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Research Article

SYSTEMS, CLINICAL IMPLICATIONS, AND FUTURE DIRECTIONS IN DRUG TOLERANCE AND RECEPTOR DESENSITIZATION

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ABSTRACT

The drug desensitization and tolerance are critical issues of long-term pharmacotherapy when the decreased drug efficacy requires higher dosages, causing safety and clinical problems. This review examines the mechanisms of receptor desensitization, such as GPCR phosphorylation, internalization and degradation through proteasomal and lysosomal pathways. Pharmacodynamic, pharmacokinetic, and behavioral types of drug tolerance are examined, as well as important receptor systems, including the μ-opioid, β-adrenergic, dopamine and serotonergic receptors. Such clinical implications as therapeutic failure, dose escalation, and cross-tolerance are mentioned. The mitigating strategies to tolerance are intermittent dosing, biased agonist, combination therapy, and downstream signaling. There are some recent developments like 2-arrestin-biased ligands, CRISPR/Cas9 gene editing and pharmacogenomic profiling which show some promising information on personalized medicine. The comprehension of these mechanisms of adaptation is important in order to optimize therapeutic regimens particularly in chronic pain, psychiatric and cardiovascular practice. This piece of work reinforces the idea of conducting translational studies and applying new methods that could enhance the responsiveness of drugs, reduce their resistance, and increase patient outcomes.

Keywords :- Drug Tolerance, Receptor Desensitization, Pharmacodynamics, GPCR Regulation, Pharmacogenomics.

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INTRODUCTION

The most important pharmacological phenomena are desensitization and drug tolerance, in which the effect of a drug on the body reduces with time as the drug is administered [1–3]. Desensitization is when there is a lowered cell or receptor-based response following repeated stimulation, usually by receptor down regulation or signal pathway damping. The concept of drug tolerance on the other hand is a clinical phenomenon that tends to require more doses of a drug to produce the same therapeutic effect as the same drug used to produce [4–6]. These two processes may be induced by pharmacodynamic or pharmacokinetic processes and are important in the perception of drug efficacy and safety with long-term use. Desensitization and tolerance are fundamental ideas in clinical pharmacology that can be used to maximize the effectiveness of therapeutic treatment and reduce adverse effects [6,7]. This knowledge assists clinicians to modify dosing schedules, avoid overdose and treatment failure in long term therapy. Drug tolerance was first noted in the circumstances of opioid and alcohol abuse, with repeated consumption, resulting in the weakening of the effect, which then led to higher doses.

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The molecular mechanism of desensitization was studied overtime particularly that of G-protein-coupled receptors (GPCRs) and ion channels. Initial pharmacological researchers such as Paul Ehrlich formulated theory on receptor interactions and adaptive mechanisms. The important concepts at this point are receptor internalization, signal transduction attenuation, enzyme induction, and homeostatic feedback that now define our current knowledge of how the body adapts to the continuous exposure to drugs [8].

Types of Drug Tolerance

Pharmacodynamics tolerance is a condition that results in reduced responsiveness of the body target sites of a drug (usually receptors) following repeated exposure [9,10]. Among the major ones is receptor downregulation (2.1.1), which involves a reduction in the amount of receptors on the cell surface, which decreases drug binding and subsequent effect. This is usually seen in the use of opioids as constant stimulation causes a decrease in analgesic action. The other mechanism is signal transduction (2.1.2) whereby intracellular pathways by which drugs act are altered or disturbed. As an example, when the affinity of a drug to bind G-protein-coupled receptors is unaltered, the desensitization of the receptor pathway can greatly decrease the activity of the drug [11–13].

Pharmacokinetic Tolerance

In pharmacokinetic tolerance the body begins to develop greater efficiency in metabolic or excretion of the drug thus leading to reduced amounts reaching the point of action [14–18]. Of importance here is enzyme induction and drug metabolism (2.2.1) - repeated administration of some drugs stimulates liver enzymes (e.g. CYP450) increasing metabolism and decreasing plasma levels. Also, there may be a contribution by altered drug distribution and clearance (2.2.2) in which alteration in plasma protein binding, tissue storage or renal elimination alters drug bioavailability resulting in reduced therapeutic response with time.

Learned and Behavioral Tolerance.

Behavioral and learned tolerance is the modification of behavior or the environment to the effects of a drug and this is usually not dependent on biochemical modification. Conditioned responses (2.3.1) are those cases when people are taught to fight the drugs with their behavior or expectation, particularly in the case of such substances as alcohol or benzodiazepines [19–21]. Tolerance (2.3.2) is also modified by environmental modulation, so that tolerant conditions can occur and result in adaptive physiological responses that minimize the effect of the drug, or intolerant conditions can occur and result in hyperirritability that is highly observed during the study of psychoactive drugs and addiction [22–25].

Internalization and Recycling of Receptors.

After phosphorylation, a large number of receptors are internalized in endocytic pathways that are well-characterized. In the case of G-protein-coupled receptors (GPCRs), the endocytosis pathways (3.2.1) play the role of regulating the availability of the receptors in the cell surface. It is an internalization by way of clathrin-coated pits and is assisted by 2 -arrestins and clathrin (3.2.2), which bind to phosphorylated receptors and promote their internalization into the cell. After internalization, the receptors can be recycled to the plasma membrane to be used again or can be degraded according to the situations of the cell and the period of stimulation. When the duration of receptor desensitization is long, the cell can lead the receptors to form degradation pathways. The massively used process is the ubiquitination and proteasomal degradation (3.3.1), in which receptors are labeled with ubiquitin molecules, and transported to the proteasome, where they are broken down [26]. Alternatively, the receptors can be internalised into lysosomes and degraded (3.3.2) especially when receptor stimulation is prolonged. This receptor depletion results in the long term down-regulation of receptors, which leaves cells less sensitive to subsequent stimulation, a serious cause of drug tolerance.

Receptors that are discussed as Common in Tolerance.

The opioid receptors, the μ-opioid receptor (MOR) is one of the most clinically relevant receptors in drug tolerance (4.1.1). Chronic MOR stimulation by morphine or fentanyl causes a phosphorylation of receptors, recruitment of 8 -arrestin, and internalization and this ultimately suppressed analgesic efficacy- a classic example of receptor desensitization [27,28]. This leads to tolerance in chronic pain management (4.1.2) where the doses must be reinforced to continue pain relief and predisposes dependence and overdose [29–31].

B-Adrenergic Receptors

The most essential pharmacotherapy of cardiovascular activity is the involvement of β-adrenergic receptors (especially β1 and β2). Receptor desensitization and internalization will occur with continuous exposure to either 8-agonists, or 8-blockers [32]. Long-term use has significant implications on the cardiovascular system (4.2.1) because it may lower the effectiveness of drugs used to treat hypertension, arrhythmias, and heart failure since decreased receptor responsiveness will reduce treatment efficacy, requiring a change in dose or rotation to a different drug [32–34].

Dopamine Receptors

The receptors of dopamine particularly D2-like receptors play a key role in the emergence of antipsychotics and dopaminergic drug tolerance. Chronic D2 receptor blockade can result in receptor upregulation or signal transduction alterations in antipsychotic therapy (4.3.1) and result in diminished drug response and side effects exacerbation. Conversely, in Parkinson disease (4.3.2), after a long period of use of the dopaminergic, such as levodopa, motor fluctuations and diminished effect occur as the receptor desensitize and the neural adaptation takes place [35–38].

Nicotinic and Serotonergic Receptors.

Nicotinic acetylcholine receptors (nAChRs) become quickly desensitized to repetitive nicotine stimulation, which is one factor that causes nicotine tolerance to tobacco use (4.4.1)[39]. This receptor adaptation is the basis of the increasing nicotine doses with time and it is a fundamental mechanism in addiction [40,41]. Likewise, serotonergic receptors, especially 5-HT1A receptors, become desensitized to the chronic application of selective serotonin reuptake inhibitors (SSRIs) (4.4.2), which not only slows the onset of therapy but is also required to sustain long-term antidepressant effects[37,41,42].

Clinical Implication of Drug Tolerance.

The most acute clinical effects of drug tolerance can be seen in the form of therapeutic efficacy loss in the long-run. This is most evident in the case of chronic opioid and benzodiazepine use (5.1.1) in which patients repeatedly report a decrease in effects despite their continued use. Tolerance to analgesia or anxiolytic responses does not only decrease the quality of life of patients but may be a source of misuse or overuse. In a similar way, the desensitization of receptors to long-term salbutamol therapy of asthma (5.1.2) may occur, leading to decreased bronchodilatory activity and heightened asthma exacerbation [43].

Need for Dose Escalation

In a bid to counter the diminished drug effect, clinicians usually respond by increasing the dose which is very dangerous. These include the risks of toxicity and dependence (5.2.1), particularly in those with a narrow spectrum of activity, or with the potential to cause addiction, including opioids and tranquillisers[44]. Moreover, there is also the issue of economic and safety issues (5.2.2) such as more expensive healthcare due to the increased drug use, frequent checks, as well as the possibility of adverse events, which complicates and makes long-term treatment quite expensive[45–47].

Cross-Tolerance and Substitution of Drugs.

The other clinical issue is the cross-tolerance whereby tolerance to one drug decreases the responsiveness of other drugs having the same mechanism of action [48,49]. This is commonly discussed by opioid rotation (5.3.1) in which patients receive another form of opioid in order to restore analgesic effect because of an incomplete cross-tolerance. Such strategies should however be managed well. In more general therapeutic situations, cross-tolerance may confound polypharmacy (5.3.2) where various drugs engage with each other pharmacodynamically to diminish the overall effect of treatment and complicate the process of care management [50–52].

Desensitization strategies can be defeated through the use of strategies.

The introduction of drug holidays or intermittent dosing is one of the most widely used methods in order to avoid desensitization. This approach is a temporary withdrawal of a drug to help receptor systems to reset down and make them potentially sensitive to drugs again [53]. It is especially useful in drugs such as dopaminergic agents in Parkinson, or psychostimulants in ADHD, where the effect is reduced with a persistent exposure to the drug. Prudent dosage pauses would decrease the occurrence of tolerance and postpone dose increase [54].

Biased Agonists and Partial Agonist.

A second possible solution is biased agonist/partial agonist which activate advantageous signaling pathways without stimulating agensitization-inducing pathways [55–59]. As an illustration, biased μ-opioid receptor agonists may also induce analgesia by stimulating the activity of 5-hydrotryptophan without recruiting β-arrestinto a great extent to limit tolerance and side effects. Buprenorphine, used to treat opioid dependence, is an example of a partial agonist that can generate different levels of receptor activation, as well as maintain a therapeutic level without causing quick receptor desensitization [60–62].

The analysis of the downstream effects involves several different targets, which are detailed below.

Other strategies attempt to influence downstream effectors within the signaling cascade as opposed to acting on the receptor level. These interventions do not use desensitized receptors but rather regulate intracellular pathways or transcriptional reactions [63]. As an illustration, a protein kinase or second messenger inhibitor can maintain drug activity when the receptors become unresponsive. This method is

especially applicable in complicated diseases such as cancer or neurodegeneration, in which several signaling axes can be considered [64,65].

New Developments and Research Notes.

One of the most recent advances in receptor pharmacology is the generation of so-called 2arrestin-biased ligands, able to selectively activate the receptor signaling without activating the pathways that result in desensitization and internalization.[66-70] The ligands are capable of selectively activating G-protein signaling and reducing recruitment of 2 -arrestin, thereby maintaining therapeutic activity and decreasing tolerance and side effects. This principle has been investigated in opioid medicine especially using new μ-opioid receptor ligands that minimize respiratory depression and dependence potential.

Table 1: Types of Drug Tolerance

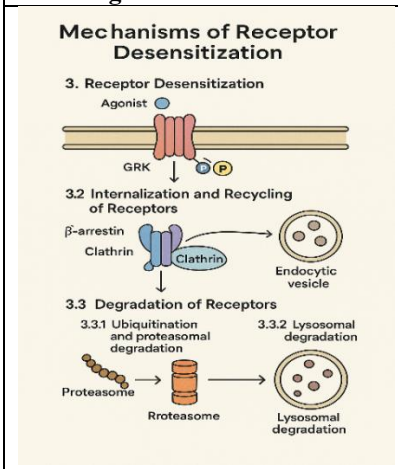
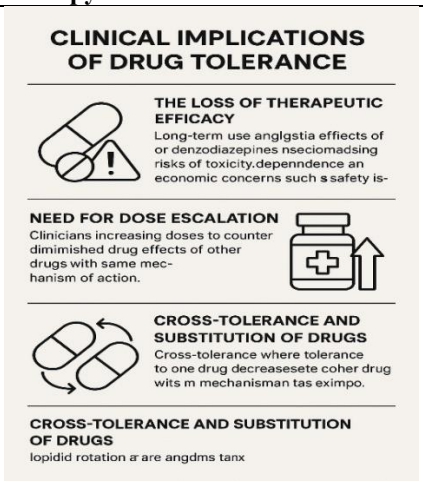
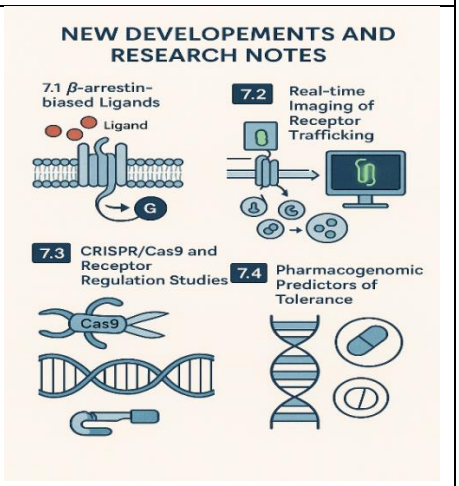
Type of Tolerance	Mechanism	Examples
Pharmacodynamic	Changes at the receptor level such as downregulation or altered signaling	Opioids, benzodiazepines
Pharmacokinetic	Increased metabolism or elimination due to enzyme induction or distribution	Barbiturates, alcohol
Behavioral/Learned	Psychological or environmental adaptations that reduce drug impact	Alcohol tolerance in familiar settings

Table 2: Receptors Involved in Drug Tolerance and Clinical Implications (N = 75)

Receptor Type	Drug Class	Mechanism of Tolerance	Clinical Implication
μ-Opioid Receptor (MOR)	Opioids	Desensitization via β-	Reduced analgesia; need for dose escalation
β-Adrenergic Receptor	β-blockers/β-agonists	Receptor downregulation and uncoupling	Decreased effect in heart failure/asthma
Dopamine D2 Receptor	Antipsychotics	Signal alteration or receptor adaptation	Motor side effects; reduced therapeutic response
Nicotinic Acetylcholine Receptor	Nicotine	Rapid desensitization and internalization	Tolerance in smoking; addiction potential
Serotonin 5-HT1A Receptor	SSRIs	Desensitization with chronic use	Delayed antidepressant response

Table 3: Strategies to Overcome Drug Desensitization and Tolerance

Strategy	Mechanism	Example/Use
Drug Holidays / Intermittent Dosing	Allows receptor systems to recover sensitivity	ADHD meds, Parkinson's therapy
Biased or Partial Agonists	Selectively activate pathways that reduce tolerance	Buprenorphine for opioid dependence
Combination/Add-on Therapy	Target multiple pathways; reduce overload on one receptor	NMDA antagonists with opioids
Targeting Downstream Effectors	Modulate intracellular signaling beyond receptor level	Protein kinase inhibitors in cancer
Pharmacogenomic	Tailor therapy based on genetic profile	Genotype-guided dosing in psychiatry

Figure1: Molecular Pathways of Receptor Desensitization and Downregulation	Figure2: Key Clinical Consequences of Drug Tolerance in Long-Term Therapy	Figure3: Emerging Innovations in Receptor Desensitization and Drug Tolerance Research
		

CONCLUSION

Knowledge of the mechanisms of desensitization and drug tolerance presents important information on the mechanisms of molecular behavior of receptors and the problem of pharmacotherapy in the long-term perspective. Central processes that include receptor phosphorylation, internalization and downregulation, especially of G-protein-coupled receptors (GPCRs), mediate the reduced activity that is apparent with chronic drug use. Such processes lead to not only the loss of responsiveness, but also to important molecular targets of therapeutic intervention. The clinical impacts of drug tolerance have immense implications particularly in the treatment of chronic diseases including pain, asthma, cardiovascular disease, and psychiatric disorders. Dose escalation, greater susceptibility to side effects and difficult.

Management of patients due to potential cross-tolerance and drug interactions are required in tolerance. These effects must be known to clinicians in order to maximize long term treatment, observe therapeutic windows, and tailor treatment plans to maximize efficacy and minimize harm. Future research on the area is set to take advantage of the theoretical developments in molecular biology, imaging, and pharmacogenomics. To develop drugs that maintain therapeutic efficacy and avoid desensitization, there is scientific evidence supporting the development of biased agonism, receptor trafficking and gene-editing technologies like CRISPR/Cas9. Moreover, the application of pharmacogenomics data in regular care can potentially provide a possibility to predict and prevent tolerance on a personal basis. The future development of these innovative strategies will play the crucial role in eliminating the shortcomings of existing pharmacotherapies and improve patient outcomes in chronic cases of drug treatments.

REFERENCES

1. Anghel SA, Dinu-Pirvu C-E, Costache M-A, Voiculescu AM, Ghica MV, Anuța V, (2024). Receptor pharmacogenomics: Deciphering genetic influence on drug response. *IJMS*, 25, 9371.
2. Thompson MD, Reiner-Link D, Berghella A, Rana BK, Rovati GE, Capra V, (2024). G protein-coupled receptor (GPCR) pharmacogenomics. *Critical Reviews in Clinical Laboratory Sciences*, 61, 641–684.
3. Chen Q, Tesmer JJG. (2022). G protein-coupled receptor interactions with arrestins and GPCR kinases: The unresolved issue of signal bias. *Journal of Biological Chemistry*, 298, 102279.
4. Debonis J, Veiseh O, Igoshin OA. (2024). Uncovering the interleukin-12 pharmacokinetic desensitization mechanism and its consequences with mathematical modeling. *CPT Pharmacometrics & Systems Pharmacology*, 14, 217–228.
5. Yang Y, Feng YH, Chao S, Li Z, Xue J, Zhang J, (2022). Improved pharmacodynamics of epidermal growth factor via microneedles-based self-powered transcutaneous electrical stimulation. *Nature Communications*, 13, 6908.
6. Kang S-Y, Seo J, Kang H-R. (2022). Desensitization for the prevention of drug hypersensitivity reactions. *Korean Journal of Internal Medicine*, 37, 261–270.

7. Laubach S, Kim EH, Greenhawt M, Bailey S, Anagnostou A. (2024). A review of shared decision-making, published protocols, and post-desensitization strategies in oral immunotherapy (OIT). *Current Allergy and Asthma Reports*, 24, 173–197.
8. Conflitti P, Lyman E, Sansom MSP, Hildebrand PW, Gutiérrez-De-Terán H, Carloni P, (2025). Functional dynamics of G protein-coupled receptors reveal new routes for drug discovery. *Nature Reviews Drug Discovery*, 24, 251–275.
9. Armani S, Geier A, Forst T, Merle U, Alpers DH, Lunnon MW. (2024). Effect of changes in metabolic enzymes and transporters on drug metabolism in the context of liver disease: Impact on pharmacokinetics and drug-drug interactions. *British Journal of Clinical Pharmacology*, 90, 942–958.
10. Pintori N, Miliano C, Mostallino R, Castelli MP, Di Chiara G, Pistis M, (2021). Repeated exposure to JWH-018 induces adaptive changes in the mesolimbic and mesocortical dopaminergic pathways, glial cells alterations, and behavioural correlates. *British Journal of Pharmacology*, 178, 3476–3497.
11. Kise R, Inoue A. (2024). GPCR signaling bias: An emerging framework for opioid drug development. *The Journal of Biochemistry*, 175, 367–376.
12. Sun N, Kim K-M. (2021). Mechanistic diversity involved in the desensitization of G protein-coupled receptors. *Archives of Pharmacal Research*, 44, 342–353.
13. Zhang L, Zhang J-T, Hang L, Liu T. (2020). Mu opioid receptor heterodimers emerge as novel therapeutic targets: Recent progress and future perspective. *Frontiers in Pharmacology*, 11, 1078.
14. Wu Y, Jensen N, Rossner MJ, Wehr MC. (2024). Exploiting cell-based assays to accelerate drug development for G protein-coupled receptors. *IJMS*, 25, 5474.
15. Zhang M, Chen T, Lu X, Lan X, Chen Z, Lu S. (2024). G protein-coupled receptors (GPCRs): Advances in structures, mechanisms and drug discovery. *Signal Transduction and Targeted Therapy*, 9, Article number not provided.
16. Zhao J, Wei K, Jiang P, Chang C, Xu L, Xu L, (2022). G-protein-coupled receptors in rheumatoid arthritis: Recent insights into mechanisms and functional roles. *Frontiers in Immunology*, 13, 907733.
17. Ayoub MA, Vijayan R. (2021). Hemorphins targeting G protein-coupled receptors. *Pharmaceuticals*, 14, 225.
18. Patwardhan A, Cheng N, Trejo J. (2020). Post-translational modifications of G protein-coupled receptors control cellular signaling dynamics in space and time. *Pharmacological Reviews*, 73, 120–151.
19. Wu K, Kwon SH, Zhou X, Fuller C, Wang X, Vadgama J, (2024). Overcoming challenges in small-molecule drug bioavailability: A review of key factors and approaches. *IJMS*, 25, 13121.
20. Dvořáčková E, Slanař O, Matoulek M, Pilková A, Hartinger JM. (2024). Bioavailability of orally administered drugs after bariatric surgery. *Current Obesity Reports*, 13, 141–153.
21. Dubovsky SL, Marshall D. (2022). Benzodiazepines remain important therapeutic options in psychiatric practice. *Psychotherapy and Psychosomatics*, 91, 307–334.
22. Osyntseva A. (2022). Polydrug addiction: Multidisciplinary forensic and pharmaceutical, organizational and legal, and technological study of factors of formation and development. *SSPMPM*, 2, 1–14.
23. Rauschert C, Kraus L, Möckl J, Olderbak S, Wilms N, Seitz N-N. (2022). The use of psychoactive substances in Germany. *Deutsches Ärzteblatt International*, 119, 527–534.
24. Kanno M, Hiramatsu S, Kondo S, Tanimoto H, Ichinose T. (2021). Voluntary intake of psychoactive substances is regulated by the dopamine receptor Dop1R1 in Drosophila. *Scientific Reports*, 11, Article number not provided.
25. María-Ríos CE, Morrow JD. (2020). Mechanisms of shared vulnerability to post-traumatic stress disorder and substance use disorders. *Frontiers in Behavioral Neuroscience*, 14, 6.
26. Carroll EC, Marqusee S, Martin A, Greene ER. (2020). Site-specific ubiquitination affects protein energetics and proteasomal degradation. *Nature Chemical Biology*, 16, 866–875.
27. Zhou J, Ma R, Jin Y, Fang J, Du J, Shao X, et al. (2021). Molecular mechanisms of opioid tolerance: From opioid receptors to inflammatory mediators (Review). *Experimental and Therapeutic Medicine*, 22, Article number not provided.
28. Faouzi A, Varga BR, Majumdar S. (2020). Biased opioid ligands. *Molecules*, 25, 4257.
29. Rangari VA, O'Brien ES, Powers AS, Slivicki RA, Bertels Z, Appourchaux K, (2025). A cryptic pocket in CB1 drives peripheral and functional selectivity. *Nature*, 640, 265–273.
30. Coluzzi F, Rullo L, Scerpa MS, Losapio LM, Rocco M, Billeci D, (2022). Current and future therapeutic options in pain management: Multi-mechanistic opioids involving both MOR and NOP receptor activation. *CNS Drugs*, 36, 617–632.
31. Fürst S, Al-Khrasani M, Spetea M, Galambos AR, Schmidhammer H, Romualdi P, (2020). On the role of peripheral sensory and gut mu opioid receptors: Peripheral analgesia and tolerance. *Molecules*, 25, 2473.
32. Mahmood A, Ahmed K, Zhang Y. (2022). B-Adrenergic receptor desensitization/down-regulation in heart failure: A friend or foe? *Frontiers in Cardiovascular Medicine*, 9, 925692.

33. Weerasinghe DK, AzimiManavi B, Williams LJ, Samarasinghe RM, Pasco JA, Hodge JM. (2023). Antipsychotic-induced bone loss: The role of dopamine, serotonin and adrenergic receptor signalling. *Frontiers in Cell and Developmental Biology*, 11, 1184550.
34. Sun X, Jiang W, Lu Y, Yuan H, Zhou M, Wu J, (2020). Paroxetine attenuates cardiac hypertrophy via blocking GRK2 and ADRB1 interaction in hypertension. *JAHA*, 10, Article number not provided.
35. Pifl C, Wolf A, Elevado M, Scholze P. (2025). A7-Nicotinic acetylcholine receptor and mutated α-synuclein interact in motor behaviour and nigrostriatal dopamine-findings with potential relevance for a protective effect of cigarette smoking and Parkinson's disease. *European Journal of Neuroscience*, 61, 1–11.
36. Soares ÉN, Tizabi Y, Costa SL, Da Silva VDA, Ferrolho GDJ, Costa ACDS, (2024). Nicotinic acetylcholine receptors in glial cells as molecular target for Parkinson's disease. *Cells*, 13, 474.
37. Arias HR, Targowska-Duda KM, García-Colunga J, Ortells MO. (2021). Is the antidepressant activity of selective serotonin reuptake inhibitors mediated by nicotinic acetylcholine receptors? *Molecules*, 26, 2149.
38. Gonzalez-Latapi P, Fox SH, Bhowmick SS, Saranza G. (2020). Non-dopaminergic treatments for motor control in Parkinson's disease: An update. *CNS Drugs*, 34, 1025–1044.
39. Tiwari RK, Sharma V, Pandey RK, Shukla SS. (2020). Nicotine addiction: Neurobiology and mechanism. *Journal of Pharmacopuncture*, 23, 1–7.
40. Tseilikman VE, Lipatov IA, Novak J, Shatilov VA, Yegorov ON, Aristov MR, (2024). Unraveling the serotonergic mechanism of stress-related anxiety: Focus on co-treatment with resveratrol and selective serotonin reuptake inhibitors. *Biomedicines*, 12, 2455.
41. Ruiz-Santiago C, Rodríguez-Pinacho CV, Pérez-Sánchez G, Acosta-Cruz E. (2024). Effects of selective serotonin reuptake inhibitors on endocrine system (Review). *Biomedical Reports*, 21, Article number not provided.
42. Thom RP, Alexander JL, Slaby A, Garakani A, Gross L, Sumner CR, (2021). Selective serotonin reuptake inhibitors: How long is long enough? *Journal of Psychiatric Practice*, 27, 361–371.
43. Botsula I, Schavikin J, Heinämäki J, Laidmäe I, Mazur M, Raal A, (2024). Application of nanofiber-based drug delivery systems in improving anxiolytic effect of new 1,2,3-triazolo-1,4-benzodiazepine derivatives. *European Journal of Pharmaceutical Sciences*, 195, 106712.
44. Wilkinson A, Woodcock A. (2021). The environmental impact of inhalers for asthma: A green challenge and a golden opportunity. *British Journal of Clinical Pharmacology*, 88, 3016–3022.
45. Kacha-Ochana A, Robbins RS, Guy GP, Green JL, Jones CM, Dunphy C,. (2022). Characteristics of adults aged ≥18 years evaluated for substance use and treatment planning - United States, 2019. *MMWR Morbidity and Mortality Weekly Report*, 71, 749–756.
46. Peterson C, Li M, Xu L, Mikosz CA, Luo F. (2021). Assessment of annual cost of substance use disorder in US hospitals. *JAMA Network Open*, 4, e210242.
47. Coffin PO, Rowe C, Oman N, Sinchek K, Santos G-M, Faul M, (2020). Illicit opioid use following changes in opioids prescribed for chronic non-cancer pain. *PLoS ONE*, 15, e0232538.
48. Wang X, Li Z, Hu L, Yue L, Bao C. (2022). Side effects of opioids are ameliorated by regulating TRPV1 receptors. *IJERPH*, 19, 2387.
49. Khan F, Mehan A. (2021). Addressing opioid tolerance and opioid-induced hypersensitivity: Recent developments and future therapeutic strategies. *Pharmacology Research & Perspectives*, 9, Article number not provided.
50. Stolfo D, Iacoviello M, Chioncel O, Anker MS, Bayes-Genis A, Braunschweig F, et al. (2025). How to handle polypharmacy in heart failure. A clinical consensus statement of the Heart Failure Association of the ESC. *European Journal of Heart Failure*, 27, 747–759.
51. Alsanosi SM, Padmanabhan S. (2024). Potential applications of artificial intelligence (AI) in managing polypharmacy in Saudi Arabia: A narrative review. *Healthcare*, 12, 788.
52. Kurczewska-Michalak M, Lewek P, Jankowska-Polańska B, Giardini A, Granata N, Maffoni M, (2021). Polypharmacy management in older adults: A scoping review of available interventions. *Frontiers in Pharmacology*, 12, 734045.
53. Pozzi M, Bertella S, Gatti E, Peeters GGAM, Carnovale C, Zambrano S, et al. (2020). Emerging drugs for the treatment of attention-deficit hyperactivity disorder (ADHD). *Expert Opinion on Emerging Drugs*, 25, 395–407.
54. Newman AH, Ku T, Jordan CJ, Bonifazi A, Xi Z-X. (2021). New drugs, old targets: Tweaking the dopamine system to treat psychostimulant use disorders. *Annual Review of Pharmacology and Toxicology*, 61, 609–628.
55. Santino F, Gentilucci L. (2023). Design of κ-opioid receptor agonists for the development of potential treatments of pain with reduced side effects. *Molecules*, 28, 346.
56. Kelly E, Conibear A, Henderson G. (2022). Biased agonism: Lessons from studies of opioid receptor agonists. *Annual Review of Pharmacology and Toxicology*, 63, 491–515.
57. Miyano K, Takahashi H, Nonaka M, Komatsu A, Ono H, Uezono Y, (2021). Oxytocin is a positive allosteric modulator of κ-opioid receptors but not δ-opioid receptors in the G protein signaling pathway. *Cells*, 10, 2651.

58. He L, Gooding SW, Lewis E, Felth LC, Gaur A, Whistler JL. (2021). Pharmacological and genetic manipulations at the μ-opioid receptor reveal arrestin-3 engagement limits analgesic tolerance and does not exacerbate respiratory depression in mice. *Neuropsychopharmacology*, 46, 2241–2249.
59. Kelly B, Torella R, Warmus JS, Aydin D, Hollingsworth SA, Swain NA, (2021). Delineating the ligand-receptor interactions that lead to biased signaling at the μ-opioid receptor. *Journal of Chemical Information and Modeling*, 61, 3696–3707.
60. Giravi HY, Biskupiak Z, Tyler LS, Bulaj G. (2022). Adjunct digital interventions improve opioid-based pain management: Impact of virtual reality and mobile applications on patient-centered pharmacy care. *Frontiers in Digital Health*, 4, Article number not provided.
61. Hale M, Raffa RB, Garofoli M. (2021). Benefit-risk analysis of buprenorphine for pain management. *JPR*, 14, 1359–1369.
62. Robbins JL, Gregg J, Englander H. (2021). Buprenorphine microdose induction for the management of prescription opioid dependence. *Journal of the American Board of Family Medicine*, 34, S141–S146.
63. Poluri KM. (2020). Molecular insights into kinase mediated signaling pathways of chemokines and their cognate G protein coupled receptors. *Frontiers in Bioscience*, 25, 1361–1385.
64. Bitsina C, Einstein O, Michailidou I, Boziki M, Bakirtzis C, Kesidou E, (2024). The role of amino acid metabolism in neurodegenerative diseases. *GPD*, 3, 3294.
65. Gledhill LJ, Babey A-M. (2021). Synthesis of the mechanisms of opioid tolerance: Do we still say NO? *Cellular and Molecular Neurobiology*, 41, 927–948.
66. Kong X, Li T, Yang H. (2024). AAV-mediated gene therapies by miniature gene editing tools. *Science China Life Sciences*, 67, 2540–2553.
67. Ambrósio CE, Mariano CG, de Oliveira VC. (2024). Gene editing in small and large animals for translational medicine: A review. *Animal Reproduction*, 21, Article number not provided.
68. Cardi T, Yıldırım K, Hensel G, Bruegmann T, Nicolia A, Bull SE, (2023). CRISPR/Cas-mediated plant genome editing: Outstanding challenges a decade after implementation. *Trends in Plant Science*, 28, 1144–1165.
69. Richardson C, Kelsh RN, Richardson RJ. (2023). New advances in CRISPR/Cas-mediated precise gene-editing techniques. *Disease Models & Mechanisms*, 16, Article number not provided.
70. Belshaw N, Hopes A, Aram L, Gal A, Grouneva I, Mock T. (2022). Efficient gene replacement by CRISPR/Cas-mediated homologous recombination in the model diatom *Thalassiosira pseudonana*. *New Phytologist*, 238, 438–452.

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