AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Comparative Pharmacology of Cephalosporins and Sulfonylureas: Mechanisms, Clinical Applications, and Safety

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ABSTRACT

Cephalosporins and sulfonylureas represent clinically important drug classes used in the management of bacterial infections and type 2 diabetes mellitus, respectively. Their distinct molecular targets, pharmacokinetic properties, therapeutic benefits, and adverse-effect profiles illustrate fundamental principles of pharmacological selectivity and rational drug utilization. This review examines the pharmacodynamics, pharmacokinetics, classification, therapeutic applications, mechanisms of resistance or treatment failure, safety considerations, and contemporary clinical relevance of cephalosporins and sulfonylureas. A narrative literature review was undertaken using established pharmacology literature, biomedical review articles, and accessible clinical reference sources. Relevant evidence was synthesized to explain the mechanisms of action, therapeutic positioning, drug interactions, and limitations of both classes. Cephalosporins inhibit bacterial cell-wall synthesis through interactions with penicillin-binding proteins. Their antibacterial spectrum varies with molecular structure, generation, susceptibility patterns, and resistance mechanisms, including β-lactamase production and altered target proteins. Sulfonylureas stimulate pancreatic β-cell insulin secretion by binding sulfonylurea receptors associated with ATP-sensitive potassium channels. Although effective glucose-lowering agents, they can cause hypoglycaemia and weight gain, with risks influenced by renal function, nutrition, age, and concomitant medicines. Both classes require individualized selection, appropriate dosing, monitoring, and consideration of patient-specific factors. Rational use of these pharmacologically distinct agents depends on understanding their molecular mechanisms, therapeutic indications, limitations, and safety profiles. Antimicrobial stewardship and individualized diabetes management are essential to optimize clinical outcomes and minimize preventable harm.

Keywords: Antimicrobial stewardship; β-lactam resistance; insulin secretion; hypoglycaemia; rational pharmacotherapy.

*Corresponding Author Name: Devanssh Mehta
Received 12 October 2026, Accepted 30 October 2026

Please cite this article as: Mehta D., Comparative Pharmacology of Cephalosporins and Sulfonylureas: Mechanisms, Clinical Applications, and Safety. American Journal of PharmTech Research 2026.

INTRODUCTION

Pharmacology provides the scientific foundation for understanding the interaction between drugs and biological systems, the relationship between drug concentration and therapeutic response, and the mechanisms underlying adverse reactions. Within clinical pharmacology, the study of antimicrobial agents and antidiabetic medicines is particularly important because both therapeutic areas require careful balancing of efficacy, safety, resistance or treatment failure, and individual patient characteristics.

Cephalosporins constitute a major group of β-lactam antibiotics employed against susceptible bacterial infections. Their clinical utility derives from inhibition of bacterial cell-wall synthesis, a process essential for maintaining bacterial structural integrity. Chemical modification of the cephalosporin nucleus has produced compounds with different antibacterial spectra, pharmacokinetic characteristics, and degrees of stability against bacterial β-lactamases. Nevertheless, the activity of an individual agent cannot be inferred from its generation alone; it also depends on the infecting organism, local resistance patterns, infection site, and achievable drug exposure [1–3].

Sulfonylureas, in contrast, are oral glucose-lowering agents primarily used in type 2 diabetes mellitus. They act by stimulating insulin secretion from pancreatic β-cells through interaction with ATP-sensitive potassium channels. Their glucose-lowering effect can be clinically substantial, particularly in individuals who retain sufficient pancreatic β-cell function. However, their mechanism is associated with an important limitation: insulin secretion may continue even when circulating glucose concentrations fall, thereby creating a risk of hypoglycaemia [4,5].

These two classes are not pharmacologically related, nor do they share a common therapeutic indication. Their consideration within a single review is educational rather than mechanistic, permitting comparison of drug-target interactions, pharmacokinetic determinants, clinical decision-making, and adverse-effect prevention.

The continuing development of antimicrobial resistance has increased the importance of evidence-based cephalosporin selection, susceptibility-guided therapy, and responsible antibiotic prescribing. Similarly, contemporary diabetes management requires balancing glycaemic efficacy against hypoglycaemia, weight gain, comorbidities, treatment affordability, and the availability of alternative glucose-lowering medicines [3,5,6].

The purpose of this review is to provide an integrated account of the pharmacology of cephalosporins and sulfonylureas, with emphasis on their mechanisms of action, classification,

pharmacokinetics, therapeutic applications, resistance or treatment limitations, adverse effects, interactions, and principles of rational use.

Review Methodology

This article employs a narrative review approach. The literature base comprises established pharmacology and clinical reference sources, biomedical reviews, and research publications addressing the molecular mechanisms, clinical applications, pharmacokinetics, safety, and resistance profiles of the two drug classes.

Relevant literature was identified through biomedical reference resources, including PubMed-indexed publications and the National Center for Biotechnology Information Bookshelf. Priority was given to sources describing established pharmacological mechanisms, clinically relevant adverse effects, and evidence-based approaches to therapeutic selection.

The material was organized into thematic sections covering classification, molecular pharmacology, absorption and disposition, therapeutic indications, resistance or treatment limitations, drug interactions, and clinical safety. The final synthesis emphasises broadly accepted pharmacological principles rather than an exhaustive quantitative comparison of clinical trials.

This review was not designed as a systematic review or meta-analysis. No formal protocol, comprehensive reproducible database-search strategy, duplicate screening procedure, risk-of-bias assessment, or quantitative pooling of results was undertaken. Consequently, the findings should be interpreted as a narrative synthesis rather than as the product of a systematic evidence-grading process.

Pharmacology of Cephalosporins

Historical development and chemical structure

Cephalosporins originated from antimicrobial compounds associated with the mould historically known as Cephalosporium acremonium, now classified within Acremonium. Giuseppe Brotzu's observations in the 1940s contributed to the discovery of cephalosporin-producing organisms. Subsequent investigations by Edward Abraham, Guy Newton, and colleagues helped establish the chemistry and antibacterial potential of cephalosporin C, supporting the development of semisynthetic derivatives [1,2].

The characteristic cephalosporin structure consists of a β-lactam ring fused to a six-membered dihydrothiazine ring. The 7-aminocephalosporanic acid nucleus provides the structural framework from which different compounds are developed through modification of side chains. Substitutions around the molecular nucleus influence antibacterial potency, β-lactamase stability, penetration into bacterial cells, protein binding, metabolic characteristics, and elimination [1,2].

The β-lactam ring is essential to the antibacterial activity of conventional cephalosporins. Its interaction with bacterial penicillin-binding proteins interferes with the enzymatic reactions required for peptidoglycan cross-linking. However, structural changes that improve activity against one group of organisms may alter activity against another, illustrating the importance of structure–activity relationships in antimicrobial drug development.

Classification of cephalosporins

Cephalosporins are traditionally classified into five generations according to their spectrum of activity and historical development. This framework is useful for teaching and clinical orientation, although it is an approximation rather than a precise ranking of antibacterial potency. Newer agents do not necessarily provide superior activity against every bacterial species [1–3].

First-generation cephalosporins

Examples include cefazolin, cephalexin, and cefadroxil. These agents generally provide useful activity against susceptible streptococci and methicillin-susceptible staphylococci, together with limited activity against selected Gram-negative organisms, including susceptible strains of Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis.

Cefazolin is widely used for perioperative prophylaxis when appropriate for the anticipated organisms and procedure. Oral agents such as cephalexin may be used for selected skin and soft-tissue infections caused by susceptible bacteria.

Second-generation cephalosporins

Examples include cefuroxime, cefaclor, cefprozil, cefoxitin, and cefotetan. This group generally extends activity against selected Gram-negative organisms compared with first-generation compounds. Cephamycins, including cefoxitin and cefotetan, have useful activity against certain anaerobic organisms, although susceptibility must be considered and these agents do not cover every clinically important anaerobe.

Cefuroxime may be used in selected respiratory and other infections when the causative organism is susceptible. The precise role of any second-generation agent depends on the clinical syndrome and local guidelines.

Third-generation cephalosporins

Examples include ceftriaxone, cefotaxime, ceftazidime, cefixime, and cefpodoxime. These compounds generally provide improved activity against many Gram-negative organisms compared with earlier generations. Ceftriaxone and cefotaxime achieve clinically useful cerebrospinal fluid concentrations under appropriate conditions and are important in the treatment of selected cases of bacterial meningitis.

Ceftazidime provides activity against susceptible Pseudomonas aeruginosa, whereas ceftriaxone does not provide reliable antipseudomonal coverage. This difference illustrates why individual drug properties are more informative than generation labels alone.

Fourth-generation cephalosporins

Cefepime is the principal representative. It combines activity against numerous Gram-positive and Gram-negative organisms and has antipseudomonal activity. Its role includes selected serious infections caused by susceptible bacteria, particularly when broader Gram-negative coverage is required. However, cefepime is not reliably active against all extended-spectrum β-lactamase-producing organisms or carbapenem-resistant bacteria.

Fifth-generation and advanced cephalosporins

Ceftaroline is distinguished by activity against methicillin-resistant Staphylococcus aureus (MRSA), mediated by its affinity for the altered penicillin-binding protein PBP2a. It does not provide reliable antipseudomonal activity. Other advanced cephalosporin derivatives have been developed for particular resistant Gram-negative infections.

Ceftazidime–avibactam and ceftolozane–tazobactam combine cephalosporins with β-lactamase inhibitors. Cefiderocol is a siderophore cephalosporin that exploits bacterial iron-transport systems to facilitate entry into susceptible Gram-negative bacteria. These agents have specialized roles determined by resistance mechanisms, organism susceptibility, regulatory indications, and clinical guidance [1–3].

Mechanism of action

Cephalosporins exert bactericidal activity by interfering with bacterial cell-wall biosynthesis. The bacterial cell wall contains peptidoglycan, a mesh-like structure that provides mechanical strength and protects the organism against osmotic stress. Peptidoglycan formation requires the polymerization and cross-linking of structural components through enzymatic reactions involving penicillin-binding proteins.

Cephalosporins enter the bacterial environment and bind to susceptible penicillin-binding proteins. Their β-lactam ring reacts with the active site of these enzymes, producing a covalent acyl-enzyme complex that inhibits normal enzymatic activity. Inhibition of transpeptidation prevents effective cross-linking of peptidoglycan strands, resulting in defective cell-wall construction.

The consequences include weakening of bacterial structural integrity and, in susceptible organisms under appropriate conditions, cell death. The precise contribution of individual penicillin-binding proteins differs among bacterial species and cephalosporin molecules. Therefore, antibacterial

efficacy depends on both drug exposure and the susceptibility characteristics of the organism [2,3,7].

The bactericidal effect of β-lactams is generally associated with the duration for which unbound drug concentrations remain above the minimum inhibitory concentration of the target organism. This pharmacodynamic parameter is commonly expressed as percentage of the dosing interval during which free drug concentration exceeds the minimum inhibitory concentration (%fT>MIC). Its relevance explains why dosing interval, infusion strategy, renal clearance, and organism susceptibility can influence treatment success.

Cephalosporins do not directly inhibit human cell-wall synthesis because human cells lack bacterial peptidoglycan. This selective toxicity underlies their therapeutic utility, although it does not eliminate the possibility of allergic reactions, organ-specific toxicity, microbiome disruption, or other adverse effects.

Pharmacokinetics and pharmacodynamics

The pharmacokinetic behaviour of cephalosporins varies considerably among individual agents. Oral absorption differs according to molecular structure and formulation. Cephalexin is well absorbed orally, whereas cefazolin is administered parenterally. Other cephalosporins have distinct oral bioavailability and food-related absorption characteristics.

After absorption, cephalosporins distribute into extracellular fluid and tissues to varying degrees. Distribution into cerebrospinal fluid is particularly important when treating meningitis, but it depends on the drug, dose, inflammation of the meninges, and physiological conditions. Ceftriaxone and cefotaxime are established options for selected susceptible bacterial meningitis pathogens, subject to appropriate clinical guidance.

Many cephalosporins are eliminated primarily by the kidneys, often through glomerular filtration and tubular secretion. Reduced renal function may increase systemic exposure and prolong elimination, making dose adjustment necessary for several agents. Ceftriaxone has substantial biliary elimination in addition to renal elimination and differs from predominantly renally cleared compounds. Drug-specific prescribing information should therefore guide dose adjustment rather than applying a single rule to the entire class.

The relationship between pharmacokinetics and pharmacodynamics is central to treatment optimization. Inadequate exposure may result in clinical failure and potentially contribute to resistance selection, whereas excessive exposure can increase toxicity. In serious infections, clinicians may use extended or prolonged infusion strategies for selected β-lactams when supported by local protocols and the agent's pharmacological characteristics [2,3,7].

Therapeutic applications

Cephalosporins are used for infections caused by susceptible bacteria across multiple anatomical systems. Their selection should be based on the probable or confirmed pathogen, severity of illness, infection site, host characteristics, culture results, and local susceptibility data.

Important clinical applications include:

1. Skin and soft-tissue infections: Selected first-generation agents may be effective against susceptible streptococci and methicillin-susceptible staphylococci.
2. Respiratory infections: Selected second- and third-generation compounds may be appropriate for specific bacterial respiratory infections when local guidance and susceptibility support their use.
3. Urinary tract infections: Certain oral or parenteral cephalosporins may be used for susceptible pathogens, depending on infection severity and site.
4. Bacterial meningitis: Ceftriaxone or cefotaxime may form part of empirical or directed treatment regimens, with additional agents selected when indicated by age, risk factors, or suspected pathogen.
5. Gonorrhoea: Ceftriaxone has an important role in current treatment guidance, with regimen and dose determined by the applicable national or international recommendations.
6. Perioperative prophylaxis: Cefazolin is commonly used for appropriate surgical procedures, with timing and redosing determined by procedural and pharmacokinetic considerations.
7. Selected resistant Gram-negative infections: Advanced cephalosporin–β-lactamase inhibitor combinations and cefiderocol may be considered for infections caused by susceptible resistant organisms when supported by specialist guidance [1–3].

These indications are not interchangeable. A cephalosporin effective against one pathogen may be inappropriate for another because of intrinsic resistance, acquired resistance, inadequate tissue exposure, or an unfavourable safety profile.

Mechanisms of bacterial resistance

Antimicrobial resistance is a major limitation of cephalosporin therapy. Bacteria may resist these agents through enzymatic degradation, alteration of drug targets, reduced penetration, active efflux, or combinations of these mechanisms [2,3,7].

B-Lactamase production: β-Lactamases hydrolyse the β-lactam ring and thereby inactivate susceptible antibiotics. Extended-spectrum β-lactamases can confer resistance to many penicillins and cephalosporins, including clinically important third-generation agents. AmpC β-lactamases

and carbapenemases create additional treatment challenges. The activity of an inhibitor-containing combination depends on the enzyme type, inhibitor properties, bacterial permeability, and other resistance mechanisms.

Altered penicillin-binding proteins: Changes in the structure or expression of target proteins may reduce antibiotic binding. MRSA, for example, expresses PBP2a, which has reduced affinity for most conventional β-lactams. Ceftaroline is an important exception among cephalosporins because of its activity against susceptible MRSA isolates.

Reduced permeability: Gram-negative bacteria possess an outer membrane that restricts entry of many compounds. Alterations or loss of porin channels can decrease antibiotic penetration and contribute to resistance, particularly when combined with β-lactamase production.

Efflux mechanisms: Some bacteria possess transport systems that remove antimicrobial agents from the cell or periplasmic compartment, reducing the concentration available at the target site.

Combined resistance mechanisms: A bacterium may simultaneously produce a β-lactamase, reduce membrane permeability, and modify target proteins. Such combinations can produce clinically important resistance even when a cephalosporin has favourable intrinsic activity.

Laboratory susceptibility testing is therefore essential when indicated, particularly in serious infections, treatment failure, or suspected resistant organisms. Empirical therapy should be reassessed when microbiological results become available, and treatment should be narrowed where clinically appropriate [2,3,7].

Adverse effects and safety

Cephalosporins are generally well tolerated when appropriately prescribed, but their safety profile varies by agent, dose, duration, and patient characteristics.

Hypersensitivity: Reactions range from mild rash to rare severe immediate hypersensitivity. Cross-reactivity with penicillin's is influenced substantially by side-chain similarity rather than simply by the shared β-lactam ring. A careful history of the original reaction, its severity, and the specific implicated drug is important when evaluating treatment options.

Gastrointestinal effects: Nausea, abdominal discomfort, and diarrhea may occur. Antibiotic exposure can disrupt the intestinal microbiome and contribute to Clostridioides difficile infection, which may present with clinically significant diarrhea and colitis.

Neurological toxicity: Excessive exposure to certain cephalosporins, particularly cefepime in patients with impaired renal clearance, can produce encephalopathy, altered consciousness, myoclonus, or seizures. Risk reduction requires appropriate dosing, renal assessment, and clinical monitoring.

Hematological and hepatic effects: Some agents may cause changes in blood counts or liver-associated laboratory parameters. The relevance of these effects depends on the particular compound, duration of exposure, and patient context.

Renal considerations: Several cephalosporins require dose adjustment in renal impairment. Accumulation can increase toxicity, making assessment of renal function particularly important in older adults and critically ill patients.

Agent-specific precautions: Ceftriaxone requires particular consideration in neonates because of bilirubin displacement concerns and the risk associated with concomitant intravenous calcium-containing solutions under specified conditions. The applicable product information should be consulted.

Unnecessary antibiotic exposure should be avoided because it increases the risk of adverse effects and contributes to selection of resistant organisms. Monitoring should be proportionate to the severity of infection, treatment duration, agent-specific risks, and the patient's clinical status [1–3].

Clinically relevant drug interactions

Drug interactions involving cephalosporins are agent-specific. Some cephalosporins may influence coagulation parameters, particularly in susceptible patients, and certain compounds have been associated with hypoprothrombinaemia. The potential relevance of anticoagulant therapy, nutritional status, liver dysfunction, and prolonged treatment should be evaluated when appropriate.

Concurrent nephrotoxic medicines may complicate the assessment of renal injury in patients receiving antibiotics, although the magnitude of risk varies with the agents involved and the patient's condition. Probenecid can affect renal tubular secretion of some β-lactams and may alter their elimination.

Cephalosporins can also interact indirectly with other treatments through changes in the intestinal microbiome, gastrointestinal function, or laboratory-test results. Consequently, interaction screening should consider the specific cephalosporin rather than assuming that every member of the class has identical interactions.

Antimicrobial stewardship and rational prescribing

Antimicrobial stewardship encompasses interventions designed to improve the selection, dosing, route, and duration of antimicrobial therapy. For cephalosporins, stewardship requires avoiding unnecessary broad-spectrum treatment, obtaining appropriate microbiological samples when indicated, using local susceptibility data, and reviewing treatment as diagnostic information becomes available.

Empirical therapy may initially require broader coverage in severe infections. Once the causative organism and susceptibility profile are established, narrowing the regimen can reduce collateral ecological effects and limit unnecessary exposure. Conversely, an excessively narrow regimen may be inadequate when the pathogen or resistance pattern is not sufficiently established.

Treatment duration should be determined by the infection syndrome, clinical response, source control, host factors, and applicable guidelines. Neither prolonged treatment nor early discontinuation should be adopted as a universal rule. The objective is to deliver sufficient effective therapy while minimizing avoidable toxicity and resistance selection.

In contemporary practice, stewardship is not simply a matter of reducing antibiotic consumption. It is a structured pharmacological and clinical process that seeks to maximize the probability of cure while preserving the effectiveness of existing antimicrobial agents [2,3,7].

Pharmacology of Sulfonylureas

Introduction and classification

Sulfonylureas are oral glucose-lowering medicines used in the treatment of type 2 diabetes mellitus. They are particularly relevant when pancreatic β-cells retain sufficient capacity to produce and release insulin. Their effects depend on functioning β-cells; consequently, they do not replace insulin in type 1 diabetes or diabetic ketoacidosis [4,5].

Historically, sulfonylureas are classified into first- and second-generation agents. First-generation compounds include tolbutamide, chlorpropamide, and tolazamide. Second-generation agents include glibenclamide, also known as glyburide; glipizide; gliclazide; and glimepiride. The availability and preferred use of individual drugs vary across countries.

Second-generation compounds generally have greater glucose-lowering potency by weight than first-generation agents. However, potency does not automatically imply superior overall clinical value. Duration of action, active metabolites, hypoglycaemia risk, renal and hepatic function, affordability, and patient-specific treatment goals influence selection [4,5].

Sulfonylureas are insulin secretagogues: they stimulate endogenous insulin release rather than directly replacing insulin or primarily improving peripheral insulin sensitivity. Their effectiveness may diminish as type 2 diabetes progresses and pancreatic β-cell function declines.

Molecular mechanism of action

The principal pharmacological action of sulfonylureas occurs in pancreatic β-cells. Their target is the sulfonylurea receptor 1 (SUR1), a regulatory subunit of the ATP-sensitive potassium channel complex. The channel also contains Kir6.2, which forms the potassium-conducting pore.

Under normal physiological conditions, the metabolism of glucose influences the intracellular ATP-to-ADP ratio. Changes in cellular energy status regulate ATP-sensitive potassium channels and thereby link glucose metabolism to electrical activity in β-cells.

Sulfonylureas bind to SUR1 and promote closure of ATP-sensitive potassium channels. Reduced potassium efflux depolarises the β-cell plasma membrane. Membrane depolarisation opens voltage-dependent calcium channels, permitting calcium ions to enter the cell. The resulting rise in intracellular calcium triggers exocytosis of insulin-containing secretory granules.

The sequence can be summarized as follows:

Sulfonylurea binding to SUR1 closure of ATP-sensitive potassium channels membrane depolarization opening of voltage-dependent calcium channels increased intracellular calcium insulin secretion.

This mechanism explains both the therapeutic effect and a major safety limitation. Because the secretory response is not fully dependent on the prevailing glucose concentration, insulin release may occur when blood glucose is already low. Consequently, sulfonylureas can produce clinically significant hypoglycaemia, particularly when meals are missed, renal function is impaired, or interacting medicines increase exposure [4,5,8].

ATP-sensitive potassium channels are also expressed in tissues outside the pancreatic β-cell, including cardiac and vascular smooth muscle. Differences in sulfonylurea receptor interactions have therefore generated interest in potential cardiovascular effects. Nevertheless, mechanistic differences between drugs should not be interpreted as proof of superior cardiovascular outcomes without appropriate clinical evidence.

Pharmacodynamic effects

The primary pharmacodynamic outcome of sulfonylurea administration is increased insulin secretion and reduced blood glucose concentration. Their effect is generally most evident when pancreatic β-cells retain functional insulin-secretory capacity.

Sulfonylureas can lower fasting and postprandial glucose concentrations, although the magnitude and duration of response depend on the individual agent, dose, baseline glycaemia, β-cell function, diet, physical activity, and adherence. Their glucose-lowering efficacy may be limited by progressive β-cell dysfunction, which is characteristic of the natural history of type 2 diabetes.

A clinically important distinction exists between glucose-lowering efficacy and the overall suitability of a drug. Sulfonylureas may be effective and relatively affordable, but the risk of hypoglycaemia and weight gain can make them less attractive for some patients than alternatives with lower hypoglycaemia risk or additional cardiovascular and renal benefits.

Thus, therapeutic evaluation should consider the magnitude of glucose reduction alongside the risk of symptomatic hypoglycaemia, the patient's capacity to recognize and manage low glucose, treatment cost, comorbidities, and individualized glycaemic goals [5,6].

Pharmacokinetics

Sulfonylureas differ in absorption, protein binding, metabolism, half-life, and elimination. These differences help explain variation in the timing and duration of glucose-lowering activity and the likelihood of prolonged hypoglycaemia.

Most sulfonylureas are administered orally and are absorbed from the gastrointestinal tract. Many are extensively bound to plasma proteins, particularly albumin. Protein binding can influence the free fraction available for distribution and elimination, although the clinical consequences of displacement interactions depend on several factors and should not be inferred from protein binding alone.

Hepatic metabolism is important for many members of the class. Some agents produce metabolites with pharmacological activity, while others are converted primarily to less active compounds. Renal impairment can increase the risk of hypoglycaemia, particularly when active metabolites accumulate or drug clearance is reduced.

Glibenclamide is associated with a comparatively important risk of prolonged hypoglycaemia, particularly in older people and those with impaired renal function. Glipizide is often preferred over glibenclamide when a sulfonylurea is considered necessary in renal impairment, although careful dose selection and monitoring remain essential. Gliclazide and glimepiride have their own pharmacokinetic properties and precautions; none should be considered risk-free.

Chlorpropamide has a prolonged duration of action and has historically been associated with prolonged hypoglycaemia and hyponatraemia. These considerations have reduced its suitability in many contemporary settings.

Because pharmacokinetic properties differ among compounds, the choice and dosing of sulfonylureas should follow individual product information and applicable clinical guidance rather than assuming a uniform class-wide regimen [4,5].

Therapeutic applications in type 2 diabetes mellitus

Sulfonylureas are used to improve glycaemic control in type 2 diabetes when endogenous insulin secretion remains sufficient. They may be prescribed as monotherapy in selected circumstances or combined with other glucose-lowering medicines when additional glycaemic reduction is required.

Their relatively rapid glucose-lowering effect, oral administration, familiarity, and low cost in many settings have contributed to their continuing use. These attributes are particularly relevant where healthcare resources are constrained or newer treatments are financially inaccessible.

Nevertheless, the choice of treatment should be guided by more than glycaemic efficacy alone. Current diabetes management places substantial emphasis on cardiovascular disease, heart failure, chronic kidney disease, body weight, hypoglycaemia risk, patient preferences, and affordability. In patients with established cardiovascular disease, heart failure, or chronic kidney disease, certain sodium–glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists may offer benefits that influence treatment selection independently of glucose lowering [5,6].

Sulfonylureas may therefore remain appropriate for selected patients, but they should not automatically be considered the preferred second-line treatment for every individual. Treatment decisions should be individualized, and the expected benefits should be weighed against adverse effects and available alternatives.

Adverse effects

Hypoglycaemia

Hypoglycaemia is the most important adverse effect of sulfonylureas. Symptoms may include sweating, tremor, palpitations, hunger, dizziness, irritability, impaired concentration, and confusion. Severe episodes can lead to seizures, loss of consciousness, injury, or other serious consequences.

Risk increases when a patient takes medication without adequate food intake, misses meals, performs unplanned strenuous exercise, consumes substantial alcohol, or receives an excessive dose. Older age, renal impairment, hepatic dysfunction, frailty, and interacting medicines can further increase vulnerability.

Long-acting compounds and agents with active metabolites may produce prolonged or recurrent episodes. A patient who experiences recurrent hypoglycaemia requires clinical reassessment of the drug, dose, meal pattern, comorbidities, and other medicines.

Weight gain

Weight gain may occur because increased insulin secretion promotes energy storage and reduces urinary glucose loss as glycaemia improves. The degree of weight change varies between individuals and treatment regimens. This effect can be disadvantageous in patients who are already overweight or who have obesity-associated metabolic complications.

Gastrointestinal and dermatological effects

Some patients experience nausea or other gastrointestinal symptoms. Rash, pruritus, and other hypersensitivity reactions can occur. Severe reactions are uncommon but require appropriate clinical assessment.

Haematological effects

Rare haematological adverse reactions have been described with individual sulfonylureas. Their clinical significance depends on the compound and the patient's circumstances.

Hyponatraemia

Chlorpropamide has been associated with inappropriate antidiuretic hormone activity and hyponatraemia. This effect is particularly relevant when considering its prolonged pharmacological action and its limited role in contemporary treatment.

The possibility of hypoglycaemia is not eliminated by good average glycaemic control. Indeed, an apparently satisfactory long-term glycated haemoglobin concentration may coexist with episodes of dangerously low glucose. Assessment should therefore consider symptomatic events and, where indicated, self-monitoring or continuous glucose monitoring rather than relying exclusively on glycated haemoglobin [4–6].

Drug interactions

Drug interactions may increase or decrease sulfonylurea exposure, alter glucose regulation, or compound the risk of hypoglycaemia. Their importance depends on the specific drug, dose, duration of use, renal and hepatic function, and the patient's dietary intake.

Some medicines may increase sulfonylurea effects through metabolic inhibition, altered protein binding, or other pharmacokinetic mechanisms. Examples requiring attention include selected azole antifungals, some antibiotics, and other medicines known to influence the metabolism or action of particular sulfonylureas. The relevance of an interaction must be checked against the prescribing information for the exact agents involved.

Other glucose-lowering medicines may produce additive glucose reduction when combined with a sulfonylurea. Insulin and certain combination regimens may therefore require dose reassessment to avoid hypoglycaemia. Alcohol can complicate glucose regulation and impair recognition or management of low glucose in some circumstances.

B-Blockers may mask some adrenergic warning symptoms of hypoglycaemia, particularly palpitations and tremor, although not every symptom is necessarily concealed. Patients using medicines that may obscure warning signs should receive appropriate education and monitoring.

The interaction assessment should extend beyond prescription medicines to non-prescription products, dietary supplements, alcohol consumption, irregular eating patterns, and acute illness.

Patients should be advised not to independently change doses in response to a suspected interaction without appropriate professional guidance.

Contraindications and special populations

Sulfonylureas are not suitable for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis because their mechanism depends on functional pancreatic β-cells and does not provide the insulin replacement required in those conditions.

Pregnancy, severe hepatic dysfunction, substantial renal impairment, frailty, and recurrent hypoglycaemia require particular attention when selecting glucose-lowering treatment. The appropriateness of an individual sulfonylurea varies with the clinical setting and applicable guidance.

In older adults, the consequences of hypoglycaemia may be especially serious because of falls, cognitive impairment, polypharmacy, irregular food intake, and comorbid disease. Less stringent glycaemic targets may be appropriate for some patients, and agents with lower hypoglycaemia risk may offer a safer treatment strategy.

In renal impairment, both drug elimination and the patient's physiological response to hypoglycaemia may be altered. A compound with active metabolites or a prolonged effect may be particularly problematic. Dose adjustment alone may not always be sufficient; an alternative medicine may be more appropriate.

Patients should receive individualized instructions about meals, missed doses, symptoms of hypoglycaemia, glucose monitoring, and circumstances requiring urgent medical attention. The precise recommendations depend on the selected medicine and the patient's clinical circumstances [4–6].

Cardiovascular considerations

The cardiovascular pharmacology of sulfonylureas has attracted sustained interest because ATP-sensitive potassium channels participate in the regulation of pancreatic insulin secretion and are also present in cardiac and vascular tissues.

Experimental evidence suggests that different sulfonylureas may interact differently with channel subtypes. Such differences have led to investigation of their potential effects on myocardial ischaemic preconditioning and cardiac electrophysiology. However, experimental findings cannot by themselves establish differences in clinical cardiovascular outcomes.

Severe hypoglycaemia may provoke sympathetic activation, alter cardiac electrical stability, and contribute to cardiovascular stress. This risk is particularly relevant in patients with established cardiovascular disease or a high burden of comorbidity.

Clinical decisions should therefore distinguish mechanistic hypotheses from demonstrated patient outcomes. Where a patient has heart failure, atherosclerotic cardiovascular disease, or chronic kidney disease, contemporary diabetes guidelines should inform the selection of agents with demonstrated outcome benefits. Sulfonylureas may still have a role, but their affordability and glucose-lowering efficacy must be balanced against the absence of equivalent class-wide evidence for specific cardiovascular or renal benefits [5,6,9].

Sulfonylureas and the evolution of diabetes treatment

The treatment landscape for type 2 diabetes has expanded considerably with the introduction of medicines acting through different physiological pathways. These include metformin, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and other therapeutic options.

These classes differ in their effects on insulin sensitivity, urinary glucose excretion, incretin signalling, body weight, cardiovascular outcomes, and renal outcomes. Sulfonylureas remain valuable in some circumstances because of their efficacy, oral administration, clinical familiarity, and comparatively low acquisition cost.

However, the modern therapeutic objective extends beyond lowering blood glucose. It includes prevention of microvascular and macrovascular complications, reduction of hypoglycaemic events, preservation of quality of life, and selection of treatment according to comorbid disease and patient priorities.

The appropriate role of sulfonylureas is consequently contextual. In a patient with limited access to newer agents, preserved β-cell function, reliable meal intake, and an acceptable hypoglycaemia risk, a carefully selected sulfonylurea may be a reasonable option. In a patient with recurrent hypoglycaemia, irregular nutrition, advanced frailty, or a strong indication for a medicine with proven cardiovascular or renal benefits, a different approach may be preferable.

Comparative Pharmacological Analysis

Although cephalosporins and sulfonylureas differ in their therapeutic purposes, their comparison illustrates several important principles of rational pharmacotherapy.

Drug targets and selectivity

Cephalosporins act primarily on bacterial penicillin-binding proteins, disrupting a structural process that is essential for susceptible bacterial survival. Their selective toxicity arises from the absence of peptidoglycan cell walls in human cells.

Sulfonylureas act on SUR1-containing ATP-sensitive potassium channels in pancreatic β-cells, stimulating insulin release. Their effect depends on a functional physiological system rather than direct antimicrobial activity.

Both classes demonstrate the importance of target engagement, but their safety limitations arise through different pathways. Cephalosporin adverse effects may involve hypersensitivity, microbiome disruption, neurological toxicity, or agent-specific organ effects. Sulfonylurea toxicity is strongly associated with excessive insulin-mediated glucose reduction.

Pharmacokinetic–pharmacodynamic relationships

For cephalosporins, treatment success is closely related to the time that unbound drug concentration remains above the pathogen's minimum inhibitory concentration. The dosing schedule must therefore account for the compound's half-life, renal function, infection severity, and organism susceptibility.

For sulfonylureas, pharmacokinetics determine the duration and intensity of insulin-secretagogue activity. Prolonged exposure can increase the risk of sustained hypoglycaemia, particularly when clearance is impaired or meals are missed.

The comparison highlights a broader principle: drug concentration is clinically meaningful only when interpreted alongside the pharmacodynamic response, the target tissue, and the patient's physiological condition.

Resistance and loss of therapeutic response

Cephalosporin resistance is primarily a microbiological phenomenon involving β-lactamases, altered target proteins, permeability changes, efflux, and combinations of these mechanisms. Resistance can render a previously effective antimicrobial regimen ineffective against a particular organism.

Reduced sulfonylurea effectiveness may instead arise from progressive pancreatic β-cell dysfunction, inconsistent adherence, changes in diet or body weight, intercurrent illness, or progression of type 2 diabetes. It should not be described as bacterial-type antimicrobial resistance.

The distinction is clinically important because the corrective strategies differ. Cephalosporin treatment failure may require cultures, susceptibility testing, source control, or a change in antimicrobial coverage. Diminished sulfonylurea response requires reassessment of glycaemia, adherence, disease progression, treatment goals, and the suitability of combination or alternative therapy.

Safety monitoring

Cephalosporin monitoring may involve clinical response, microbiological findings, renal function, hypersensitivity symptoms, gastrointestinal complications, and selected laboratory parameters according to the agent and treatment context.

Sulfonylurea monitoring centres on blood glucose, symptoms of hypoglycaemia, glycated haemoglobin, meal regularity, renal and hepatic function, and weight. The appropriate monitoring strategy depends on the patient's risk profile and the wider diabetes regimen.

For both classes, a prescription should be viewed as a clinical decision requiring reassessment rather than as an isolated pharmacological event.

Individualized treatment

The rational selection of a cephalosporin depends on the organism, infection site, severity, local resistance patterns, allergy history, renal function, and availability of alternatives.

The rational selection of a sulfonylurea depends on glycaemic goals, β-cell function, hypoglycaemia risk, nutritional stability, renal and hepatic function, comorbidities, affordability, and patient preference.

Thus, the two classes illustrate a common principle: pharmacological efficacy must be interpreted in the context of individual patient characteristics and clinically meaningful outcomes.

Clinical Implications and Future Perspectives

The future use of cephalosporins will depend partly on the ability of healthcare systems to preserve their effectiveness in the face of antimicrobial resistance. Drug development remains important, particularly for infections caused by resistant Gram-negative bacteria, but new agents alone cannot resolve the problem. Infection prevention, timely diagnosis, appropriate culture collection, susceptibility-guided prescribing, and effective stewardship remain indispensable.

Advances in pharmacokinetic modelling and therapeutic drug monitoring may improve the optimization of selected β-lactam regimens in critically ill patients. These approaches can help clinicians account for altered renal clearance, expanded distribution volumes, extracorporeal support, and other physiological changes that make antibiotic exposure less predictable.

For sulfonylureas, the principal challenge is not simply achieving lower glucose concentrations but doing so without exposing patients to unacceptable hypoglycaemia or other adverse effects. Improved glucose monitoring, patient education, medication reconciliation, and treatment individualization can reduce preventable harm.

The expanding availability of newer glucose-lowering agents has also changed the context in which sulfonylureas are prescribed. Future research should continue to clarify comparative effectiveness, long-term safety, cost-effectiveness, and outcomes in populations underrepresented

in clinical trials. Decisions should be based on reliable clinical evidence rather than assuming that all agents within a class produce identical benefits or risks.

In both therapeutic areas, accessible healthcare and affordability remain important. A pharmacologically appropriate medicine must also be available, correctly prescribed, appropriately administered, and monitored. The integration of scientific evidence with practical healthcare delivery is therefore central to improving therapeutic outcomes.

Limitations of the Review

This review is narrative in design and does not provide a systematic or exhaustive appraisal of every cephalosporin and sulfonylurea. The drugs within each class differ substantially in molecular structure, pharmacokinetics, clinical indications, and safety profiles; consequently, class-level statements should not replace individual prescribing information.

No pooled estimates of clinical efficacy, adverse-event rates, or comparative mortality were calculated. The review also does not establish a ranking of individual agents based on original experimental or clinical data. In addition, recommendations may vary across countries because of differences in antimicrobial resistance, medicine availability, regulatory approval, and clinical guidelines.

Before submission, the manuscript should undergo a final reference verification, editorial review, and check against the journal's current author instructions. Any claims that depend on a specific national guideline or product label should be updated against the version applicable at the time of submission.

CONCLUSION

Cephalosporins and sulfonylureas exemplify two distinct but fundamental areas of clinical pharmacology. Cephalosporins inhibit bacterial cell-wall synthesis through interactions with penicillin-binding proteins and provide a range of therapeutic options for susceptible infections. Their clinical effectiveness depends on the relationship between drug exposure, pathogen susceptibility, infection site, and the mechanisms of bacterial resistance. Responsible prescribing, appropriate dosing, and antimicrobial stewardship are essential to maintain efficacy and reduce avoidable harm.

Sulfonylureas stimulate pancreatic β-cell insulin secretion by closing ATP-sensitive potassium channels through interaction with sulfonylurea receptors. They can provide substantial glycaemic improvement and remain relevant in selected treatment settings, particularly when affordability is an important consideration. However, hypoglycaemia, weight gain, pharmacokinetic variation, and the progression of β-cell dysfunction limit their suitability for some patients.

The central lesson is that pharmacological knowledge must be translated into individualised clinical decisions. A drug's mechanism of action, therapeutic potential, safety profile, and patient-specific context must be considered together. Evidence-based prescribing, regular reassessment, and clear patient education provide a foundation for safer and more effective pharmacotherapy.

Funding: No external funding has been declared for the preparation of this narrative review.

Conflict of interest: The author should confirm and disclose any actual financial, professional, or other competing interests before submission. If none exist, the author may state: "The author declares no conflict of interest."

Author contributions: Devanssh Mehta: conceptualization, literature review, synthesis, and manuscript preparation.

Ethics approval: Not applicable to a narrative review that does not involve new research on human participants or animals.

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