification and Refinement:
   Chose Human Serum Albumin (HSA) as the target protein, important for drug binding and distribution.
   Refined and validated the HSA structure using PDB-REDO for fit results.
4. Molecular Docking:
   Docked the 20 compounds against the refined HSA structure using CB-Dock 2 to predict binding strength.
5. Best Compound Selection:
   The compound with the best docking results was carvedilol, displaying the strongest binding to HSA.

2.4 Protein Refinement and Validation [22]

To ensure the 3D structure of HSA was reliable for our docking simulations, we refined and validated it using PDB ReDO, which enhances the quality of protein models stored in the Protein Data Bank (PDB). The refinement involved correcting issues like missing atoms or inconsistencies, along with ensuring proper atomic arrangements. Post-refinement, we validated the model by examining its stereochemistry, bond angles, and torsion angles to ensure biological relevance and computational accuracy. The finalized structure of HSA was then prepared for docking studies to analyze the binding affinity of carvedilol and the 20 similar compounds.

2.5 Molecular Docking [23]

Molecular docking simulations were conducted with CB-Dock 2, a robust tool for predicting how small molecules bind to target proteins. The procedure started with preparing the HSA structure, which then served as the receptor for docking studies. The 20 selected compounds, including carvedilol, were docked into HSA's binding site to assess their potential interactions. This involved generating multiple poses for each compound and evaluating binding energies and interactions with key amino acids in the target protein. Results were ranked based on docking scores and binding affinities, allowing us to identify the most promising compound for further exploration. Carvedilol stood out as the most favorable candidate, demonstrating strong binding affinity and a positive interaction profile with HSA, making it the focus of further evaluation in the study.

2.6 ADME and Toxicity Analysis [24]

To evaluate the pharmacokinetic properties and safety of carvedilol as a possible fibromyalgia treatment, we utilized ADMET Lab 2.0 for predicting its ADME (Absorption, Distribution, Metabolism, and Excretion) characteristics. This tool models the pharmacokinetics of small molecules based on their chemical structure. We estimated parameters like oral bioavailability, solubility, permeability, and metabolic stability to see how well carvedilol could be.

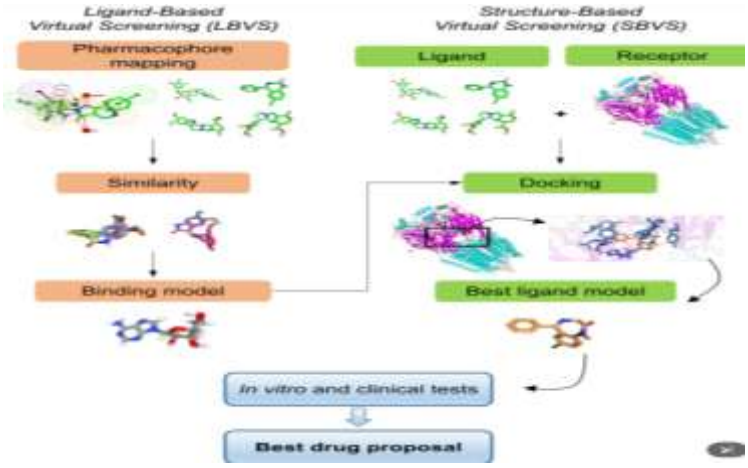

Figure 1. Schematic of ligand-based virtual screening, where input ligands are aligned using various algorithms and searched against diverse drug libraries, with results sorted and visualized

3. RESULT AND DISCUSSION

3.1 Results of ligand-based drug repurposing :

Table 1: Justification for selecting duloxetine as the primary ligand for designing new agent treating fibromyalgia :

Justification	Description
Established Efficacy	Duloxetine is well-documented in treating fibromyalgia, showing significant pain relief and improved quality of life, making it a solid foundation for exploring similar compounds.
Mechanism of Action	As a serotonin-norepinephrine reuptake inhibitor (SNRI), duloxetine helps balance serotonin and norepinephrine levels. This balance is crucial for managing pain and mood, which are key in fibromyalgia symptoms.
Existing Safety Profile	Duloxetine has undergone extensive clinical trials, proving its safety and tolerability, which lowers the risks associated with developing new analogues.
Pharmacological Insights	By studying duloxetine's ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties, we gain essential knowledge that can inform the design of new agents with better profiles.
Opportunity for Improvement	While duloxetine is effective, it's not a one-size-fits-all solution and can cause side effects. This emphasizes the necessity for analogues that

	maintain effectiveness while reducing unwanted effects.
Potential for Synergistic Effects	New analogues could be crafted to boost therapeutic benefits by targeting multiple pain management pathways, potentially leading to multi-target treatments.
Structural Basis for Design	The chemical structure of duloxetine serves as a model for rational drug design, allowing for methodical modification to enhance pharmacological attributes.
Ligand-Based Drug Repurposing	Duloxetine acts as a benchmark for drug repurposing, aiding in finding similar compounds with established actions effective for treating fibromyalgia.

3.2 Docking studies and Validation process results:

Table 2: Validation metrics from PDB-REDO

Metric	Original	PDB-REDO
Crystallographic Refinement		
R	0.1960	0.1661
R-free	0.2503	0.2147
Bond Length RMS Z-score	0.962	0.440
Bond Angle RMS Z-score	0.962	0.651
Model Quality Raw Scores		
Ramachandran Plot Normality	3	21
Rotamer Normality	9	33
Coarse Packing	95	98
Fine Packing	59	83
Bump Severity	29	33
Hydrogen Bond Satisfaction	20	30

By lowering the R-factor from 0.1960 to 0.1661 and the R-free from 0.2503 to 0.2147, the PDB-REDO refinement has really enhanced the structure and aligned it more closely with the experimental data. This process ensures better geometric accuracy by reducing the deviations in bond lengths and angles.The increase in rotamer normality from 9 to 33 and Ramachandran normality from 3 to 21 shows that the side-chain and backbone conformations have improved, leading to a higher quality model. Structural stability has also been bolstered by better hydrogen bond satisfaction, which rose from 20 to 30, and improved packing quality, with coarse packing going from 95 to 98 and fine packing from 59 to 83.When you look at the overall enhancements, the slight rise in bump severity from 29 to 33 is pretty minor. Overall, the structure provided by PDB-REDO is clearly more refined.

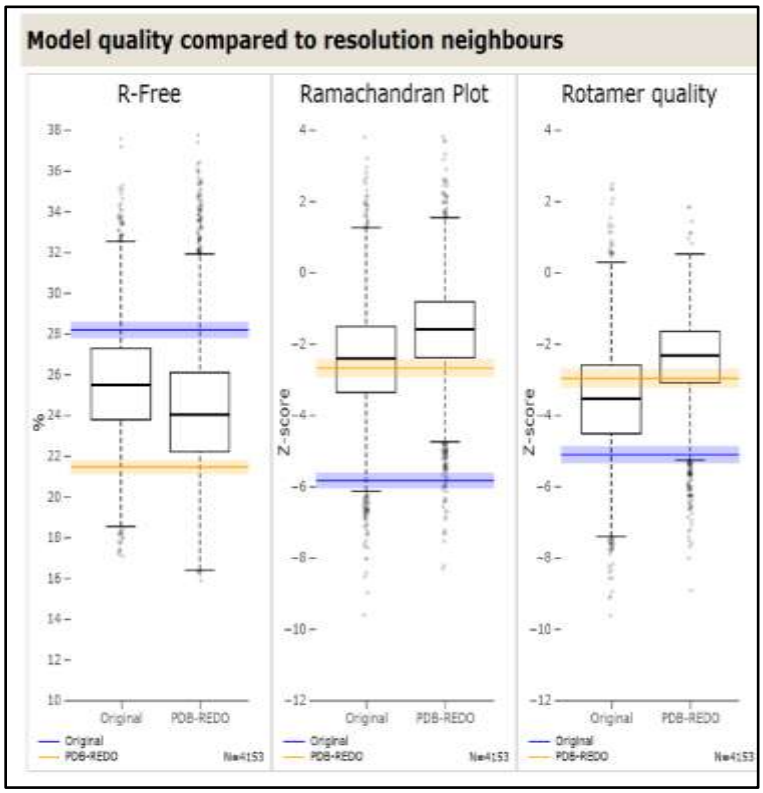

Figure 2: Comparison of R-Free Values Between Original and PDB- REDO Models

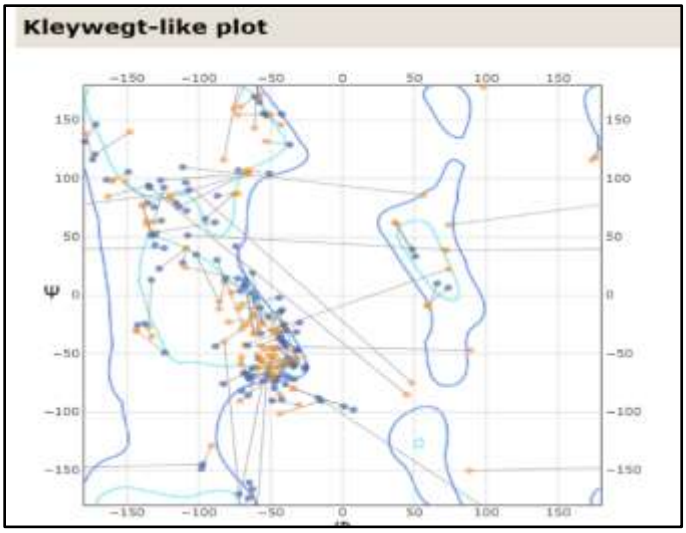

Figure 3: Ramachandran Plot Analysis

The Kleywegt-like plot provides a visual representation of the ϕ (phi) and ψ (psi) dihedral angles that make up the backbone conformations of proteins. It compares two models: the original, marked by orange dots, and the refined structures, shown with blue dots from PDB-REDO. The contour lines in blue illustrate the regions where certain angles are allowed or not, based on Ramachandran distributions. You'll notice

gray lines connecting corresponding residues between the two models, which highlight the shifts in dihedral angles. The refined structure, represented in blue, has fewer outliers, indicating better backbone geometry and a closer alignment with the expected conformations.

This plot effectively showcases the structural enhancements in the PDB-REDO model, which reduces Ramachandran outliers and boosts the overall quality of the model

3.3 Results of Ligand –Based Screening using the DrugRep platform:

Table 3: Binding scores and target interaction of various compounds

Rank	Compound (ID name)	Score	Rank	Compound (ID-name)	Score
1	DB00476 Duloxetine	0.984	11	DB01151 desipramine	0.326
2	DB00289 Atomoxetine	0.516	12	DB01136 carvedilol	0.325
3	DB00571 propranolol	0.427	13	DB00934 maprotiline	0.361
4	DB0047 fluoxetine	0.420	14	DB00555 tolnaftate	0.321
5	DB01012 cinacalcet	0.384	15	DB11160 phenyltoloxamine	0.311
6	DB00735 nafitifine	0.376	16	DB00857 terbinafine	0.302
7	DB00344 protriptyline	0.356	17	DB07776 flavone	0.229
8	DB01091 butenafine	0.351	18	DB01182 propafenone	0.298
9	DB06711 naphazoline	0.337	19	DB00985 dimenhydrinate	0.297
10	DB00540 nortriptyliene	0.326	20	DB13219-Medifoxamine	0.297

3.4 Docking results:

Table 4: Binding Affinity Analysis of Drug Bank Compounds to Target Pockets: Identification of Potential Drug Candidates:

Drug bank ID	pocket	score	Chain	Drug bank ID	Pocket	score	Chain
DB00476	C1	-7.4	A	DB01151	C4	-8.1	A
DB00289	C1	-7.7	A	DB01136	C5	-8.9	A
DB00571	C2	-7.7	A, B	DB00934	C5	-8.9	A
DB00472	C2	-8.8	A, B	DB00525	C1	-8.8	A
DB01012	C2	-10.3	A, B	DB11160	C1	-7.8	A
DB00735	C2	-9.2	A, B	DB00857	C2	-8.9	A, B
DB00344	C5	-8.2	A	DB00776	C2	-8.9	A,B
DB01091	C5	-9.2	A	DB01182	C2	8.9	A, B
DB06711	C3	-7.6	B	DB000985	C1	-8.3	A
DB00540	C2	-8.6	A B	DB13219	C2	-7.7	A, B

The data shows that Pocket C2 and C5 are frequently associated with several drugs, suggesting they are key targets for these compounds. Chain A is the most common interaction site, appearing in every entry, while Chain B is less frequent. The binding scores range from -7.4 to -10.3, with the lowest score observed for DB01012 (C2) at -10.3, indicating strong binding affinity. Other notable drugs with high binding affinities include DB01091 (C5) and DB01136 (C5), both with scores of -9.2. Overall, higher affinity drugs like DB01012, DB01091, and DB01136 may be promising candidates for furtherstudy.

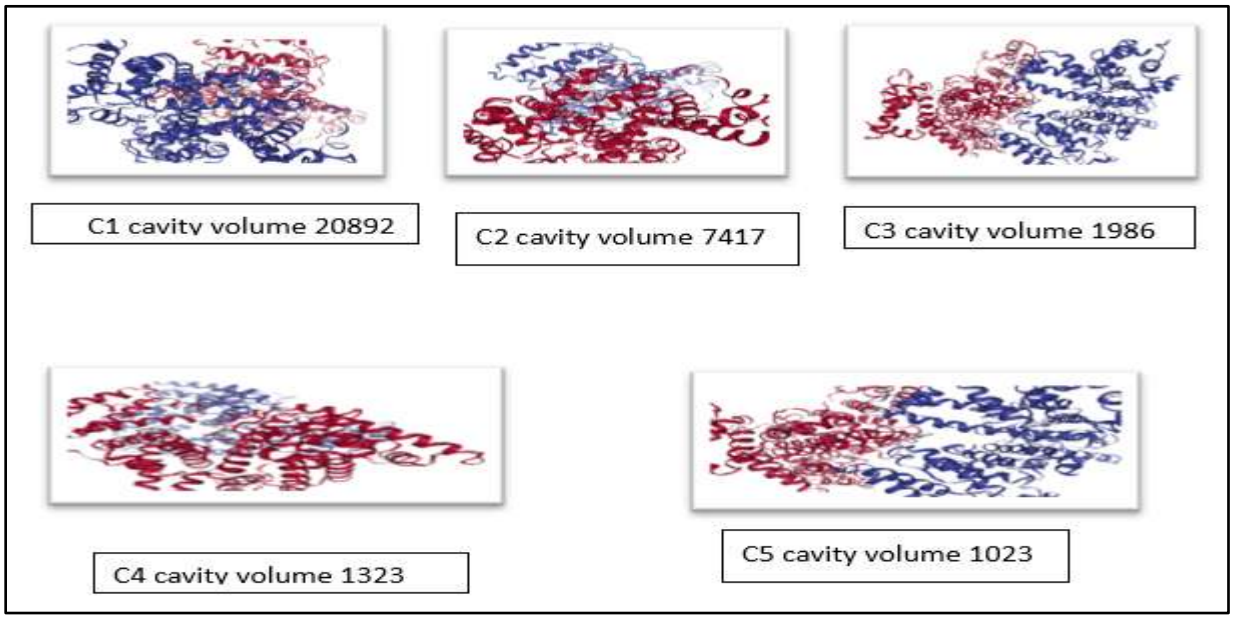

Figure 4: Visualisation of Five Binding Pocket (Curpocket Id C1-C5) On Target Protein

The picture shows five protein shapes (C1–C5) with spaces inside them ranging from 1023 cubic Å to 7417 cubic Å. C2, with the biggest space (7417cubic Å), suggests it can bind with larger things or be flexible in interactions. C1 (cubic 20892Å) has a medium space, showing it can bind with things of moderate size. C3 (1986 cubic Å), C4 (1323 cubic Å), and C5 (1023 cubic Å) have smaller spaces, which means they bind with smaller, more specific things. These space sizes are important to know for seeing how proteins interact with other molecules, and can help in creating drugs where different-sized molecules may target these spaces for health benefits.

CONCLUSION

The ligand-based screening conducted with the DrugRep platform uncovered several promising drug candidates based on their binding scores and interactions with targets.Duloxetine (DB00476) topped the list with a score of 0.984, followed by atomoxetine at 0.516 and propranolol at 0.427, indicating strong interactions with the targets.

When we analyzed the binding affinity, it became clear that Pocket C2 and C5 are crucial binding sites, often linked to various drugs, highlighting their significance as target areas.Chain A serves as the main interaction site, while Chain B is less

commonly involved. Among the compounds we screened, DB01012 (cinacalcet) exhibited the strongest binding affinity at -10.3 in Pocket C2, followed by DB01091 at -9.2 in Pocket C5, and DB01136 at -8.9 in Pocket C5.These compounds, with their higher binding affinities, could be excellent candidates for further explorationin drug development and design.

REFERENCES

1. Brown N. The'I'in fibromyalgia: the construction of academic identity under the influence of fibromyalgia. University of Kent (United Kingdom); 2020. DOI:10.22024/UniKent/01.02.47661
2. Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative review: the pathophysiology of fibromyalgia. Annals of internal medicine. 2007 May 15;146(10):726-34. https://doi.org/10.7326/0003-4819-146-10-200705150-00006
3. Allely CS. Pain sensitivity and observer perception of pain in individuals with autistic spectrum disorder. The Scientific World Journal. 2013;2013(1):916178. https://doi.org/10.1155/2013/916178
4. Slim M, Calandre EP, Rico-Villademoros F. An insight into the gastrointestinal component of fibromyalgia: clinical manifestations and potential underlying mechanisms. Rheumatology international. 2015 Mar;35:433-44. https://doi.org/10.1007/s00296-014-3109-9
5. Hallberg LR, Carlsson SG. Coping with fibromyalgia: a qualitative study. Scandinavian journal of caring sciences. 2000 Mar;14(1):29-36. https://doi.org/10.1111/j.1471-6712.2000.tb00558.x
6. Kwekkeboom KL, Cherwin CH, Lee JW, Wanta B. Mind-body treatments for the pain-fatigue-sleep disturbance symptom cluster in persons with cancer. Journal of pain and symptom management. 2010 Jan 1;39(1):126-38. https://doi.org/10.1016/j.jpainsymman.2009.05.022
7. Van Rensburg R, Reuter H. An overview of analgesics-anticonvulsants, antidepressants, and other medications (Part 3). South African Family Practice. 2019 May 1;61(3):59-62. https://hdl.handle.net/10520/EJC-175897d736
8. Bonilla-Jaime H, Sánchez-Salcedo JA, Estevez-Cabrera MM, Molina-Jiménez T, Cortes-Altamirano JL, Alfaro-Rodríguez A. Depression and pain: use of antidepressants. Current neuropharmacology. 2022 Feb 1;20(2):384-402. DOI: https://doi.org/10.2174/1570159X19666210609161447
9. Pound P, Britten N, Morgan M, Yardley L, Pope C, Daker-White G, Campbell R. Resisting medicines: a synthesis of qualitative studies of medicine taking. Social science & medicine. 2005 Jul 1;61(1):133-55.https://doi.org/10.1016/j.socscimed.2004.11.063

10. Maffei ME. Fibromyalgia: recent advances in diagnosis, classification, pharmacotherapy and alternative remedies. International journal of molecular sciences. 2020 Oct 23;21(21):7877. https://doi.org/10.3390/ijms21217877
11. Penney LS, Ritenbaugh C, DeBar LL, Elder C, Deyo RA. Provider and patient perspectives on opioids and alternative treatments for managing chronic pain: a qualitative study. BMC Family Practice. 2016 Dec;17:1-5. https://doi.org/10.1186/s12875-016-0566-0
12. Kazdin AE. Evidence-based treatment and practice: new opportunities to bridge clinical research and practice, enhance the knowledge base, and improve patient care. American psychologist. 2008 Apr;63(3):146. https://doi.org/10.1037/0003-066X.63.3.146
13. Demain S, Goncalves AC, Areia C, Oliveira R, Marcos AJ, Marques A, Parmar R, Hunt K. Living with, managing and minimising treatment burden in long term conditions: a systematic review of qualitative research. PloS one. 2015 May 29;10(5):e0125457. https://doi.org/10.1371/journal.pone.0125457
14. Neumann PJ, Sandberg EA, Bell CM, Stone PW, Chapman RH. Are Pharmaceuticals Cost-Effective? A Review of The Evidence: Do drug treatments give value for the money? Careful analysis can yield useful information, this study finds. Health affairs. 2000 Mar;19(2):92-109.https://doi.org/10.1377/hlthaff.19.2.92
15. A Eltabeeb M, Rabe Hamed R, A El-Nabarawi M, H Teaima M, M Abdellatif M. Recent Advances of β-blockers as drug repurposing approach: a systematic review. Bulletin of Pharmaceutical Sciences Assiut University. 2024 Dec 1;47(2):681-98. DOI: 10.21608/bfsa.2024.283788.2091
16. Satapathy T, Sahu D, Sahu H, Pandey RK, Shukla SS, Gidwani B. Trends on Nanomedicines as Novel therapeutics Approach in Targeting Nociceptors for Relieving Pain. Current Drug Targets. 2024 Sep;25(12):796-818. DOI: https://doi.org/10.2174/0113894501315521240725065617
17. Krum H, Sackner-Bernstein JD, Goldsmith RL, Kukin ML, Schwartz B, Penn J, Medina N, Yushak M, Horn E, Katz SD, Levin HR. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. Circulation. 1995 Sep 15;92(6):1499-506. https://doi.org/10.1161/01.CIR.92.6.1499
18. Parmar MB. *Repositioning Opportunities for Antidiabetic and Cardiovascular Drugs with Reference to Pharmacovigilance* (Doctoral dissertation, Institute of Pharmacy, Nirma University,

A'bad).http://10.1.7.192:80/jspui/handle/123456789/10281

19. Gan JH, Liu JX, Liu Y, Chen SW, Dai WT, Xiao ZX, Cao Y. DrugRep: an automatic virtual screening server for drug repurposing. Acta Pharmacologica Sinica. 2023 Apr;44(4):888-96. https://doi.org/10.1038/s41401-022-00996-2
20. Brenner SE. Target selection for structural genomics. nature structural biology. 2000 Nov;7(11):967-9. https://doi.org/10.1038/80747
21. McCabe B, Liberante F, Mills KI. Repurposing medicinal compounds for blood cancer treatment. Annals of hematology. 2015 Aug;94:1267-76. https://doi.org/10.1007/s00277-015-2412-1
22. Levin EJ, Kondrashov DA, Wesenberg GE, Phillips GN. Ensemble refinement of protein crystal structures: validation and application. Structure. 2007 Sep 11;15(9):1040-52. DOI: 10.1016/j.str.2007.06.019
23. Fan J, Fu A, Zhang L. Progress in molecular docking. Quantitative Biology. 2019 Jun;7:83-9. https://doi.org/10.1007/s40484-019-0172-y
24. Han Y, Zhang J, Hu CQ, Zhang X, Ma B, Zhang P. In silico ADME and toxicity prediction of ceftazidime and its impurities. Frontiers in pharmacology. 2019 Apr 24;10:434. https://doi.org/10.3389/fphar.2019.00434

HOW TO CITE THIS ARTICLE

Vaishnavi Alloli*, Aparna Kakad, Neha Chavan, Ankita Dhere, Shivtej Devane, Ishwari Nimbalkar, Babaso Udugade: Repurposing of carvedilol, a beta-antagonist, against selective serotonin and norepinephrine reuptake inhibitors for fibromyalgia. International Journal of Institutional Pharmacy and Life Sciences, Vol 15[2] March-April 2025 : 39-50.