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Molecular mechanisms of action (MOA) of some selected drug classes

Sunday Olajide Awofisayo[1], Precious Joshua Edem [2], Elijah Asuquo Ekong ,[3] Gbola Olayiwola[4]

1. Department of Clinical Pharmacy and Biopharmacy, Faculty of Pharmacy, University of Uyo, Uyo, Nigeria
2. Department of Microbiology, Faculty of Biological Sciences, University of Uyo, Uyo, Nigeria
3. Quality Assurance Department, Bioscientifics Research and Development, LtdGte, Aba Road, Ikot Ekpene, Nigeria
4. Department of Clinical Pharmacy and Pharmacy Administration, Faculty of Pharmacy, Obafemi Awolowo, University, Ile-Ife, Nigeria

Correspondence:
Sunay O. Awofisayo
Department of Clinical Pharmacy and Biopharmacy, Faculty of Pharmacy, Box 4257, University of Uyo, Uyo, Nigeria. Email: sundayawofisayo@uniuyo.edu.ng; bioscird69@gmail.com Phone: +234-8037947338

ABSTRACT

Understanding the molecular mechanism of action (MOA) of drug classes is fundamental to pharmacology, therapeutics, and drug development. This review provides a comprehensive overview of the molecular and cellular mechanisms by which major classes of drugs exert their effects. It explores how drugs interact with biological targets such as receptors, enzymes, ion channels, and transporters to modulate physiological processes and produce therapeutic outcomes. The keywords and Boolean operators used in the search included "mechanism of action" AND "drug classes", "pharmacodynamics" OR "MOA" AND "therapeutic agents", "antibiotics", "antivirals", "antifungals", "analgesics", "antidepressants", "antihypertensives", and "drug mechanism" AND "clinical pharmacology". Publications were within the years 2020 -2025. Key drug classes discussed include analgesics, antibiotics, antihypertensives, antidepressants, antineoplastics, and more, with emphasis on both classical mechanisms and emerging insights from recent research. The review also highlights the clinical relevance of MOA knowledge in guiding drug selection, predicting therapeutic responses, and anticipating adverse effects. By

KEYWORDS: Therapeutic agents, Antibiotics, Clinical pharmacology, Drug classes, Cellular mechanisms

INTRODUCTION

Understanding the mechanism of action (MOA) of drug classes is a cornerstone of pharmacology and therapeutics. The MOA refers to the specific biochemical interaction through which a drug produces its pharmacological effect. This typically involves binding to a molecular target such as a receptor, enzyme, ion channel, or nucleic acid and modulating its activity to alter a physiological process [1]. By elucidating these interactions, researchers and clinicians can better predict therapeutic outcomes, optimize drug selection, and anticipate adverse effects.

Drug classes are typically grouped based on shared structural features, target sites, or pharmacodynamic properties. Each class operates via a characteristic MOA that defines its clinical utility. For instance, beta-blockers exert their effects by antagonizing beta-adrenergic receptors, leading to reduced cardiac output and blood pressure, while antibiotics like penicillins inhibit bacterial cell wall synthesis by targeting penicillin-binding proteins. These fundamental differences underscore the importance of class-specific mechanisms in guiding clinical application and drug development [2].

Recent advances in molecular biology, structural bioinformatics, and high-throughput screening have greatly expanded our understanding of how drugs interact with their targets at the atomic level. This has not only facilitated the discovery of novel agents but also enabled the repurposing of existing drugs and the development of precision medicine approaches tailored to individual patients' genetic profiles [3].

This review provides a comprehensive overview of the mechanisms of action of major drug classes, highlighting the molecular targets, signal transduction pathways, and therapeutic implications associated with each. By integrating classical pharmacological principles with contemporary scientific insights, this work aims to serve as a reference for students, researchers, and healthcare professionals seeking a deeper understanding of drug function at the mechanistic level.

Method

This review was conducted using a structured, narrative approach to compile and synthesize current knowledge on the mechanisms of action of major drug classes. The methodology involved a comprehensive literature search, selection of relevant publications, and critical evaluation of findings.

Literature search strategy

A systematic search was performed using electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, covering literature published up to May, 2025. Keywords and Boolean operators used in the search included:"mechanism of action" AND "drug classes", "pharmacodynamics" OR "MOA" AND "therapeutic agents", "antibiotics", "antivirals", "antifungals","analgesics","antidepressants","anti hypertensives",and"drug mechanism" AND "clinical pharmacology".

Inclusion and exclusion criteria

Publications were included if they provided detailed descriptions of the mechanisms of action of one or more drug classes. Similarly considered were peer-reviewed articles, reviews, and authoritative pharmacology textbooks published in English. Excluded were articles focusing solely on pharmacokinetics without MOA discussion. Case reports or anecdotal studies without mechanistic insights alongside non-English publications and preprints not peer-reviewed.

Data extraction and synthesis

Key data were extracted from selected sources, including the molecular targets of drug classes, downstream biochemical pathways, cellular or systemic effects, and clinical implications. Information was grouped and categorized by therapeutic class, such as antimicrobials, cardiovascular drugs, central nervous system agents, and anticancer drugs. Mechanisms were described at the molecular, cellular, and systemic levels, where appropriate, with emphasis on clinically relevant targets such as receptors, enzymes, ion channels, and

transporters. Where applicable, known resistance or tolerance mechanisms or pathway redundancies were also noted that provide context for drug efficacy and limitations.

Quality assessment

To ensure reliability, priority was given to high-impact review articles, recent pharmacology textbooks, and clinical guidelines. Conflicting information was resolved through cross-referencing with authoritative sources, and consensus viewpoints were emphasized.

Results and Discussion

Antibiotics

Beta-lactams

These include penicillins, cephalosporins, carbapenems, and monobactams. They inhibit bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs), disrupting peptidoglycan cross-linking. β-lactam antibiotics, a class that encompasses penicillins, cephalosporins, carbapenems, and monobactams, exert their potent antibacterial effects through a precise and highly targeted mechanism that disrupts the integrity of the bacterial cell wall which is a critical structural component essential for bacterial survival, particularly in Gram-positive and Gram-negative organisms. These agents are unified by the presence of a highly reactive β-lactam ring, which is central to their mechanism of action.

At the core of their bactericidal activity lies the ability to inhibit bacterial cell wall synthesis, specifically by interfering with the final stages of peptidoglycan biosynthesis [4]. The peptidoglycan layer is a rigid, mesh-like polymer composed of linear chains of alternating N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) residues, which are cross-linked by short peptide bridges [5]. This complex structure provides mechanical strength and osmotic protection to the bacterial cell. β-lactams act by covalently binding to and inactivating penicillin-binding proteins (PBPs) a group of essential bacterial enzymes that catalyze the cross-linking of the peptidoglycan chains via transpeptidation and transglycosylation reactions [6]. These PBPs are located in the bacterial cytoplasmic membrane and are so named because they were initially identified by their ability to bind radiolabeled penicillin.

When a β-lactam antibiotic binds irreversibly to the active site of a PBP, it forms a stable acyl-enzyme complex that blocks the enzyme's catalytic activity. This inhibition prevents the formation of cross-links between the peptidoglycan strands, thereby compromising the structural integrity of the cell wall. As a result, the bacterial cell becomes increasingly susceptible to osmotic lysis due to the internal turgor pressure that the weakened cell wall can no longer withstand [7]. Moreover, the accumulation of cell wall precursors and incomplete peptidoglycan fragments may trigger the activation of autolytic enzymes, such as a utolysins and murein

In summary, β-lactam antibiotics eliminate susceptible bacteria by sabotaging the fundamental architecture of their protective cell walls through the inactivation of the PBPs, culminating in cell lysis and death. This elegant mechanism underscores both their clinical effectiveness and the ongoing need to understand and overcome bacterial resistance

Macrolides

Macrolides inhibit bacterial protein synthesis by binding to ribosomal subunit, blocking translocation [9]. Macrolides exert their antibacterial effect by specifically targeting bacterial protein synthesis. Their action is centered on the bacterial ribosome, a complex molecular machine responsible for translating messenger RNA (mRNA) into functional proteins. The bacterial ribosome is composed of two subunits: the 30S (small) subunit, which decodes the mRNA, and the 50S (large) subunit, which catalyzes peptide bond formation and provides an exit tunnel for the nascent polypeptide chain.

This class of drugs are characterized structurally by a large macrocyclic lactone ring which are typically 14 to 16 atoms in size decorated with deoxy sugar residues such as desosamine and cladinose [10]. These structural features are critical for the antibiotic's interaction with the ribosome. The primary binding site for macrolides is located within the 50S ribosomal subunit, specifically in a region of the 23S ribosomal RNA (rRNA) known as domain V [11]. Within this domain lies the nascent peptide exit tunnel (NPET), a conduit through which the newly synthesized polypeptide chain must pass as it emerges from the ribosome [12].

Upon binding to the NPET, macrolides occupy a position adjacent to the peptidyl transferase center (PTC), the enzymatic core of the ribosome responsible for forming peptide bonds [13]. The interaction is stabilized through multiple non-covalent forces, including hydrogen bonding and hydrophobic contacts with key nucleotides of the 23S rRNA. Of particular importance is the adenine residue at position 2058 (A2058, in *E. coli* numbering), which plays a central role in anchoring the macrolide molecule within the exit tunnel [14].

Unlike antibiotics such as chloramphenicol, which directly inhibit peptide bond formation, macrolides do not interfere with the catalytic activity of the peptidyl transferase center itself. Rather, they block the elongation of the polypeptide chain by physically obstructing its passage through the exit tunnel. This steric hindrance prevents proper translocation, a key step in which the ribosome shifts along the mRNA to allow the entry of a new aminoacyl-tRNA into the A site [14]. As a result, the ribosome stalls on the mRNA template, leading to premature termination of translation and an overall inhibition of protein synthesis.

Interestingly, the inhibitory effect of macrolides can be context-dependent. That is, the degree of ribosomal stalling and translational arrest may vary depending on the sequence of the nascent peptide and the structure of the macrolide itself. In some cases, specific amino acid sequences enhance the likelihood of ribosome stalling when a macrolide is bound, illustrating a nuanced interplay between the antibiotic, the ribosome, and the emerging peptide [16].

Macrolides are typically bacteriostatic, meaning they suppress bacterial growth without directly killing the cells. However, under certain conditions such as high drug concentrations or in specific bacterial species they can exhibit bactericidal activity. Importantly, macrolides demonstrate a high degree of selectivity for bacterial ribosomes over eukaryotic ones. This selectivity arises from structural differences between prokaryotic and eukaryotic ribosomes, particularly at the macrolide [17].

As a result, macrolides prevent the progression of translation by inhibiting the translocation step the movement of the ribosome along the messenger RNA (mRNA) after a peptide bond has formed. This prevents the addition of further amino acids to the growing polypeptide chain. Interestingly, recent research has shown that this inhibition can be context-specific: macrolides can cause ribosomes to stall at specific amino acid sequences, depending on the nature of the nascent peptide and the conformation of the ribosome. This selective inhibition means that not all proteins are equally affected, leading to nuanced and often organism-specific effects on bacterial protein synthesis.

Macrolides are particularly effective against Gram-positive bacteria and several atypical pathogens, including *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, and *Legionella pneumophila*. Their effectiveness against Gram-negative bacteria is generally limited due to the outer membrane barrier and the presence of efflux pumps that reduce intracellular drug concentration. Additionally, mutations in the 23S rRNA or in ribosomal proteins L4 and L22 can

alter ribosomal conformation in ways that reduce macrolide binding. In rare cases, macrolides can be inactivated by bacterial enzymes through hydrolysis or phosphorylation [18].

Their excellent tissue penetration, including into phagocytes and other immune cells, enhances their efficacy against intracellular pathogens. Macrolides also have notable anti-inflammatory and immunomodulatory properties, which contribute to their use in certain non-infectious inflammatory conditions.

To address resistance, newer macrolide derivatives such as ketolides have been developed. Ketolides, like telithromycin, have modifications that improve their binding affinity and efficacy even in the presence of methylated rRNA. They also tend to have dual binding interactions within the ribosome, making them more resilient to resistance mechanisms.

Fluoroquinolones

Fluoroquinolones are a potent class of broad-spectrum antibiotics whose molecular mode of action centers on the inhibition of bacterial DNA replication and transcription. They exert their bactericidal effects by targeting two essential bacterial enzymes: DNA gyrase and topoisomerase IV [19]. These enzymes are members of the type II topoisomerase family and play critical roles in maintaining the topology of bacterial DNA during replication and cell division. DNA in bacterial cells is tightly coiled and supercoiled. For replication and transcription to proceed, this supercoiling must be dynamically modulated. DNA gyrase, which is particularly important in Gram-negative bacteria, introduces negative supercoils into DNA using the energy from ATP hydrolysis. This process relieves the torsional strain that builds up ahead of replication forks. Topoisomerase IV, which is especially important in Gram-positive organisms, is primarily involved in decatenation the separation of interlinked daughter DNA molecules following replication.

Fluoroquinolones, such as ciprofloxacin, levofloxacin, and moxifloxacin, work by stabilizing the transient DNA-enzyme complex that is formed during the normal catalytic cycle of these topoisomerases. Under normal circumstances, these enzymes cut both strands of DNA, pass another segment of the double helix through the break, and then re-ligate the DNA to restore its integrity. Fluoroquinolones bind at the interface of the DNA and the enzyme, effectively "freezing" this complex in its cleaved state [20].

This stabilization of the DNA cleavage complex leads to the accumulation of double-stranded breaks in the bacterial chromosome. These breaks are highly toxic because they cannot be easily repaired, especially given the concurrent inhibition of replication forks and the interference with cell division. The persistence of these unrepaired breaks eventually triggers cell death, making fluoroquinolones bactericidal rather than merely bacteriostatic.

At the molecular level, fluoroquinolones interact with conserved amino acid residues and magnesium ions within the catalytic core of the topoisomerase enzymes. The presence of a fluorine atom at position 6 of the quinolone core increases the compound's lipophilicity and enhances its ability to penetrate bacterial cells and bind its target with high affinity. The carboxyl and ketone groups on the quinolone ring are involved in chelating the divalent metal ions necessary for enzyme function and binding to the DNA-enzyme complex. The relative importance of DNA gyrase versus topoisomerase IV as the primary target varies between bacterial species. In *Escherichia coli* and other Gram-negative organisms, DNA gyrase is the main target. In contrast, in *Streptococcus pneumoniae* and other Gram-positive organisms, topoisomerase IV tends to be the more critical enzyme for fluoroquinolone activity. This dual targeting contributes to the broad spectrum and potency of fluoroquinolone **[21].** Despite their effectiveness, resistance to fluoroquinolones has become increasingly common. Resistance mechanisms primarily include point mutations in the quinolone resistance-determining regions

(QRDRs) of the genes encoding DNA gyrase (gyrA and gyrB) and topoisomerase IV (parC and parE). These mutations reduce the binding affinity of fluoroquinolones to their targets. Additionally, efflux pumps can actively expel the drug from bacterial cells, and plasmid-mediated resistance mechanisms (e.g., qnr proteins) can protect DNA gyrase from fluoroquinolone binding [22].

In summary, fluoroquinolones kill bacteria by inhibiting DNA gyrase and topoisomerase IV, enzymes essential for DNA replication and chromosome segregation. They act by stabilizing a normally transient enzyme-DNA complex, resulting in lethal double-stranded DNA breaks. Their precise targeting and bactericidal activity have made them essential in the treatment of a wide range of infections, though growing resistance poses a significant clinical challenge [23].These drugs inhibit DNA gyrase and topoisomerase IV, enzymes critical for bacterial DNA replication and transcription [24].

Antihypertensives

Angiotensin converting enzyme (ACE) inhibitors

Angiotensin Converting Enzyme (ACE) inhibitors are a widely used class of medications that function by interfering with the body's renin–angiotensin–aldosterone system (RAAS), a critical regulator of blood pressure, fluid balance, and vascular tone. At the molecular level, ACE inhibitors exert their effects by blocking the activity of the angiotensin-converting enzyme, a

key zinc-dependent metalloprotease found predominantly on the surface of endothelial cells, especially in the lungs [25].

ACE plays two primary roles in the RAAS pathway. First, it converts angiotensin I, an inactive decapeptide, into angiotensin II, an octapeptide that is a potent vasoconstrictor and stimulator of aldosterone secretion. Angiotensin II raises blood pressure by constricting blood vessels, increasing sodium and water retention through aldosterone, and enhancing sympathetic nervous activity. Second, ACE also degrades bradykinin, a peptide that normally acts as a vasodilator by promoting the release of nitric oxide and prostaglandins from the endothelium [26].

ACE inhibitors, such as captopril, enalapril, lisinopril, and ramipril, are designed to bind directly to the active site of the ACE enzyme. They mimic the natural substrate, angiotensin I, and occupy the catalytic site in a competitive manner. A defining feature of their molecular action is their interaction with a zinc ion located at the core of the ACE active site. This zinc ion is essential for the enzyme's catalytic function. ACE inhibitors typically possess functional groups—such as thiol, carboxyl, or phosphinyl moieties—that can chelate the zinc ion, thereby preventing the enzyme from converting angiotensin I to angiotensin II [27].

By blocking this enzymatic activity, ACE inhibitors reduce the production of angiotensin II, leading to a cascade of physiological effects. Vasoconstriction is diminished, resulting in lowered systemic vascular resistance and blood pressure. Aldosterone secretion is reduced, decreasing sodium and water reabsorption in the kidneys, which contributes to a decrease in blood volume. The reduction in angiotensin II also leads to less stimulation of the sympathetic nervous system and reduced oxidative stress and inflammation in the cardiovascular system. These effects are particularly beneficial in patients with hypertension, heart failure, or diabetic nephropathy [28].

An additional consequence of ACE inhibition is the accumulation of bradykinin, since its degradation is also suppressed. Elevated bradykinin levels further contribute to vasodilation and enhanced endothelial function by stimulating the production of nitric oxide and prostacyclin. While this effect adds to the antihypertensive and cardioprotective properties of ACE inhibitors, it also explains some of their common side effects. For example, increased bradykinin is thought to be responsible for the persistent dry cough experienced by some

patients, as well as the rare but potentially serious occurrence of angioedema [29].

Structurally, different ACE inhibitors vary in how they interact with the ACE enzyme, which influences their pharmacokinetics and potency. Captopril, for instance, contains a thiol group that binds strongly to the zinc ion and has a relatively short half-life, requiring multiple daily doses. In contrast, enalapril and lisinopril use carboxyl groups for zinc binding and have longer durations of action.

In summary, ACE inhibitors lower blood pressure and provide cardiovascular and renal protection by directly blocking the angiotensin-converting enzyme. This action reduces angiotensin II production, enhances bradykinin levels, and leads to vasodilation, decreased fluid retention, and reduced sympathetic activity. The molecular specificity of these drugs for the ACE active site particularly their interaction with the enzyme's catalytic zinc ion—is central to their therapeutic effectiveness [30].

Calcium channel blockers

Calcium channel blockers (CCBs) are a class of pharmacological agents that inhibit the influx of calcium ions (Ca^{2+}) through voltage-gated calcium channels, with a primary focus on the L-type calcium channels found in cardiac muscle, vascular smooth muscle, and nodal tissues. Calcium ions play a critical role in excitation-contraction coupling and signal transduction in excitable cells. By modulating the function of these ion channels, CCBs exert significant effects on vascular tone, myocardial contractility, and cardiac electrophysiology [31].

The L-type calcium channel, also known as Cav1.2, is a high-voltage-activated channel composed of several subunits, of which the α1C subunit forms the ion-conducting pore and contains the voltage-sensing domains. This subunit is organized into four homologous domains (I–IV), each containing six transmembrane segments (S1–S6). The fourth segment in each domain (S4) functions as a voltage sensor, responding to changes in membrane potential by undergoing conformational shifts that lead to channel opening.

When open, the channel permits the selective entry of extracellular calcium ions into the cytoplasm, a process crucial for initiating muscle contraction and propagating electrical signals [32].

Calcium channel blockers interfere with this process by binding to specific sites on the α1C subunit, thereby altering the channel's gating behavior. Importantly, CCBs do not physically occlude the pore like some other ion channel inhibitors. Instead, they function as allosteric modulators, stabilizing the channel in a non-conductive conformation, typically the inactivated state, or hindering the voltage-induced transitions that lead to opening. This results in a decreased probability that the channel will open during depolarization, thereby reducing the magnitude of calcium influx [33].

There are three major classes of calcium channel blockers, each with distinct binding characteristics and tissue selectivity. Dihydropyridines (e.g., amlodipine, nifedipine) preferentially target vascular smooth muscle and are potent vasodilators. Phenylalkylamines (e.g., verapamil) act primarily on cardiac myocytes and nodal tissue, while benzothiazepines (e.g., diltiazem) exert intermediate effects on both vascular and cardiac tissues [34]. The binding affinity of these drugs can be influenced by the state of the channel; for instance, verapamil and diltiazem exhibit use-dependent binding, meaning they bind more effectively to channels that open frequently or are held in depolarized states—a characteristic particularly relevant in fast-firing cardiac cells.

At the molecular level, inhibition of calcium influx leads to tissue-specific effects. In vascular smooth muscle, the reduction in intracellular calcium limits the activation of calmodulin and myosin light chain kinase (MLCK), enzymes essential for initiating contraction. The result is relaxation of the smooth muscle, vasodilation, and a

subsequent decrease in blood pressure. In cardiac myocytes, calcium influx through L-type channels during the plateau phase (phase 2) of the action potential triggers further calcium release from the sarcoplasmic reticulum—a process known as calcium-induced calcium release. By limiting this initial calcium entry, CCBs reduce the strength of myocardial contraction, resulting in a negative inotropic effect [34].

In nodal tissue, particularly the sinoatrial (SA) and atrioventricular (AV) nodes, calcium currents are responsible for the upstroke of the action potential

(phase 0). Inhibition of L-type calcium channels in these cells leads to a slowed rate of depolarization, reducing heart rate (a negative chronotropic effect) and delaying conduction through the AV node (a negative dromotropic effect). These effects make CCBs particularly useful in managing conditions such as supraventricular tachycardia and angina [35].

In summary, calcium channel blockers act at the molecular level by binding allosterically to L-type voltage-gated calcium channels, specifically targeting the α1C subunit. This binding alters the channel's voltage-dependent gating properties, reducing calcium influx into excitable cells. The downstream effects vasodilation, reduced cardiac contractility, and slowed nodal conduction form the basis of their clinical utility in treating hypertension, angina pectoris, and certain cardiac arrhythmias.

Beta-blockers

Beta blockers, also known as beta-adrenergic receptor antagonists, are a class of drugs that exert their effects by blocking the action of endogenous catecholamines primarily adrenaline (epinephrine) and noradrenaline (norepinephrine) on beta-adrenergic receptors. These receptors are part of the sympathetic nervous system and play a critical role in regulating cardiovascular function, including heart rate, contractility, and vascular tone [36].

There are three main types of beta-adrenergic receptors: β_1, β_2, and β_3**.** The β_1 receptors are primarily located in the heart and kidneys, while β_2 receptors are found predominantly in the lungs, vascular smooth muscle, liver, and skeletal muscle. β_3 receptors, though less well understood, are found in adipose tissue and are involved in lipolysis and thermogenesis. Most beta blockers used clinically target β_1 and β_2 receptors, though some are selective for β_1 (cardioselective), while others block both β_1 and β_2 receptors (non-selective).

At the molecular level, beta blockers act as competitive antagonists. They bind to the β-adrenergic receptors without activating them, thereby blocking the binding of catecholamines like adrenaline. This inhibition prevents the normal downstream signaling cascade mediated by the activation of the G-protein-coupled

receptor (GPCR) pathway. Under normal circumstances, stimulation of β_1 receptors in the heart activates the Gs protein, which in turn activates adenylate cyclase. This enzyme converts ATP to cyclic AMP (cAMP), which activates protein kinase A (PKA). PKA then phosphorylates various target proteins, including calcium channels, leading to increased intracellular calcium and, consequently, enhanced heart rate (positive chronotropy), increased contractility (positive inotropy), and faster conduction through the atrioventricular node (positive dromotropy) [37].

By blocking this pathway, beta blockers reduce the effects of sympathetic stimulation on the heart**.** This results in a decrease in heart rate, myocardial contractility, and cardiac output, thereby lowering blood pressure and reducing myocardial oxygen demand. These effects are particularly beneficial in conditions like hypertension, angina pectoris, myocardial infarction, arrhythmias, and chronic heart failure. In heart failure, long-term use of certain beta blockers (such as carvedilol, bisoprolol, and

metoprolol succinate) has been shown to improve survival by attenuating the harmful effects of chronic sympathetic overactivity on the heart [38].

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors are a widely prescribed class of antidepressant medications that work by modulating the levels of serotonin, a key neurotransmitter involved in mood regulation, anxiety, sleep, and appetite.

These drugs are used primarily in the treatment of major depressive disorder, anxiety disorders, obsessive-compulsive disorder, and other psychiatric conditions associated with dysregulation of serotonin signalling [39].

At the molecular level, SSRIs act on the serotonergic synapse, where neurons communicate using serotonin (5-hydroxytryptamine, or 5-HT). Under normal conditions, serotonin is released from the presynaptic neuron into the synaptic cleft in response to neuronal firing. It then binds to specific receptors on the postsynaptic membrane to exert its effects. Once the signal is transmitted, serotonin is typically reabsorbed by the serotonin transporter protein (SERT) located on the presynaptic neuron. This process, known as reuptake, terminates the action of serotonin and recycles it for future use [40].

SSRIs exert their therapeutic effect by selectively inhibiting the serotonin transporter (SERT). By blocking this transporter, SSRIs prevent the reuptake of serotonin back into the presynaptic neuron, thereby increasing the concentration of serotonin in the synaptic cleft. The elevated serotonin levels result in prolonged stimulation of postsynaptic serotonin receptors, which helps to enhance and stabilize mood over time. It is important to note that while SSRIs increase serotonin levels relatively quickly, their clinical effects typically take several weeks to manifest. This delay is thought to be due to downstream neuroadaptive changes in the brain, such as receptor desensitization, changes in gene expression, and enhanced neuroplasticity. For example, chronic SSRI use has been associated with increased expression of brain-derived neurotrophic factor (BDNF), which supports neuronal survival and synaptic remodeling, particularly in regions like the hippocampus that are affected in depression [41].

SSRIs are considered "selective" because they primarily target serotonin reuptake, with minimal effects on other neurotransmitters, such as norepinephrine or dopamine. This selectivity contributes to their relatively favorable side effect profile compared to older antidepressants like tricyclics or monoamine oxidase inhibitors (MAOIs), which affect multiple neurotransmitter systems.

However, because serotonin is involved in many physiological processes, SSRIs can still cause side effects. Common adverse effects include nausea, insomnia, sexual dysfunction, and gastrointestinal disturbances. In some individuals, especially at the beginning of treatment or during dose changes, SSRIs can increase anxiety or agitation. Rarely, they may contribute to serotonin syndrome, a potentially life-threatening condition resulting from excessive serotonergic activity, particularly when combined with other serotonergic agents.

Examples of commonly prescribed SSRIs include fluoxetine, sertraline, citalopram, escitalopram, paroxetine, and fluvoxamine. Although their mechanism of action is similar, these agents differ in terms of pharmacokinetics, side effect profiles, and specific indications, allowing clinicians to tailor treatment based on individual patient needs [42].

Tricyclic antidepressants (TCAs)

Tricyclic antidepressants (TCAs) are a class of psychotropic agents named for their characteristic chemical structure, which consists of three fused rings. Developed in the 1950s, TCAs were among the first pharmacological treatments for major depressive disorder. Although largely supplanted in clinical practice by newer antidepressants with improved safety profiles, TCAs remain therapeutically relevant,

particularly for treatment-resistant depression, chronic pain syndromes, and certain anxiety disorders [44].

At the molecular level, TCAs exert their primary antidepressant effect by inhibiting the reuptake of monoamine neurotransmitters, particularly norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT), from the synaptic cleft. This action is mediated by high-affinity binding to the presynaptic transporters responsible for the reuptake of these neurotransmitters—namely, the norepinephrine transporter (NET) and the serotonin transporter (SERT) [45].

By blocking NET and/or SERT, TCAs prevent the reabsorption of NE and 5-HT into the presynaptic neuron following their release into the synaptic cleft. The resulting elevation in extracellular concentrations of these monoamines enhances their postsynaptic signaling, which is believed to contribute to the antidepressant effect over time. Chronic elevation of monoamines leads to downstream adaptive changes, including receptor desensitization, gene expression modulation, and neurotrophic factor regulation, particularly the upregulation of brain-derived neurotrophic factor (BDNF). These neuroadaptive processes are thought to underlie the delayed onset of therapeutic effects observed with TCAs and other antidepressants [45]. In addition to their effects on monoamine transporters, TCAs interact with a variety of other molecular targets, contributing to their side effect profile [46]:

Muscarinic acetylcholine receptors (M1 blockade) causes anticholinergic effects such as dry mouth, blurred vision, constipation, urinary retention, and cognitive disturbances. Histamine H1 receptors antagonism results in sedation and weight gain. Similarly, alpha-1 adrenergic receptors blockade causes orthostatic hypotension and dizziness. The pharmacodynamics of individual TCAs vary depending on their relative affinity for SERT vs. NET. For instance, imipramine and amitriptyline show relatively balanced inhibition of both SERT and NET, whereas nortriptyline and desipramine preferentially inhibit NET. These differences can influence both efficacy and side effect profiles in clinical use [47].

From a pharmacokinetic standpoint, TCAs are lipophilic and well-absorbed, with high protein binding and extensive hepatic metabolism, primarily via cytochrome P450 enzymes (e.g., CYP2D6). Their metabolites may retain pharmacologic activity, and polymorphisms in metabolic enzymes can significantly impact drug levels and tolerability [48].

In summary, the primary molecular mechanism of tricyclic antidepressants involves inhibition of norepinephrine and serotonin reuptake through blockade of their respective transporters (NET and SERT), thereby enhancing monoaminergic neurotransmission in the central nervous system. While effective, their non-selective receptor binding contributes to a broad range of anticholinergic, antihistaminic, and cardiovascular side effects, which limits their tolerability and necessitates caution in their clinical use—particularly in overdose settings.

TCAs inhibit the reuptake of both norepinephrine and serotonin but also interact with other receptors, contributing to side effects.

Monoamine oxidase inhibitors (MAOIs)

Monoamine oxidase inhibitors (MAOIs) are a class of antidepressant agents that exert their therapeutic effect by increasing the levels of monoamine neurotransmitters—primarily serotonin (5-hydroxytryptamine, 5-HT), norepinephrine (NE), and dopamine (DA)—within the central nervous system. These neurotransmitters play key roles in regulating mood, arousal, and emotional stability, and their dysregulation has been closely associated with depressive disorders and certain anxiety conditions [49].

The molecular target of MAOIs is the enzyme monoamine oxidase (MAO), which is responsible for the oxidative deamination and inactivation of monoamines both in the brain and peripheral tissues. This enzyme exists in two isoforms:

MAO-A, which preferentially metabolizes serotonin, norepinephrine, and epinephrine, and MAO-B, which primarily breaks down phenylethylamine and dopamine. Both isoforms are flavin adenine dinucleotide (FAD)-dependent enzymes, located on the outer mitochondrial membrane of neurons and other cells. MAOIs function by binding to these enzymes and inhibiting their catalytic activity, thereby reducing the breakdown of monoamine neurotransmitters. This inhibition leads to an accumulation of neurotransmitters in the synaptic cleft, enhancing monoaminergic signaling and, over time, exerting antidepressant effects. The precise therapeutic action is not solely due to the immediate increase in neurotransmitter levels, but also involves downstream neuroadaptive changes such as altered receptor sensitivity, modulation of intracellular signaling cascades, and increased expression of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which supports neuronal plasticity and survival [50].

MAOIs can be classified based on their reversibility and selectivity. Some MAOIs, such as phenelzine and tranylcypromine, are irreversible and non-selective, meaning they covalently bind to both MAO-A and MAO-B, resulting in long-lasting inhibition that persists until new enzymes are synthesized—a process that may take up to two weeks. Others, like moclobemide, are reversible and selective, primarily inhibiting MAO-A in a competitive and transient manner. Selective MAO-B inhibitors such as selegiline are used in the treatment of Parkinson's disease, where they enhance dopaminergic transmission [51].

Despite their efficacy, MAOIs are associated with significant clinical limitations, particularly due to their interaction with dietary amines, most notably tyramine. Under normal conditions, MAO in the gut and liver breaks down tyramine, a naturally occurring compound found in aged cheeses, cured meats, and fermented products. Inhibition of this metabolic pathway allows tyramine to accumulate and enter the systemic circulation, where it displaces norepinephrine from presynaptic vesicles, causing a potentially dangerous hypertensive crisis—a reaction sometimes referred to as the "cheese effect" [52]. Moreover, MAOIs pose a risk for serotonin syndrome when used concurrently with other serotonergic drugs, such as SSRIs, SNRIs, or certain opioids. This condition is characterized by autonomic instability, neuromuscular hyperactivity, and altered mental status and it can be life-threatening without prompt intervention.

Antidiabetics

Biguanides

Biguanides are a class of oral antihyperglycemic agents, with metformin being the only widely used drug in this group today. Metformin is considered the first-line pharmacologic treatment for type 2 diabetes mellitus due to its efficacy, safety profile, and positive effects on weight and cardiovascular outcomes [53]. Metformin's primary mechanism of action is reduction of hepatic glucose production, particularly by inhibiting gluconeogenesis in the liver. This effect is largely mediated by activation of AMP-activated protein kinase (AMPK), a central energy-sensing enzyme that regulates cellular metabolism. At the molecular level, metformin enters hepatocytes via organic cation transporters (OCTs). Inside the cell, it accumulates in mitochondria and inhibits complex I of the electron transport chain, leading to a reduction in ATP production and an increase in the cellular AMP:ATP ratio. This shift activates AMPK, which subsequently suppresses expression of genes involved in gluconeogenesis, promotes fatty acid oxidation, enhances insulin sensitivity and inhibits hepatic lipogenesis [54].

By reducing hepatic glucose output and improving peripheral glucose uptake, metformin lowers fasting and postprandial blood glucose levels without stimulating insulin secretion. This insulin-independent mechanism greatly reduces the risk of hypoglycemia, a major advantage over

some other antidiabetic agents. Metformin also has beneficial cardiometabolic effects, including modest weight loss, improved lipid profiles, and anti-inflammatory actions. Recent research has explored its potential use in conditions such as polycystic ovary syndrome (PCOS), certain cancers, and aging-related diseases, due to its effects on metabolic and cellular stress pathways. The most common side effects of metformin are gastrointestinal, including nausea, diarrhea, and abdominal discomfort. Rarely, it can cause lactic acidosis, a serious complication, particularly in patients with renal or hepatic impairment [55].

Sulfonylureas

Sulfonylureas are a class of antidiabetic drugs that lower blood glucose levels by stimulating insulin secretion from the pancreatic beta cells. They are particularly effective in individuals with type 2 diabetes who retain some degree of endogenous insulin production. Unlike metformin, sulfonylureas act directly on the pancreatic islets,

and their action is glucose-independent, meaning they can trigger insulin release even when blood glucose levels are not elevated—a feature that increases the risk of hypoglycemia. The molecular mechanism of sulfonylureas involves their binding to the sulfonylurea receptor **1** (SUR1), a regulatory subunit of the ATP-sensitive potassium (K-ATP) channel on the surface of pancreatic beta cells. Normally, these potassium channels remain open during low glucose states, keeping the cell membrane hyperpolarized and preventing insulin release. When glucose levels rise, intracellular ATP increase, closing these channels, leading to membrane depolarization, calcium influx, and insulin secretion [55].

Sulfonylureas mimic this natural process by binding to SUR1 and forcibly closing the K_ATP channels, regardless of the actual glucose level. This triggers membrane depolarization, opens voltage-dependent calcium channels, and allows calcium to enter the cell, which in turn promotes the exocytosis of insulin granules. As a result, sulfonylureas significantly increase circulating insulin levels, promoting glucose uptake by peripheral tissues and suppressing hepatic glucose production. However, their reliance on beta cell function means they may become less effective over time as pancreatic function declines—a phenomenon known as secondary failure.

Sulfonylureas are generally well-tolerated but are associated with weight gain and a higher risk of hypoglycemia, particularly in the elderly or those with renal or hepatic impairment. Common agents in this class include glipizide, glyburide, and glimepiride, each with slight variations in potency, half-life, and risk profiles [56].

Sodium-glucose cotransporter 2(SGLT2) inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a relatively new class of oral antidiabetic drugs used primarily for the treatment of type 2 diabetes mellitus, and more recently, for chronic kidney disease and heart failure, due to their broad metabolic and cardiovascular benefits [57].

The molecular target of this drug class is the SGLT2 protein, a transporter located in the proximal convoluted tubule of the nephron in the kidney. Under normal physiological conditions, approximately 90% of the filtered glucose in the glomerular filtrate is reabsorbed back into the bloodstream via SGLT2, which couples glucose

reabsorption with sodium reabsorption. The remaining 10% is reabsorbed by SGLT1, primarily in the distal tubule.

SGLT2 inhibitors, such as empagliflozin, canagliflozin, and dapagliflozin, act by selectively and reversibly inhibiting the SGLT2 protein. By blocking this transporter, these drugs prevent the reabsorption of glucose and sodium from the renal tubular lumen back into the blood. As a result, excess glucose is excreted in the urine, a process known as glucosuria. This directly lowers

blood glucose levels in an insulin-independent manner [58-60].

The insulin-independent mechanism is a key advantage of SGLT2 inhibitors, as it means their efficacy does not rely on beta-cell function or insulin sensitivity. This allows them to be used effectively in combination with other antidiabetic agents, including metformin, insulin, and sulfonylureas.

Conclusion

In conclusion, this review underscores the critical importance of understanding the molecular mechanisms of action across major drug classes in advancing pharmacological knowledge and improving clinical practice. By integrating classical pharmacodynamic principles with recent research findings, it provides a comprehensive framework for interpreting how therapeutic agents achieve their effects at the cellular and molecular levels.

Ethical Considerations

Data availability

The data that supported the findings in this study are available on request from the corresponding author

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest.

Compliance with ethical guidelines

Approval for this study and related cases was obtained from the University of Uyo Health Research Ethics Committee

Author's contribution

The authors confirm contributions as follows: study conception and design by SOA; data collection by PJE and AEA; Analysis and interpretation of results by all authors; Draft manuscript preparation by SOA; all authors reviewed the result and approved the final version of the manuscript.

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References

1. Li Q, Kang C. Mechanisms of Action for Small Molecules Revealed by Structural Biology in Drug Discovery. International Journal Molecular Science. 2020 24;21(15):5262. doi: 10.3390/ijms21155262.
2. Austin D, Biswas K, Pollock K, Nguyen L. Interdisciplinary analysis of drugs: Structural features and clinical data. Journal of Clinical and Translational Science, 2022;6(1):e43. doi: 10.1017/cts.2022.375.
3. Liang Z, Verkhivker GM, Hu G. Integration of network models and evolutionary analysis into high-throughput modeling of protein dynamics and allosteric regulation: theory, tools and applications. Brief Bioinformatics, 2020;21(3):815-835. doi: 10.1093/bib/bbz029.
4. Kim D, Kim S, Kwon Y, Kim Y, Park H, Kwak K, Lee H, Lee JH, Jang KM, Kim D, Lee SH,Kang LW. Structural Insights for β-Lactam Antibiotics. Biomolecular Therapy (Seoul), 2023 1;31(2):141-147. doi: 10.4062/biomolther.2023.008.
5. Typas A, Banzhaf M, Gross CA, Vollmer W. From the regulation of peptidoglycan synthesis to bacterial growth and morphology. Nature Review Microbiology, 2011 28;10(2):123-36. doi: 10.1038/nrmicro2677.
6. Flanders PL, Contreras-Martel C, Brown NW, Shirley JD, Martins A, Nauta KN, Dessen A, Carlson EE, Ambrose EA. Combined Structural Analysis and Molecular Dynamics Reveal Penicillin-Binding Protein Inhibition Mode with

β-Lactones. ACS Chemical Biology, 2022;17(11):3110-3120. doi: 10.1021/acschembio.2c00503.
7. Edoo Z, Arthur M, Hugonnet JE. Reversible inactivation of a peptidoglycan transpeptidase by a β-lactam antibiotic mediated by β-lactam-ring recyclization in the enzyme active site. Scientific Reports, 2017;7(1):9136. doi: 10.1038/s41598-017-09341-8.
8. Boutte CC, Localized Production of Cell Wall Precursors May Be Critical for Regulating the Mycobacterial Cell Wall. Journal of Bacteriology, 2022;204(6):e0012522. doi: 10.1128/jb.00125-22.
9. Dinos GP, The macrolide antibiotic renaissance. British Journal of Pharmacology, 2017;174(18):2967-2983. doi: 10.1111/bph.13936.
10. Jednačak T, Mikulandra I., Novak P. Advanced Methods for Studying Structure and Interactions of Macrolide Antibiotics. International Journal of Molecular Sciences, 2020; 21(20), 7799. https://doi.org/10.3390/ijms21207799
11. Garza-Ramos G, Xiong L, Zhong P, Mankin A. Binding site of macrolide antibiotics on the ribosome: new resistance mutation identifies a specific interaction of ketolides with rRNA. Journal of Bacteriology, 2001;183(23):6898-907. doi: 10.1128/JB.183.23.6898-6907.2001.
12. Wilson DM, Li Y, LaPeruta A, Gamalinda M, Gao N, Woolford JL Jr. Structural insights into assembly of the ribosomal nascent polypeptide exit tunnel. Nature Communications, 2020; 11(1):5111. doi: 10.1038/s41467-020-18878-8.
13. Svetlov MS, Syroegin EA, Aleksandrova EV, Atkinson GC, Gregory ST, Mankin AS, Polikanov YS. Structure of Erm-modified 70S ribosome reveals the mechanism of macrolide resistance. Nature Chemical Biology, 2021; 17(4):412-420. doi: 10.1038/s41589-020-00715-0.
14. Ahmadi Tehrani A, Omranpoor MM, Vatanara A, Seyedabadi M, Ramezani V. Formation of nanosuspensions in bottom-up approach: theories and optimization. Daru, 2019; 27(1):451-473. doi: 10.1007/s40199-018-00235-2.
15. Berbel D, González-Díaz A, López de Egea G, Càmara J, Ardanuy C. An Overview of Macrolide Resistance in Streptococci: Prevalence, Mobile Elements and Dynamics. Microorganisms, 2022;10(12):2316. doi: 10.3390/microorganisms10122316.
16. Zhang L, Xu X, Badawy S, Ihsan A, Liu Z, Xie C, Wang X, Tao Y. A Review: Effects of Macrolides on CYP450 Enzymes. Current Drug Metabolism, 2020;21(12):928-937. doi: 10.2174/1389200221666200817113920.
17. Svetlov, MS, Koller, TO., Meydan S, Context-specific action of macrolide antibiotics on the eukaryotic ribosome. Nature Communication, 2021; 12: 2803. https://doi.org/10.1038/s41467-021-23068-1
18. Nor Amdan NA, Shahrulzamri NA, Hashim R, Mohamad Jamil N. Understanding the evolution of macrolides resistance: A mini review. Journal Global Antimicrobial Resistance, 2024;38:368-375. doi: 10.1016/j.jgar.2024.07.016.
19. Lungu IA, Moldovan OL, Biriș V, Rusu A. Fluoroquinolones Hybrid Molecules as Promising Antibacterial Agents in the Fight against Antibacterial Resistance. Pharmaceutics, 2022;14(8):1749. doi: 10.3390/pharmaceutics14081749.
20. Collins JA, Osheroff N. Gyrase and Topoisomerase IV: Recycling Old Targets for New Antibacterials to Combat Fluoroquinolone Resistance. ACS Infectious Diseases, 2024 12;10(4):1097-1115. doi:

10.1021/acsinfecdis.4c00128.

21. Strahilevitz J, Hooper DC. Dual targeting of topoisomerase IV and gyrase to reduce mutant selection: direct testing of the paradigm by using WCK-1734, a new fluoroquinolone, and ciprofloxacin. Antimicrobial Agents Chemotherapy, 2005;49(5):1949-56. doi: 10.1128/AAC.49.5.1949-1956.2005.
22. Hooper DC, Jacoby GA. Mechanisms of drug resistance: quinolone resistance. The Annals of New York Academy of Science, 2015;1354(1):12-31. doi: 10.1111/nyas.12830.
23. Yang B, Fang D, Lv Q, Wang Z, Liu Y. Targeted Therapeutic Strategies in the Battle Against Pathogenic Bacteria. Frontiers in Pharmacology, 2021; 12:673239. doi: 10.3389/fphar.2021.673239.
24. Junier I, Ghobadpour E, Espeli O, Everaers R. DNA supercoiling in bacteria: state of play and challenges from a viewpoint of physics based modeling Frontiers in. Microbiology, 2023; Sec. Microbial Physiology and Metabolism, 2023; 14 | https://doi.org/10.3389/fmicb.2023.1192831
25. Wang X, Khalil RA. Matrix Metalloproteinases, Vascular Remodeling, and Vascular Disease. Advances in Pharmacology, 2018;81:241-330. doi: 10.1016/bs.apha.2017.08.002.
26. Rex DAB, Vaid N, Deepak K, Dagamajalu S, Prasad TSK. A comprehensive review on current understanding of bradykinin in COVID-19 and inflammatory diseases. Molecular Biology Reports, 2022;49(10):9915-9927. doi: 10.1007/s11033-022-07539-2.
27. Zheng W, Tian E, Liu Z, Zhou C, Yang P, Tian K, Liao W, Li J, Ren C. Small molecule angiotensin converting enzyme inhibitors: A medicinal chemistry perspective. Frontiers in Pharmacology, 2022;13:968104. doi: 10.3389/fphar.2022.968104.
28. Van Buren PN, Toto R. Hypertension in diabetic nephropathy: epidemiology, mechanisms, and management. Advances in Chronic Kidney Disease, 2011;18(1):28-41. doi: 10.1053/j.ackd.2010.10.003.
29. Jayasinghe M, Caldera D, Prathiraja O, Jena R, Coffie-Pierre JA, Agyei J, Silva MS, Kayani AMA, Siddiqui OS. A Comprehensive Review of Bradykinin-Induced Angioedema Versus Histamine-Induced Angioedema in the Emergency Department. Cureus, 2022 Nov 30;14(11):e32075. doi: 10.7759/cureus.32075.
30. Jayasinghe M, Caldera D, Prathiraja O, Jena R, Coffie-Pierre JA, Agyei J, Silva MS, Kayani AMA, Siddiqui OS. A Comprehensive Review of Bradykinin-Induced Angioedema Versus Histamine-Induced Angioedema in the Emergency Department. Cureus, 2022;14(11):e32075. doi: 10.7759/cureus.32075.
31. Triggle DJ. The physiological and pharmacological significance of cardiovascular T-type, voltage-gated calcium channels. American Journal of Hypertension, 1998;11(4 Pt 3):80S-87S. doi: 10.1016/s0895-7061(98)00004-1.
32. Pikor D, Hurła M, Słowikowski B, Szymanowicz O, Poszwa J, Banaszek N, Drelichowska A, Jagodziński PP, Kozubski W, Dorszewska J. Calcium Ions in the Physiology and Pathology of the Central Nervous System International Journal of Molecular Sciences, 2024; 25(23):13133. https://doi.org/10.3390/ijms252313133
33. Scarnati MS, Clarke SG, Pang ZP, Paradiso KG. Presynaptic Calcium Channel Open Probability and Changes in Calcium Influx Throughout the Action Potential Determined Using AP-Waveforms. Frontiers in Synaptic Neuroscience, 2020;12:17. doi: 10.3389/fnsyn.2020.00017.
34. Jones KE, Hayden SL, Meyer HR, Sandoz JL, Arata WH, Dufrene K, Ballaera C, Lopez Torres Y, Griffin P, Kaye AM. The

Evolving Role of Calcium Channel Blockers in Hypertension Management: Pharmacological and Clinical Considerations. *Current Issues in Molecular Biology*, 2024; 46(7):6315-6327. https://doi.org/10.3390/cimb46070377
43. Jones KE, Hayden SL, Meyer HR, Sandoz JL, Arata WH, Dufrene K, Ballaera C, Lopez Torres Y, Griffin P, Kaye AM, Shekoohi S, Kaye AD. The Evolving Role of Calcium Channel Blockers in Hypertension Management: Pharmacological and Clinical Considerations. Current Issues in Molecular Biology, 2024;46(7):6315-6327.
44. Gordan R, Gwathmey JK, Xie LH. Autonomic and endocrine control of cardiovascular function. World Journal of Cardiology, 2015;7(4):204-14. doi: 10.4330/wjc.v7.i4.204.
45. Kobe J, Mishra N, Arya VK, Al-Moustadi W, Nates W, Kumar B. Cardiac output monitoring: Technology and choice. Annals of Cardiac Anaesthesia, 2019;22(1):6-17. doi: 10.4103/aca.ACA_41_18.
46. Liu B, Zhang R, Zhang A, Wang G, Xu J, Zhang Y, Liu Y, Hao P. Effectiveness and safety of four different beta-blockers in patients with chronic heart failure. Medical Communications, 2020;4(1):e199. doi: 10.1002/mco2.199.
47. Xue W, Wang P, Li B, Li Y, Xu X, Yang F, Yao X, Chen YZ, Xu F, Zhu F. Identification of the inhibitory mechanism of FDA approved selective serotonin reuptake inhibitors: an insight from molecular dynamics simulation study. Physical Chemistry Chemical Physics, 2016;18(4):3260-71. doi: 10.1039/c5cp05771j.
48. Kocsis JH. Review: SSRIs and TCAs equally effective at treating chronic depression and dysthemia; SSRIs are associated with fewer adverse events than TCAs. Evid Based Mental Health, 2013;16(3):82. doi: 10.1136/eb-2013-101268.
35. Duman CH, Duman RS. Spine synapse remodeling in the pathophysiology and treatment of depression. Neuroscience Letters, 2015; 601:20-9. doi: 10.1016/j.neulet.2015.01.022.
36. Starkey ES, Sammons HM. Practical pharmacokinetics: what do you really need to know? Archives of Diseases and Children Education and Practices, 2015;100(1):37-43. doi: 10.1136/archdischild-2013-304555.
37. Telles-Correia D, Barbosa A, Cortez-Pinto H, Campos C, Rocha NB, Machado S. Psychotropic drugs and liver disease: A critical review of pharmacokinetics and liver toxicity. World Journal of Gastrointestinal Pharmacology and Therapeutics, 2017 Feb 6;8(1):26-38. doi: 10.4292/wjgpt.v8.i1.26.
38. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Preference and Adherence, 2012;6:369-88. doi: 10.2147/PPA.S29716.
39. Iversen L. Neurotransmitter transporters and their impact on the development of psychopharmacology. British Journal of Pharmacology, 2006 ;147 Suppl 1(Suppl 1):S82-8. doi: 10.1038/sj.bjp.0706428.
40. Eslami M, Monemi M, Nazari MA, Azami MH, Shariat Rad P, Oksenych V, Naderian R. The Anti-Inflammatory Potential of Tricyclic Antidepressants (TCAs): A Novel Therapeutic Approach to Atherosclerosis Pathophysiology. *Pharmaceuticals*, 2025; 18(2):197. https://doi.org/10.3390/ph18020197\
41. Zhang P, Wang F, Hu J, Sorrentino R. Exploring the relationship between drug side-effects and therapeutic indications. AMIA Annual Symposium Proceedings, 2013;2013:1568-77.
42. Tsuboi D, Nagai T, Yoshimoto J, Kaibuchi K. Neuromodulator regulation and emotions: insights from the crosstalk of cell

signaling. Front Mol Neurosci. 2024 Mar 7;17:1376762. doi: 10.3389/fnmol.2024.1376762.
53. Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical implications. Arch Med Sci. 2015 Dec 10;11(6):1164-78. doi: 10.5114/aoms.2015.56342.
54. Tan YY, Jenner P, Chen SD. Monoamine Oxidase-B Inhibitors for the Treatment of Parkinson's Disease: Past, Present, and Future. J Parkinsons Dis. 2022;12(2):477-493. doi: 10.3233/JPD-212976.
55. Garcia-Tsao G, Abraldes JG, Rich NE, Wong VW. AGA Clinical Practice Update on the Use of Vasoactive Drugs and Intravenous Albumin in Cirrhosis: Expert Review. Gastroenterology. 2024 Jan;166(1):202-210. doi: 10.1053/j.gastro.2023.10.016.
56. Baker C, Retzik-Stahr C, Singh V, Plomondon R, Anderson V, Rasouli N. Should metformin remain the first-line therapy for treatment of type 2 diabetes? Therapeutic Advances in Endocrinology and Metabolism, 2021;12:2042018820980225. doi: 10.1177/2042018820980225.
57. Mihaylova MM, Shaw RJ. The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. Nature Cell Biology, 2011;13(9):1016-23. doi: 10.1038/ncb2329.
58. Lee YG, Kim D. Tomatine Improves Glucose Metabolism and Mitochondrial Respiration in Insulin-Resistant Hepatocyte Cell Lines AML12 and HepG2 via an AMP-Activated Protein Kinase-Dependent Pathway. *Cells*, 2025; 14(5):329. https://doi.org/10.3390/cells14050329
59. Nyenwe EA, Jerkins TW, Umpierrez GE, Kitabchi AE. Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes. Metabolis, 2011;60(1):1-23. doi: 10.1016/j.metabol.2010.09.010.
60. Honda K, Kato K, Dairaku N, Iijima K, Koike T, Imatani A, Sekine H, Ohara S, Matsui H, Shimosegawa T. High levels of intracellular ATP prevent nitric oxide-induced apoptosis in rat gastric mucosal cells. International Journal of Experimental Pathology, 2003;84(6):281-8. doi: 10.1111/j.0959-9673.2003.00364.x.
49. Ferrannini E. Learning from glycosuria. Diabetes, 2011 Mar;60(3):695-6. doi: 10.2337/db10-1667.
50. Swe MT, Thongnak L, Jaikumkao K, Pongchaidecha A, Chatsudthipong V, Lungkaphin A. Dapagliflozin not only improves hepatic injury and pancreatic endoplasmic reticulum stress, but also induces hepatic gluconeogenic enzymes expression in obese rats. Clinical Sciences (Lond), 2019;133(23):2415-2430. doi: 10.1042/CS20190863.
51. Vallon V. Molecular determinants of renal glucose reabsorption. Focus on "Glucose transport by human renal Na+/D-glucose cotransporters SGLT1 and SGLT2". American Journal of Physiology and Cell Physiology, 2011;300(1):C6-8. doi: 10.1152/ajpcell.00444.2010.
52. Hummel CS, Lu C, Loo DD, Hirayama BA, Voss AA, Wright EM. Glucose transport by human renal Na+/D-glucose cotransporters SGLT1 and SGLT2. American Journal of Physiolofy and Cell Physiology, 2011;300(1):C14-21. doi: 10.1152/ajpcell.00388.2010.. Erratum in: American Journal of Physiology and Cell Physioliogy, 2011 Mar;300(3):C721.