IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Sulfonylurea And Their Use In Clinical Practice

[1]Sahil H. Nevase, [2]Pranav D. Gaikwad, [3.] Sahil P. Malshikare [4],Sudarshan D. Khatal

[1]. B.Pharmacy Final Year Students, Sarsam College Of Pharmacy, Palashiwadi,

Dr. Babasaheb Ambedkar Technological University, Lonere, Maharashtra, India

Abstract : Many anti-diabetic pills with special mechanisms of action are actually avail capable for treatment of Type2 diabetes mellitus. Sulfonylureas for a long time occupied an essential role in the management of type 2 diabetes as an alternative or a complement to metformin. However, the launch of new oral antidiabetic drugs (OADs), firstly DPP-4 inhibitors (gliptins) and more recently SGLT2 inhibitors (gliflozins), has markedly change the scene. But the sulfonylureas have been extensively used for treatment of type 2 diabetes for nearly 50 years and even in our time, are widely used for treatment of this devastating chronic illness. Here we have review some of the available data on the sulfonylureas, evaluating their mechanism of action and their effects on glycemic control. We can conclude that sulfonylureas are still the most used anti-diabetic agents: may be this is due to their low cost, to the possibility of mono-dosing and to the presence of an association with metformin in the same tablet

Key words: **Sulfonylurea, Type 2 Diabetes,** **Hypoglycemia**

INTRODUCTION

The history of sulfonylureas (SUs) commenced in 1937 with the remark of the hypoglycemic interest of artificial sulfur compounds.[1].5 years later in 1942 that positive sulphonamide antibiotics ought to initiate extreme hypoglycaemia in patients treated via the Marcel Janbon and his colleagues for typhoid fever. They act as insulin secretagogues,lowering blood glucose awareness by means of augmenting the first-segment release of right away reversable(reserve) insulin from Beta cells.[2]. Sulphonylureas (SUs),commercialized within the overdue Nineteen Fifties,have been the first pharmacological class of oral antidiabetic marketers (OADs). They had been determined in france through August Loubatieres and his crew.[3]. Those marketers stimulate insulin Secretion by closing potassium channels in beta cells of langerhans islets. SU-inspired insulin segment is independent of plasma glucose degree. For that reason SUs are associated with a excessive risk of hypoglycemia for a long term, the handiest drug alternative kind biguanides.[3]. The related biguanides regarded in the 1950s but have due to the fact that faded in importance in order that metformin is almost the simplest representative nonetheless used nowadays. Work inside the 1940s and 1950s caused the discovery and improvement of hypoglycemic sulfonylureas(SUs), a healing class unigue for its specificity and safety. Those products were determined to stimulate insulin secretion by using the endocrine pancreas.[4]. The next development in sulphonylurea (Su) therapy in the america did no longer occurs till the release of the stronger 2nd-generation dealers glipizide and glyburide in 1984, these agents have been in use in Europe for the several years before this, the following (SU) agent, glimepriride, that is once in a while referred to as a third-era agent, changed into launched in1995.[5].In 2022, It was the 42nd most commonly prescribed medication within the america, with more than 14 million prescriptions.[6,7].

Mechanism of Action:

Sulfonylureas are broadly used to deal with non- insulin dependent diabetes mellitus. these pills exert their hypoglycemic consequences through stimulating insulin secretion from the pancreatic beta-cellular. Their number one mechanism of movement is to close ATP sensitive k-channels within the beta-mobile plasma membrane, and so initiate a chain of activities which bring about insulin release.[8] Sulfonylurea bind to receptar and inhibit the ATP touchy potassium channels (ok) at the pancreatic beta cells. As a end result, potassium efflux decreases, of the beta-cell membrane depolarizes Membrane depolarization reasons calcium channels to open main to clacium inflow and growth intracellular calcium, which stimulates insulin secreation from the pancreatic beta cells.[9,10]. Potassium is made from two of the proteins, Kir 6.2 that bureaucracy the pore of the okay channels, and a sulfonylurea recrptor (SUR).[11].SUR1 and SUR2 are the subtype of the sulfonylurea receptor.[12].

The SUR1 is the maximum gift in the mind and on the beta cells inside the pancreas. SUR2 is present inside the cardiac muscle (as inform SUR2A) and the easy muscle (as isoform SUR2B). Sulfonylurea differ in their affinity to the SUR subtype receptors and their efficacy in ultimate the okay channels in contrast to the other sulfonylureas, glimperide has a lower affinity to the cardiac muscle tissue and isn't related to cardiovascular protection issues.[13]. The depolarization opens the calcium channels which

permits calcium to go into the cell If this inflow of calcium in inside the cell. The growth in level of calcium ions within the cell stimulates the release of insulin from the beta cells of pancreas.[14].

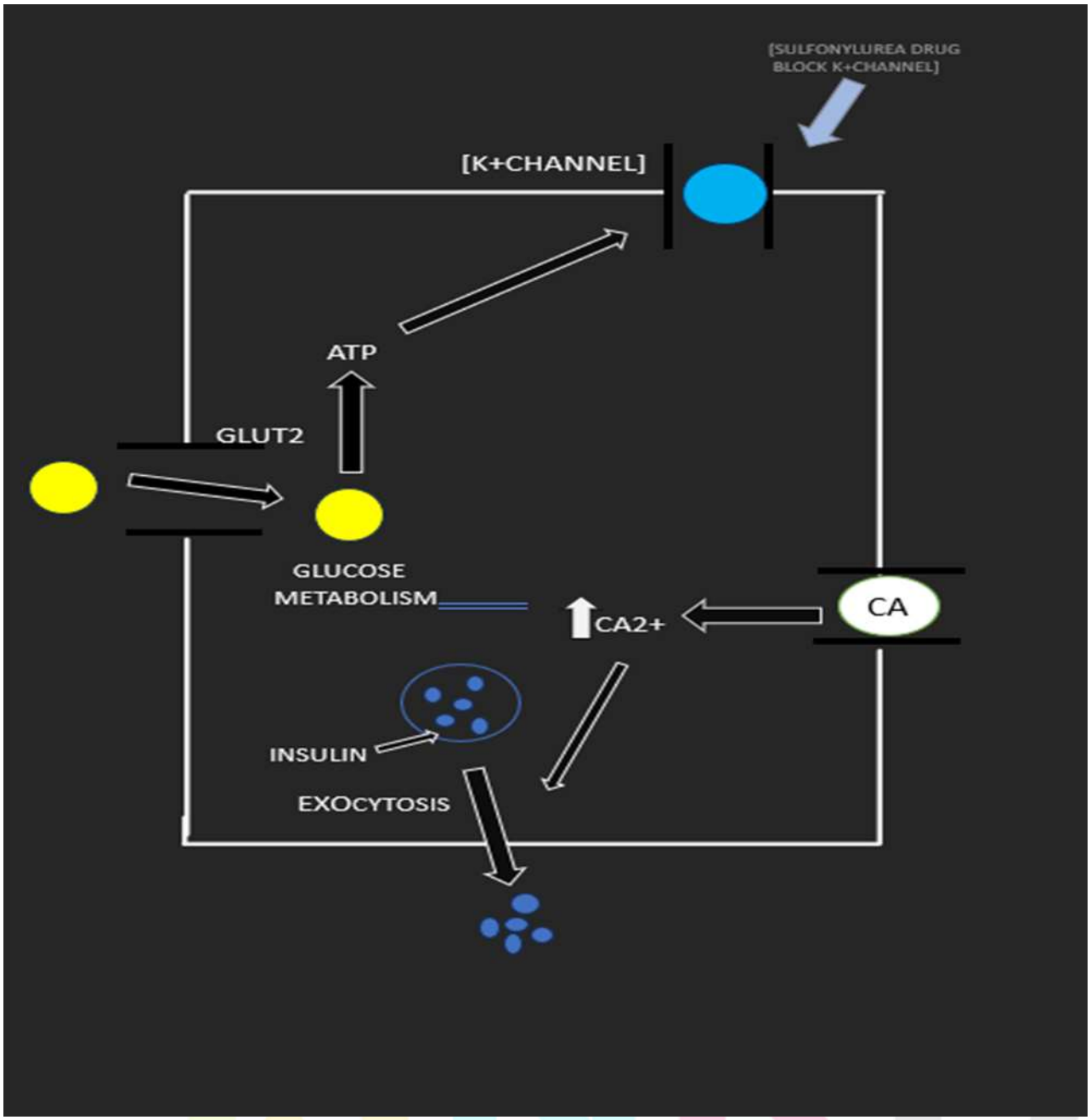


Fig:1: Mechanism of action of sulfonylurea.

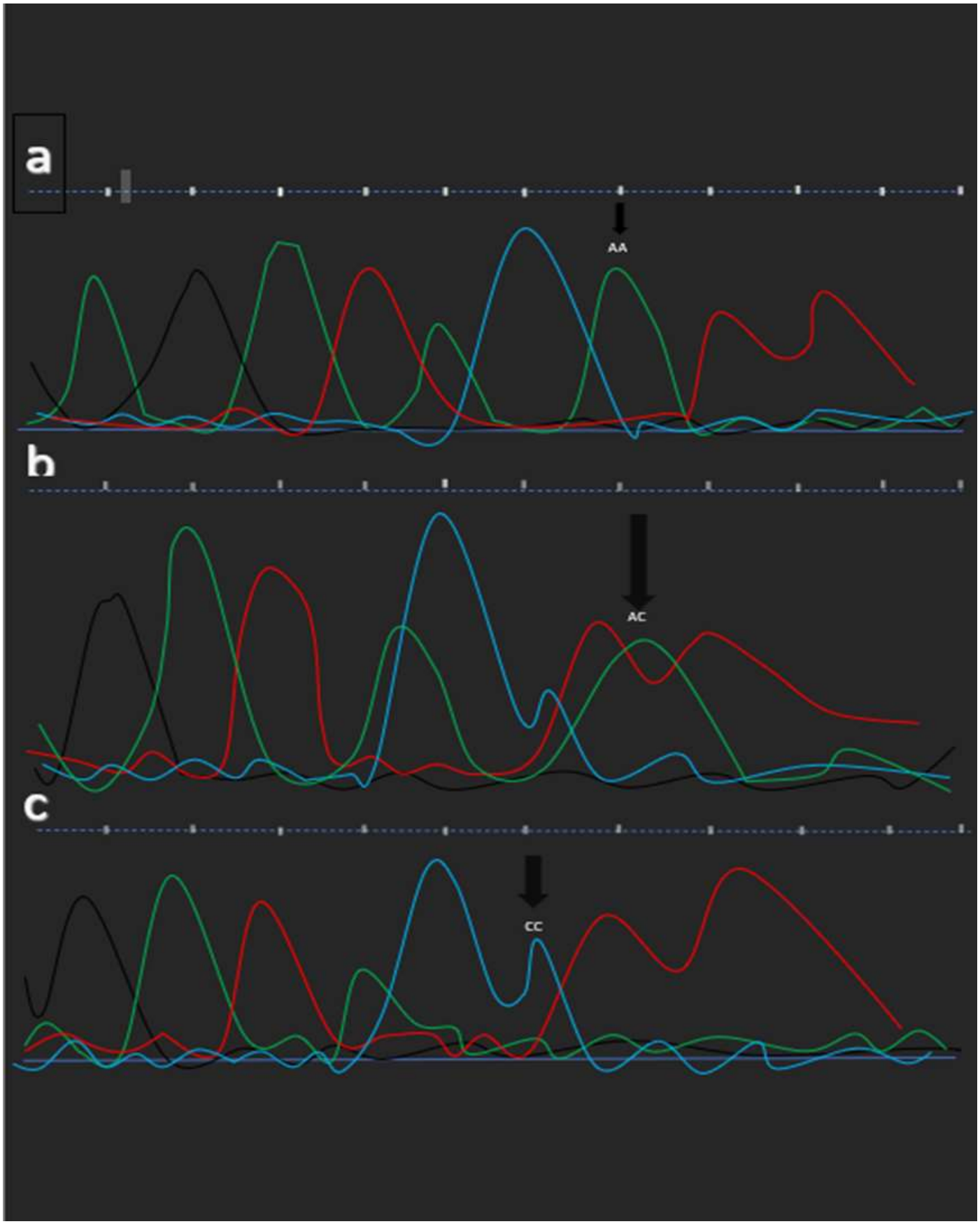
Pharmacokinatic: Absorption:

Despite the fact that with time and one-of-a-kind quantities, all sulfonylureas are absorbed by way of the intestine after oral intake, every one with its unique absorption time and bioavailability.[15].To optimize the absorption, sulfonylureas should be taken 30 min earlier than meals, and their dosages ought to be extended every 2 weeks if glycemic control has not been reached. The standard beginning dose have to be low [for example glibenclamide 2.5 mg or glimepiride 2 mg]. higher dose [for example, more then 10 mg of glibenclamide] rarely further progressed glycemic control and must be averted.[16].

Metabolism:

All sulfonylureas are appreciably metabolized inside the liver, broadly speaking by means of the cytochrome P450 2cg isoenzyme (CYP2C9). Polymorphisms in the CYP2C9 gene significantly affect the enzymetic hobby of encoded CYP2C9. Primarily based all phenotype the populace can be divided into sizable intermediate, and bad metabolizers [Ems, IMs and PMs,

respectively]. Thus far, extra than 50 extraordinary allelic editions had been diagnosed inside the CYP2C9 gene.[17].
Among them ,the maximum not unusual are [RS 1799853,430 C > T, Are 144(ys)] and [rs 1057910,1075A > C , Ile 359Leu]. Which permit for prediction of greater than eighty five% of PMs in most populations, along with caucasians. Altered pharmacokinetics of sulfonylureas due to polymorphism within the CYP2C9 gene may additionally partially provide an explanation for the difference in affected person dose requirements and frequency of damaging reactions.[17].



2 Metabolism of sulfonylurea and its different forms with specific interval of the time.[18].

Binding of Drug:

Sulfonylurea bind to the sulfonylurea receptor subunit of the k-ATP channel. The channel closes, with increasing the membrane potential. Voltage-sensitive calcium channels opens. Calcium flows into the cellular, which activates kinases. Insulin is released into the bloodstream. Insulin is launched into the bloodstreamas an end result after binding of sulfonylurea drug to their receptor. [19]. There are mainly 3 sorts of sulfonylurea receptor, SUR1, SUR2A, SUR2B.

1]SUR1: These kind of sulfonylurea receptor in particular observed in the beta-cells, these receptor are relatively sensitive to the sulfonylureas. 2]SUR2A: These type of receptor are specifically present within the cardiac and skeletal muscle cells.

3]SUR2B: Those sort of sulfonylurea receptor are determined in the vascular and non-vascular easy muscle tissues cells.[20].

Drug interaction of sulfonylurea:

Drug interplay may be defined as whilst a drug reacts with any other drug, meals, beverage, complement or medical circumstance. This can purpose the drug to be less or greater powerful or cause unexpected aspect consequences.[22] Sulfonylurea is a type of anti-diabetic medication, can interact with many other drugs, including herbal supplements, non-steroidal anti-inflammatory drugs, and anti-hypertensives. These interactions can cause hypoglycemia or low blood sugar level.[23].

1)Sulfonylurea interact with anti-inflammatory drug: Sulfonylureas are fantastically protein sure pills and can be displaced from blood protein binding sites with the aid of drugs consisting of the non-steroidal anti-anti-inflammatory capsules. This could cause a short term increase in loose (unbonded) sulfonylurea and therefore temporary hypoglycaemia.[24].

2)Sulfonylurea interact with anti-hypertensive:

A few antihypertensive marketers may favour episodes whilst co-prescribed with sulphonylureas or meglitinide derivatives, especially ACE inhibitors, however this impact seems to result from a pharmacodynamic drug-drug interplay rather than from a pharmacokinetic drug-drug interplay. No, or only modest, interferences had been described with glucose-reducing sellers and different pharmacological compounds such as digoxin or warfarin.[25,26]. The consequences of inducers or inhibitors of CYP isoenzymes at the metabolism and pharmacokinetics of the glucose-reducing retailers of each pharmacological elegance has been examined. Notably improved (with CYP inhibitors) or reduced (with CYP inducers) plasma stages of sulphonylureas, meglitinide derivatives and thiazolidinediones had been pronounced in wholesome volunteers, and these pharmacokinetic modifications may additionally lead to better or reduced glucose-lowering action, and as a consequence hypoglycaemia or worsening of metabolic manage, respectively. Similarly, some case reports have evidenced capacity drug-drug interactions with various antihyperglycaemic marketers which can be typically related to a better danger of hypoglycaemia.[27,28].

3)Sulfonylurea interact with Herbal Supplements:

Sulfonylureas are normally metabolized by way of CYP2C9 enzyme and the herbs like St. John's wort and Ginkgo biloba result in CYP2C9-mediated metabolism of sulfonylureas at the same time as fruit juices like Pomegranate juice and Pineapple juice inhibit their metabolism. In addition, the antidiabetic natural dietary supplements including sour melon, Fenugreek, Cinnamon, Gymnema, Ginseng, Ginger, Garlic, Aloe vera, Sesame, Andrographis paniculata and Neem potentiate the hypoglycemic hobby of sulfonylureas, pharmacodynamically.[29].

4)Sulfonylurea interact with alcohol:

Sulfonylurea drugs druginteractions occur with sulfonylureas.First-technology sulfonylureas, particularly chlorpropramide, may motive afacial flushing reaction while alcoholis ingested. This could be similar tothat as a result of disulfiram, whichblocks aldehyde dehydrogenase,ensuing in expanded tiers ofacetaldehyde. Acetaldehyde can resultin flushing and possibly nausea orvomiting at higher tiers .[30].

Adverse Effects:

Sulfonylureas stimulate insulin secretion no matter the serum glucose tiers. Therefore, hypoglycemia is the most not unusual facet impact and a primary challenge associated with sulfonylureas. Hypoglycemia happens whilst blood glucose stages drop below 70 mg/dL.[31,32]. Sufferers can also experience sweating, shakiness, irritability, confusion, tachycardia, and a sense of starvation. Hypoglycemia may be extreme, especially after a missed meal, exercise, or takingsulfonylureas at a excessive dose.[33,34,35]

Glipizide, glimepiride, and gliclazide are associated with a lower prevalence of hypoglycemia compared to glyburide.[36]. Because of sulfonylureas bind to plasma proteins with high affinity, the chance of hypoglycemia increases when sure medicinal drugs displace sulfonylureas from their plasma protein binding web sites. Examples include sulfonamides, gemfibrozil, and warfarin.[37]. Weight gain is common with sulfonylureas.The ADA guideline recommends thinking about the affected person's weight when deciding on an antidiabetic drug. Keep away from prescribing sulfonylureas to overweight patients.[38,39]. Different common aspect outcomes include nausea, diarrhea, dizziness, and headache.[40]. Chlorpropamide and tolbutamide reason facial flushing with alcohol.[41].

The university group Diabetes software (UGDP) trial showed an improved risk of mortality with tolbutamide.[42]. As a end result, the food and Drug management (FDA) required a boxed caution about the increased danger of cardiovascular activities with all sulfonylureas and that manufacturers should prove the cardiovascular protection of all new antidiabetic medications.[43]. Glimepiride isn't related to an expanded cardiovascular danger.[42].The Cardiovascular and Renal Microvascular outcome observe with Linagliptin (CARMELINA) showed the dipeptidyl peptidase-four (DPP-four) inhibitor, linagliptin, to have neutral cardiovascular safety consequences.[44]. The Cardiovascular outcome have a look at of Linagliptin as opposed to Glimepiride in patients with type 2 Diabetes (CAROLINA) showed comparable cardiovascular effects between glimepiride and linagliptin.[45]. If

a sulfonylurea is vital for an aged patient, the ADA tenet recommends the usage of glipizide or glimepiride over glyburide because they are shorter acting and related to less threat of hypoglycemia.[46].

Dosing of sulfonylurea:

SULFONYLUREA	STRENGTHS	DOSING
Gliclazide (immediate release)	40mg, 80mg, 160mg	Initially40-80 mg daily; increased, if necessary, up to 160 mg once daily, with breakfast. Divide dases higher than 160 mg; max.320 mg/day.
Gliclazide (modified release)	30 mg, 60 mg	Initially 30 mg daily with breakfast. Adjust dose every 4 weeks (after 2 weeks, if no decrease in blood glucose);max.120 mg/day.
Glimepiride	1 mg, 2 mg, 3 mg, 4 mg	Once daily with first main meal.
Glipizide	5 mg	Initially 2.5-5 mg daily, take shortly before breakfast or lunch, up to 15 mg may be given as asingle dose, higher doses divided; max. 20 mg/day
Tolbutamide	500 mg	0.5-1.5 g daily in divided doses, dose to be taken with or immediately after meals; alternatively after meals; alternatively 0.5-1.5 g once daily, dose to be taken with or immedistely after breakfast; maximum 2 g per day

Reference: 1]John R . White, Jr. PA-C, PharmD; A Brief History of the Development of Diabetes Medications; Diabetes Spectr 2014;27(2):82-86.
2]Jan W Seetho, John P.H Wilding , in Clinical Biochemistry: Metabolic and clinical Aspect (Third Edition),2014. 3]Andre J Scheen; Sulfonylureas in the Management of type 2 diabetes: To be or not to be? Diabetes Epidemiology and management 1 (2021)100002.
4]J Duhault et al. Diabetes Res Clinpract. 1991:14 Suppl 2:s9-13; History and evolution of the concept of oral therapy in diabetes; National Library of Medicine; PMID:1794272. DOI:10.1016/0168-8227(91)90003.v. 5]John R White, Jr. PA-C pharmD; A Brief History of the Development of Diabetes Medication; Diabetes Spectr 2014;27(2):82-86.
6]THE TOP 300 OF 2022: Provided by the Clincalc Drug States Database; Clincalc.com.
7]Glipizide Drug usage statistics, united states, 2013-2022; Clincalc. Retrieved 30 August 2024. 8] Ashcroft FM; DOI: 10.1055/s-2007-979837; Horm Metab Res 09/1996 volume 28 pages=456-463. 9] Proks P Reimann F, Green N, Gibble F, Ashcroft F. Sulfonylurea stimulation of insulin secretion. Diabetes 2002 Dec ; 51 suppl 3:s368-76 [PubMed].
10]Confederate L, Constantin S, Lupascu F, Panzaria A, Hancianu M, Profire L. HYPOGLYCEMIA INDUCED BY ANTIDIABETIC SULFONYLUREAS. Rev Med Chir Soc Med Nat Iasi. 2015; Apr-Jun; 119(2):579-84.[PubMed]. 11]Colagiuri S, Matthews D, Leiter LA, Chan SP, Sesti G, marre M. The place of gliclazide MR in the evolving type 2 diabetes landscape: A comparison with other sulfonylureas and newer oral anti hyperglycemic agents. Diabetes Resclin pract. 2018 Sep; 143: 1-14.[PubMed].
12]Hambrock A, Loffler-Walz C, Quast U Gibenclamide binding to sulfonylurea receptor sub types: Dependence on adenire nucleotides. Br J Pharmacol 2002 Aug; 136(7):995-1004.[PMC free article] (PubMed).
13]Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: Scientific review. JAMA. 2002 Jan 16;287(3):360-72[PubMed]
14]Dr Matt and Dr Mike; Glipizide[sulfonylurea] mechanism of action; 5 Jul 2021.
15]Danial Sola, Luca Rossi, Gian Piero Carnevate Schianca, Pamela Maffioli, Marcello Bigliocca Roberto Mella, Francesca Corliano, Gian paolo Fra, Ettare Bartoli, Giuseppe Derosa; Arch Med Sci 2015;11,4:840-848. DOI: 10.5114 laoms. 2015.53304.
16]Stenman S, Melander A, Groop PH, Groop LC; What is the benefit of increasing the sulfonylurea dose? Ann Intern Med;1993;118:169-72.DOI:10.732610003-4819-118-3-199302010-00002.
17]Nurgul K, Bakirhan, Bengi Usiu, Sibel A. Ozkan Ankara University, Ankara, Turkey Food Safety and preservation; Chapter-5. The Detection of pesticide in foods using Electrochemical Sensors; Science Direct; 2018,Pages 91-141 .
18]Didari E, Sarhangi N, Afshri M,et al; A Pharmacogenetic pilot stydy of CYP2C9 Common genetic variant and sulfonylureas therapeutic response in Type 2 Diabetes mellitus patients. J Diabetes Metab Disord 20,1513-1519(2021). DOI: https://doi.org/10.1007/s40200-021-00894-0.
19]Book=Haddad and Winchesters clinical management of poisoning and drug overdose; Fourth edition :2007;Edited by: MICHAEL W SHANNON, STEPHEN W BORRON and MICHAEL J BURNS.
20]F M Ashcroft et al. J Diabetes Complications.2000 Jul-Aug; Tissue-Specific effects of sulfonylurea lessons from studies of cloned K(ATP) channels; PMID:11004427. DOI:10.1016/s1056-8727(00)00081-7.
21]Ailin Luo, Zheng Xie, Yue Wang, Shan Li, Jing Yan, Gaofeng Zhan, Zhigiang Zhou, Yilin Zhao, Shiyong Li; Type-2 Diabetes Mellitus-associated cognitive dysfunction: Advances in potential mechanism and therapies; Science Direct, Neuroscience and Biobehavioral Reviews Volume 137, June 2020, 104642.
22]Definition of Drug interaction-NCI Dictionary of Cancer Terms.
23]Curtis Triplitt, PharmD, CDE; Drug Interactions of Medications Commonly used in Diabetes spectr 2006;19(4):202-211. https://doi.org/10.2337/diaspect.19.4.202.24]Gillian M Shenfield, professor in clinical pharmacology, Department of clinical pharmacology, Royal North Shore Hospital Sydney; Drug Interactions with oral hypoglycaemic drugs; Australian Prescriber. Vol.20, No.4, 2001.
25]Andre J Scheen. Drug Saf. 2005; Drug Interactions of clinical importance with antihyperglycaemic agents: An update; Drug Saf. 2005;28(7):601-31. PMID:15963007. DOI:10.2165/00002018-200528070-00004.
26]Scheen AJ. Drug Interactions of Clinical importance with Anti-hyperglycaemic Agents: An update Drug Saf. 2005 Jul;28(7):601-631. DOI: 10.2165/00002018-200528070-00004. PMID: 27722966.
27] Greg L Plosker et al. Pharmacoeconomics. 2004.Repaglinide: A pharmacoeconomic review of it is used in type 2 diabetes mellites. DOI: 10.2165/00019053-200422060-00005. PMID: 15099124.
28]Andre J Scheen. Clin pharmacokinetic .2010 Sep. Dipeptidylpeptidase-4 inhibitors(gliptins):focus on Drug-Drug interactions. DOI:10.2165/11532980-000000000-00000. PMID: 20690781.clinpharmacokinetics 2010 Sep; 49(9):573-88.
29]Naina Mohamed Pakkir Maideen, Rajkapoor Balasubramaniam; pharmacologically relevant drug interactions of sulfonylurea anti-diabetics with common herbs; J Herbmed pharmacol. 2018;7(3):200-210. DOI: 10.15171/Jhp.2018.32. Scopus ID: 85050287362.30]Curtis Triplitt, PharmD, CDE; Drug Interaction of medication commonly used in Diabetes; Diabetes Spectr 1 October 2006;19(4):202-211. https://doi.org/10.2337/diaspect.19.4.202.
31]Dhimitri Nikolla, Do, Christopher Karns, Do; How Low Can You Go? Sulfonylurea Induced, clinical; EMResident; https://www.emra.org.
32]Schopman JE, Simon AC, Hoefnagel SJ, et al. The incidence of mild and severe hypoglycemia in patients with type 2 diabetes mellitus treated with sulfonylurea: A systematic review and meta-analysis. Diabetes Metab Res, Rev.2014;30(1):11-22.
33]Klein-Schwartz W, Stassinos GL, Isbister GK. Treatment of sulfonylurea and insulin overdose. Br J Clin Pharmacol.2016 Mar;81(3):496-504. [PMC free article] [PubMed].
34]Canadian Diabetes Association Clinical practice Guidelines Expert committee. Clayten D, Woo V, Yale JF. Hypoglycemia. Can J Diabetes. 2013 Apr; 37 suppl 1:s69-71.[PubMed].
35]Kalra S, Mukherjee JJ, Venkataraman S, Bantwal G, Shaikh S, Saboo B, Das AK, Ramachandran A. Hypoglycemia: The

neglected complication. Indian J Endocrinal Metab. 2013 Sep; 17(5):819-34. [PMC free article] [PubMed].
36]Webb DR, Davies MJ, Jarvis J, Seidu S, Khunti K. The right place for sulfonylureas today. Diabetes Res Clin Prect. 2019 Nov; 157:107836.[PubMed].
37]Thule PM, Umpierrez G. Sulfonylureas: A New Look At Old Therapy. Curr Diab Res. 2014 Apr; 14(4):473.[PubMed].
38]Schwartz S, Herman M. Revisiting weight reduction and management in the diabetic patient: Novel therapies provide new strategies. Postgrad Med. 2015 Jun; 127(5):480-93. [PubMed].
39]American Diabetes Association. 8. Obesity Management for the Treatment of Type 2 Diabetes: Standards of medical care In Diabetes -2021.Diabetes care. 2021 Jan; 44(suppl 1):S100-S110.[PubMed].
40]LiverTox: Clinical and Reserch Information on Drug-Induced Liver Injury.[Internet].National Institate of Diabetes and Digestive and Kidney Disease; Bethesda(MD):Mar 16,2018. Sulfonylureas, second Generation.[PubMed].
41]Jackson JE, Bressler R. Clinical pharmacology of Sulphonylurea hypoglycamic agents: Part 2. Drugs. 1981 Oct; 22(4):295-320.[PubMed].
42]Riddle MC. A Verdict for Glimepiridin: Effective and Not Guilty of cardiovascular Harm. Diabetes Care. 2019 Dec; 42(12):2161-2163.[PubMed].
43]Yandrapalli S, Jolly G, Horblitt A, Sanaani A, Aronow WS. Cardiovascular benefits and safety of non-insulin medications used in the treatment of Type 2 Diabetes mellitus. Postgrad Med.2017 Nov;129(8):811-821.[PubMed].
44]Rosenstock J, Perkovic V, Alexander JH, Cooper ME, Marx N, Pencina MJ, Toto RD, Wanner C, Zinman B, Buanstra d, Pfarr JT ,Von Eynatten M, MC Guire DK,CARMELINA® investigators. Rationale, design and baseline characteristics of the Cardiovascular safety and Renal Microvascular outcome study with LINA gliptin [CARMELINA®]: A randomizized, double-bind, placebo-controlled clinical trials in patients with type-2 diabetes and high cardio-renal risk. Cardiovasc Diabetal 2018 Mar14;17(1):39.[PMC free article][PubMed].
45]Rosenstok J,Marxn, Kahn SE, Zinman B, Kastelein JJ, Lachin JM, Bluhmiki E, Patel S, Johansen OE, Woerle HJ.Cardiovascular outcome trials in Type 2 Diabetes and the Sulfonylurea controversy: Rationale for the active-comparator CAROLINA trial. Diab vasc Dis Res.2013 Jul;10(4):289-301.
46]American Diabetes Association. 12. Older Adults: Standards of Medical care in Diabetes-2021.Diabetes care. 2021 Jan; 44(suppl1):S168-S179.[PubMed].