= Metformin =

Metformin , marketed under the tradename Glucophage among others , is the first @-@ line medication for the treatment of type 2 diabetes . This is particularly true in people who are overweight . It is also used in the treatment of polycystic ovary syndrome . Limited evidence suggests metformin may prevent the cardiovascular disease and cancer complications of diabetes . It is not associated with weight gain . It is taken by mouth .

Metformin is generally well tolerated . Common side effects include diarrhea , nausea , and abdominal pain . It has a low risk of developing low blood sugar . High blood lactic acid levels is a concern if prescribed inappropriately and in overdose . It should not be used in those with liver disease or kidney problems . While there is no clear harm if used during pregnancy , insulin is generally preferred for gestational diabetes . Metformin is in the biguanide class . It works by decreasing glucose production by the liver and increasing the insulin sensitivity of body tissues .

Metformin was discovered in 1922 . Study in humans began in 1950s by French physician Jean Sterne . It was introduced as a medication in France in 1957 and the United States in 1995 . It is on the World Health Organization 's List of Essential Medicines , the most important medications needed in a basic healthcare system . Metformin is believed to be the most widely used medication for diabetes which is taken by mouth . It is available as a generic medication . The wholesale price in the developed world is between 0 @.@ 21 and 5 @.@ 55 USD per month as of 2014 . In the United States , it costs 5 to 25 USD per month .

= = Medical uses = =

Metformin is primarily used for type 2 diabetes , but is increasingly being used in polycystic ovary syndrome .

= = = Type 2 diabetes = = =

The American Diabetes Association recommends metformin as a first @-@ line agent to treat type 2 diabetes .

= = = = Efficacy = = = =

The UK Prospective Diabetes Study , a large clinical trial performed in 1980 @-@ 90s , provided evidence that metformin reduced the rate of adverse cardiovascular outcomes in overweight patients with type 2 diabetes relative to other antihyperglycemic agents . However , accumulated evidence from other and more recent trials has reduced confidence in the efficacy of metformin for cardiovascular disease prevention . Treatment guidelines for major professional associations including the European Association for the Study of Diabetes , the European Society for Cardiology , and the American Diabetes Association , now describe evidence for the cardiovascular benefits of metformin as equivocal . According to the American College of Physicians in 2012 , low @-@ quality evidence indicates metformin monotherapy is associated with lower cardiovascular mortality than sulfonylurea monotherapy and metformin monotherapy is associated with fewer cardiovascular events than metformin @-@ sulfonylurea combination therapy . Evidence for other comparisons is described as unclear . A 2014 review found tentative evidence that people treated with sulfonylureas have fewer non @-@ fatal cardiovascular events than those treated with metformin (RR 0 @.@ 67) but a higher risk of severe low blood sugar events (RR 5 @.@ 64) . There was not enough data available to determine the relative risk of death or of death from heart disease .

Metformin has little or no effect on body weight compared with placebo in type 2 diabetes , although it causes weight loss compared with sulfonylureas , since sulfonylureas are associated with weight gain . There is some limited evidence that metformin may be associated with weight loss in obesity in the absence of diabetes . Metformin has a lower risk of hypoglycemia than the sulfonylureas , although hypoglycemia has uncommonly occurred during intense exercise , calorie deficit , or when

used with other agents to lower blood glucose . Metformin modestly reduces LDL and triglyceride levels .

= = = Prediabetes = = =

Metformin treatment of people at risk for type 2 diabetes may decrease their chances of developing the disease , although intensive physical exercise and dieting work significantly better for this purpose . In a large U.S. study known as the Diabetes Prevention Program , participants were divided into groups and given either placebo , metformin , or lifestyle intervention , and followed for an average of three years . The intensive program of lifestyle modifications included a 16 @-@ lesson training on dieting and exercise followed by monthly individualized sessions with the goals to decrease the body weight by 7 % and engage in a physical activity for at least 150 minutes per week . The incidence of diabetes was 58 % lower in the lifestyle group and 31 % lower in individuals given metformin . Among younger people with a higher body mass index , lifestyle modification was no more effective than metformin , and for older individuals with a lower body mass index , metformin was no better than placebo in preventing diabetes . After ten years , the incidence of diabetes was 34 % lower in the group of participants given diet and exercise and 18 % lower in those given metformin . It is unclear whether metformin slowed down the progression of prediabetes to diabetes (true preventive effect) , or the decrease of diabetes in the treated population was simply due to its glucose @-@ lowering action (treatment effect) .

= = = Polycystic ovary syndrome = = =

Antidiabetic therapy has been proposed as a treatment for polycystic ovary syndrome (PCOS) , a condition frequently associated with insulin resistance , since the late 1980s . The use of metformin in PCOS was first reported in 1994 , in a small study conducted at the University of the Andes , Venezuela . The United Kingdom 's National Institute for Health and Clinical Excellence recommended in 2004 that women with PCOS and a body mass index above 25 be given metformin for anovulation and infertility when other therapies have failed to produce results . However , two clinical studies completed in 2006 ? 2007 returned mostly negative results , with metformin being no better than placebo , and a metformin @-@ clomifene combination no better than clomifene alone . Reflecting this , subsequent reviews noted large randomized controlled trials have , in general , not shown the promise suggested by the early small studies . UK and international clinical practice guidelines do not recommend metformin as a first @-@ line treatment or do not recommend it at all , except for women with glucose intolerance . The guidelines suggest clomiphene as the first medication option and emphasize lifestyle modification independently from the drug treatment .

In a dissenting opinion , a systematic review of four head @-@ to @-@ head comparative trials of metformin and clomifene found them equally effective for infertility . Four positive studies of metformin were in women not responding to clomifene , while the population in the negative studies was drug @-@ naive or uncontrolled for the previous treatment . Metformin should be used as a second @-@ line drug if clomifene treatment fails . Another review recommended metformin unreservedly as a first @-@ line treatment option because it has positive effects not only on anovulation , but also on insulin resistance , hirsutism , and obesity often associated with PCOS . A Cochrane Collaboration review found metformin improves ovulation and pregnancy rates , particularly when combined with clomifene , but is not associated with any increase in the number of live births .

= = = Gestational diabetes = = =

Several observational studies and randomized , controlled trials have found metformin to be as effective and safe as insulin for the management of gestational diabetes . Nonetheless , several concerns have been raised regarding studies published thus far , and evidence on the long @-@ term safety of metformin for both mother and child is still lacking .

Metformin is safe in pregnancy and women with gestational diabetes treated with metformin have less weight gain during pregnancy than those treated with insulin . Babies born to women treated with metformin have been found to develop less visceral fat , making them less prone to insulin resistance in later life .

= = Contraindications = =

Metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis , including kidney disorders (arbitrarily defined as creatinine levels over 150 ?mol / l (1 @.@ 7 mg / dl) ,) , lung disease and liver disease . According to the prescribing information , heart failure (in particular , unstable or acute congestive heart failure) increases the risk of lactic acidosis with metformin . A 2007 systematic review of controlled trials , however , suggested metformin is the only antidiabetic drug not associated with any measurable harm in people with heart failure , and it may reduce mortality in comparison with other antidiabetic agents .

Metformin is recommended to be temporarily discontinued before any radiographic study involving iodinated contrast agents , (such as a contrast @-@ enhanced CT scan or angiogram) , as the contrast dye may temporarily impair kidney function , indirectly leading to lactic acidosis by causing retention of metformin in the body . Metformin can be resumed after two days , assuming kidney function is normal .

= = Adverse effects = =

The most common adverse effect of metformin is gastrointestinal irritation , including diarrhea , cramps , nausea , vomiting , and increased flatulence ; metformin is more commonly associated with gastrointestinal side effects than most other antidiabetic drugs . The most serious potential side effect of metformin use is lactic acidosis ; this complication is very rare , and the vast majority of these cases seem to be related to comorbid conditions , such as impaired liver or kidney function , rather than to the metformin itself .

Metformin has also been reported to decrease the blood levels of thyroid @-@ stimulating hormone in people with hypothyroidism , The clinical significance of this is still unknown .

= = = Gastrointestinal = = =

In a clinical trial of 286 subjects , 53 @.@ 2 % of the 141 given immediate @-@ release metformin (as opposed to placebo) reported diarrhea , versus 11 @.@ 7 % for placebo , and 25 @.@ 5 % reported nausea / vomiting , versus 8 @.@ 3 % for those on placebo .

Gastrointestinal upset can cause severe discomfort ; it is most common when metformin is first administered , or when the dose is increased . The discomfort can often be avoided by beginning at a low dose (1 @.@ 0 to 1 @.@ 7 grams per day) and increasing the dose gradually .

Long @-@ term use of metformin has been associated with increased homocysteine levels and malabsorption of vitamin B12 . Higher doses and prolonged use are associated with increased incidence of vitamin B12 deficiency , and some researchers recommend screening or prevention strategies .

= = = Lactic acidosis = = =

The most serious potential adverse effect of biguanide use is lactic acidosis (" metformin @-@ associated lactic acidosis " or MALA) . Though the incidence for MALA has been measured at about nine per 100 @,@ 000 person @-@ years , this is not different from the background incidence of lactic acidosis in the general population . A systematic review concluded no data exists to definitively link metformin to lactic acidosis . Lactic acidosis can be fatal in some cases .

Phenformin , another biguanide , was withdrawn from the market because of an increased risk of lactic acidosis (rate of 40 @-@ 64 per 100 @,@ 000 patient @-@ years) . However , metformin is

safer than phenformin , and the risk of developing lactic acidosis is not increased by the medication as long as it is not prescribed to known high @-@ risk groups .

Lactate uptake by the liver is diminished with metformin administration because lactate is a substrate for hepatic gluconeogenesis , a process which metformin inhibits . In healthy individuals , this slight excess is simply cleared by other mechanisms (including uptake by the kidneys , when their function is unimpaired) , and no significant elevation in blood levels of lactate occurs . When impaired kidney function is present , however , clearance of metformin and lactate is reduced , leading to increased levels of both , and possibly causing a buildup of lactic acid . Because metformin decreases liver uptake of lactate , any condition that may precipitate lactic acidosis is a contraindication to its use . Common causes of increased lactic acid production include alcoholism (due to depletion of NAD + stores) , heart failure , and respiratory disease (due to inadequate oxygenation of tissues) ; the most common cause of impaired lactic acid excretion is kidney disease .

Metformin has also been suggested to increase production of lactate in the large intestine ; this could potentially contribute to lactic acidosis in those with risk factors . However , the clinical significance of this is unknown , and the risk of metformin @-@ associated lactic acidosis is most commonly attributed to decreased hepatic uptake rather than increased intestinal production .

= = = Overdose = = =

A review of intentional and accidental metformin overdoses reported to poison control centers over a five @-@ year period found serious adverse events were rare , though the elderly appeared to be at greater risk . A similar study where cases were reported to Texas poison control centers between 2000 and 2006 found ingested doses of more than 5 @,@ 000 mg were more likely to involve serious medical outcomes in adults . Survival following intentional overdoses with up to 63 @,@ 000 mg (63 g) of metformin have been reported in the medical literature . Fatalities following overdose are rare , but do occur . In healthy children , unintentional doses of less than 1 @,@ 700 mg are unlikely to cause any significant toxic effects .

The most common symptoms following overdose appear to include vomiting , diarrhea , abdominal pain , tachycardia , drowsiness , and , rarely , hypoglycemia or hyperglycemia . The major potentially life @-@ threatening complication of metformin overdose is lactic acidosis , which is due to lactate accumulation . Treatment of metformin overdose is generally supportive , as no specific antidote is known . Lactic acidosis is initially treated with sodium bicarbonate , although high doses are not recommended , as this may increase intracellular acidosis . Acidosis that does not respond to administration of sodium bicarbonate may require further management with standard hemodialysis or continuous venovenous hemofiltration . These treatments are recommended in severe overdoses . In addition , due to metformin 's low molecular weight and lack of plasma protein binding , these techniques also have the benefit of removing metformin from blood plasma , preventing further lactate overproduction .

Metformin may be quantified in blood , plasma , or serum to monitor therapy , confirm a diagnosis of poisoning , or assist in a medicolegal death investigation . Blood or plasma metformin concentrations are usually in a range of 1 ? 4 mg / l in persons receiving the drug therapeutically , 40 ? 120 mg / l in victims of acute overdosage , and 80 ? 200 mg / l in fatalities . Chromatographic techniques are commonly employed .

= = = Interactions = = =

The H2 @-@ receptor antagonist cimetidine causes an increase in the plasma concentration of metformin , by reducing clearance of metformin by the kidneys ; both metformin and cimetidine are cleared from the body by tubular secretion , and both , particularly the cationic (positively charged) form of cimetidine , may compete for the same transport mechanism . A small double @-@ blind , randomized study found the antibiotic cephalexin to also increase metformin concentrations by a similar mechanism ; theoretically , other cationic medications may produce the same effect .

= = Mechanism of action = =

Metformin decreases hyperglycemia primarily by suppressing glucose production by the liver (hepatic gluconeogenesis) . The " average " person with type 2 diabetes has three times the normal rate of gluconeogenesis ; metformin treatment reduces this by over one @-@ third . The molecular mechanism of metformin is incompletely understood : inhibition of the mitochondrial respiratory chain (complex I) , activation of AMP @-@ activated protein kinase (AMPK) , inhibition of glucagon @-@ induced elevation of cyclic adenosine monophosphate (cAMP) with reduced activation of protein kinase A (PKA) , inhibition of mitochondrial glycerophosphate dehydrogenase , and an effect on gut microbiota have been proposed as potential mechanisms .

Activation of AMPK , an enzyme that plays an important role in insulin signaling , whole body energy balance , and the metabolism of glucose and fats , was required for metformin 's inhibitory effect on the production of glucose by liver cells . Activation of AMPK was required for an increase in the expression of small heterodimer partner , which in turn inhibited the expression of the hepatic gluconeogenic genes Phosphoenolpyruvate carboxykinase and glucose 6 @-@ phosphatase . Metformin is frequently used in research along with AICA ribonucleotide as an AMPK agonist . More recent studies using mouse models in which the genes for AMPK?1 and ?2 catalytic subunits (Prkaa1 / 2) or LKB1 , an upstream kinase of AMPK , had been knocked out in hepatocytes , have raised doubts over the obligatory role of AMPK , since the effect of metformin was not abolished by loss of AMPK function . The mechanism by which biguanides increase the activity of AMPK remains uncertain ; however , metformin increases the concentration of cytosolic adenosine monophosphate (AMP) (as opposed to a change in total AMP or total AMP / adenosine triphosphate) . Increased cellular AMP has also been proposed to explain the inhibition of glucagon @-@ induced increase in cAMP and activation of PKA . Metformin and other biguanides may antagonize the action of glucagon , thus reducing fasting glucose levels . Metformin also induces a profound shift in the faecal microbial community profile in diabetic mice and this may contribute to its mode of action possibly through an effect on glucagon @-@ like peptide @-@ 1 secretion .

In addition to suppressing hepatic glucose production , metformin increases insulin sensitivity , enhances peripheral glucose uptake (by inducing the phosphorylation of GLUT4 enhancer factor) , decreases insulin @-@ induced suppression of fatty acid oxidation , and decreases absorption of glucose from the gastrointestinal tract . Increased peripheral use of glucose may be due to improved insulin binding to insulin receptors . The increase in insulin binding after metformin treatment has also been demonstrated in patients with NIDDM .

AMPK probably also plays a role in increased insulin , as metformin administration increases AMPK activity in skeletal muscle . AMPK is known to cause GLUT4 deployment to the plasma membrane , resulting in insulin @-@ independent glucose uptake . Some metabolic actions of metformin do appear to occur by AMPK @-@ independent mechanisms ; the metabolic actions of metformin in the heart muscle can occur independent of changes in AMPK activity and may be mediated by p38 MAPK- and PKC @-@ dependent mechanisms .

= = Chemistry = =

The usual synthesis of metformin , originally described in 1922 and reproduced in multiple later patents and publications , involves the one @-@ pot reaction of dimethylamine hydrochloride and 2 @-@ cyanoguanidine over heat .

According to the procedure described in the 1975 Aron patent , and the Pharmaceutical Manufacturing Encyclopedia , equimolar amounts of dimethylamine and 2 @-@ cyanoguanidine are dissolved in toluene with cooling to make a concentrated solution , and an equimolar amount of hydrogen chloride is slowly added . The mixture begins to boil on its own , and after cooling , metformin hydrochloride precipitates with a 96 % yield .

= = Pharmacokinetics = =

Metformin has an oral bioavailability of 50 ? 60 % under fasting conditions , and is absorbed slowly . Peak plasma concentrations (Cmax) are reached within one to three hours of taking immediate @-@ release metformin and four to eight hours with extended @-@ release formulations . The plasma protein binding of metformin is negligible , as reflected by its very high apparent volume of distribution (300 ? 1000 l after a single dose) . Steady state is usually reached in one or two days .

Metformin has acid dissociation constant values (pKa) of 2 @.@ 8 and 11 @.@ 5 , so exists very largely as the hydrophilic cationic species at physiological pH values . The metformin pKa values make metformin a stronger base than most other basic drugs with less than 0 @.@ 01 % nonionized in blood . Furthermore , the lipid solubility of the nonionized species is slight as shown by its low logP value [log (10) of the distribution coefficient of the nonionized form between octanol and water] of -1.43 . These chemical parameters indicate low lipophilicity and , consequently , rapid passive diffusion of metformin through cell membranes is unlikely . The logP of metformin is less than that of phenformin (-0.84) because two methyl substituents on metformin impart lesser lipophilicity than the larger phenylethyl side chain in phenformin . More lipophilic derivatives of metformin are presently being investigated with the aim of producing prodrugs with better oral absorption than metformin itself .

Metformin is not metabolized . It is cleared from the body by tubular secretion and excreted unchanged in the urine ; metformin is undetectable in blood plasma within 24 hours of a single oral dose . The average elimination half @-@ life in plasma is 6 @.@ 2 hours . Metformin is distributed to (and appears to accumulate in) red blood cells , with a much longer elimination half @-@ life : 17 @.@ 6 hours (reported as ranging from 18 @.@ 5 to 31 @.@ 5 hours in a single @-@ dose study of nondiabetic people) .

= = History = =

The biguanide class of antidiabetic drugs , which also includes the withdrawn agents phenformin and buformin , originates from the French lilac or goat 's rue (Galega officinalis) , a plant used in folk medicine for several centuries .

Metformin was first described in the scientific literature in 1922 , by Emil Werner and James Bell , as a product in the synthesis of N , N @-@ dimethylguanidine . In 1929 , Slotta and Tschesche discovered its sugar @-@ lowering action in rabbits , noting it was the most potent of the biguanide analogs they studied . This result was completely forgotten , as other guanidine analogs , such as the synthalins , took over and were themselves soon overshadowed by insulin .

Interest in metformin , however , picked up at the end of the 1940s . In 1950 , metformin , unlike some other similar compounds , was found not to decrease blood pressure and heart rate in animals . That same year , a prominent Philippine physician , Eusebio Y. Garcia , used metformin (he named it Fluamine) to treat influenza ; he noted the drug " lowered the blood sugar to minimum physiological limit " and was not toxic . Garcia also believed metformin to have bacteriostatic , antiviral , antimalarial , antipyretic , and analgesic actions . In a series of articles in 1954 , Polish pharmacologist Janusz Supniewski was unable to confirm most of these effects , including lowered blood sugar ; he did , however , observe some antiviral effects in humans .

While training at the Hôpital de la Pitié , French diabetologist Jean Sterne studied the antihyperglycemic properties of galegine , an alkaloid isolated from Galega officinalis , which is related in structure to metformin and had seen brief use as an antidiabetic before the synthalins were developed . Later , working at Laboratoires Aron in Paris , he was prompted by Garcia 's report to reinvestigate the blood sugar @-@ lowering activity of metformin and several biguanide analogs . Sterne was the first to try metformin on humans for the treatment of diabetes ; he coined the name " Glucophage " (glucose eater) for the drug and published his results in 1957 .

Metformin became available in the British National Formulary in 1958 . It was sold in the UK by a small Aron subsidiary called Rona .

Broad interest in metformin was not rekindled until the withdrawal of the other biguanides in the 1970s . Metformin was approved in Canada in 1972 , but did not receive approval by the U.S. Food

and Drug Administration (FDA) for type 2 diabetes until 1994 . Produced under license by Bristol @-@ Myers Squibb , Glucophage was the first branded formulation of metformin to be marketed in the United States , beginning on March 3 , 1995 . Generic formulations are now available in several countries , and metformin is believed to have become the most widely prescribed antidiabetic drug in the world .

= = Formulations = =

Metformin is the BAN , USAN and INN . It is sold under several trade names , including Glucophage XR , Carbophage SR , Riomet , Fortamet , Glumetza , Obimet , Gluformin , Dianben , Diabex , Diaformin , Siofor , and Metfogamma .

Liquid metformin is sold under the name Riomet in India . Each 5 ml of Riomet is equivalent to the 500 @-@ mg tablet form of metformin .

Metformin IR (immediate release) is available in 500 , 850 , and 1000 @-@ mg tablets . All of these are now available as generic drugs in the U.S.

Metformin SR (slow release) or XR (extended release) was introduced in 2004 . It is available in 500 , 750 , and 1000 @-@ mg strengths , mainly to counteract the most common gastrointestinal side effects , as well as to increase compliance by reducing pill burden . No difference in effectiveness exists between the two preparations .

= = = Combination with other drugs = = =

When used for type 2 diabetes , metformin is often prescribed in combination with other drugs . Several are available as fixed @-@ dose combinations , also with the purpose of reducing pill burden and making administration simpler and more convenient .

= = = = Thiazolidinediones (Glitazones) = = = =

= = = = Rosiglitazone = = = =

A combination of metformin and rosiglitazone was released in 2002 and sold as Avandamet by GlaxoSmithKline . By 2009 it had become the most popular metformin combination . In 2005 , all current stock of Avandamet was seized by the FDA and removed from the market , after inspections showed the factory where it was produced was violating good manufacturing practices . The drug pair continued to be prescribed separately , which was available again by the end of that year . A generic formulation of metformin / rosiglitazone from Teva received tentative approval from the FDA , and was expected to reach the market in early 2012 . However , following a meta @-@ analysis in 2007 that linked the drug 's use to an increased risk of heart attack , concerns were raised over the safety of medicines containing rosiglitazone . In September 2010 the European Medicines Agency (EMA) recommended that the drug be suspended from the European market because the benefits of rosiglitazone no longer outweighed the risks . It was withdrawn from the market in the UK and India in 2010 , and in New Zealand and South Africa in 2011 . From November 2011 until November 2013 the FDA in the U.S. did not allow rosiglitazone or metformin / rosiglitazone to be sold without a prescription ; moreover , people were required to be informed of the risks associated with its use , and the drug had to be purchased by mail order through specified pharmacies . In November 2013 , the FDA lifted its earlier restrictions on rosiglitazone after reviewing the results of the 2009 RECORD clinical trial (a six @-@ year , open label randomized control trial) , which failed to show elevated risk of heart attack or death associated with the drug .

The combination of metformin and pioglitazone remains available in U.S. and Europe .

= = = = DPP @-@ 4 inhibitors = = = =

Dipeptidyl peptidase @-@ 4 inhibitors inhibit dipeptidyl peptidase @-@ 4 and thus reduce glucagon and blood glucose levels .

DPP @-@ 4 inhibitors combined with metformin include a sitagliptin / metformin combination (Janumet) and a saxagliptin combination (Komboglyze / Kombiglyze) , and with alogliptin as Kazano .

In Europe , Canada , and elsewhere metformin combined with linagliptin is now sold under the trade name Jentadueto .

= = = = Sulfonylureas = = = =

Sulfonylureas act by increasing insulin release from the beta cells in the pancreas . Metformin is available combined with the sulfonylureas glipizide (Metaglip) and glibenclamide (US : glyburide) (Glucovance) . Generic formulations of metformin / glipizide and metformin / glibenclamide are available (the latter being more popular) .

= = = = Meglitinide = = = =

Meglitinides are similar to sulfonylureas . A repaglinide / metformin combination is sold as Prandimet .

= = = = Thiazolidinedione = = = =

The thiazolidinedione pioglitazone may be used in combination with metformin (Actoplus Met , Piomet , Politor) .

= = Research = =

Metformin has been studied in non @-@ alcoholic fatty liver disease (NAFLD) and premature puberty ; however these uses are still experimental .

Tentative evidence supports an anti @-@ cancer effect for metformin .

As of 2015 metformin was under study for its potential effect on slowing aging in the worm C.elegans and the cricket . Its effect on otherwise healthy humans is unknown .