26 Drug Therapy: Special Considerations in Diabetes

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Keypoints

- Many drugs interfere with glucose homeostasis or interact with antidiabetic agents and thus can disturb glycemic control in people with diabetes. Specific diabetic complications, such as nephropathy and neuropathy, may require particular drugs to be used with care.
- Hyperglycemia can be caused or worsened by numerous drugs. Those that induce insulin resistance include glucocorticoids, certain oral contraceptives, antipsychotic drugs, HIV protease inhibitors, the fluoroquinolone gatifloxacin and β-adrenoceptor antagonists. Diabetogenic drugs that damage the β-cell include pentamidine and cyclosporine (ciclosporin).
- Sulfonylureas and related agents commonly cause hypoglycemia by interacting with other drugs that block their metabolism in the liver, e.g. ciprofloxacin inhibits CYP2C9, which degrades glyburide (glibenclamide), or that impair renal function and decrease their elimination (e.g. non-steroidal anti-inflammatory agents).
- Hypoglycemia can be induced by drugs that stimulate insulin secretion (e.g. quinine, especially in children with cerebral malaria); and sulfamethoxazole, which binds to the sulfonylurea receptor. Pentamidine can induce transient hypoglycemia, by causing passive loss of insulin from the β-cell, as a prelude to permanent diabetes.
- Hypoglycemia can complicate overdosage with acetaminophen (paracetamol), following hepatic necrosis; or aspirin, which blocks hepatic glucose output and stimulates peripheral glucose uptake. Alcohol inhibits hepatic gluconeogenesis and can provoke, prolong or exacerbate hypoglycemia.
- Non-selective β-adrenoceptor antagonists inhibit insulin secretion and can impair glucose tolerance. They also decrease certain catecholamine-mediated symptomatic and metabolic responses to hypoglycemia; awareness of hypoglycemia may therefore be reduced, and recovery of normoglycemia delayed. These adverse effects are much less pronounced with cardioselective β_1-adrenoceptor antagonists.
- Thiazide diuretics used at low dosages (e.g. 2.5 mg/day bendroflumethiazide) lower blood pressure effectively and are suitable for use in patients with diabetes.
- Certain drugs require special consideration in patients with diabetic complications. Metformin and several sulfonylureas are cleared through the kidney; they are therefore contraindicated in advanced nephropathy and should not be co-administered with nephrotoxic drugs. Vasodilators and ganglion-blocking agents exacerbate postural hypotension.

This chapter discusses the problems posed by drug therapy in the management of people with diabetes. Numerous drugs can affect diabetic control, causing hyperglycemia or hypoglycemia, by interfering with insulin secretion or action or both, or by interacting with antidiabetic agents. Some important examples are illustrated in Figure 26.1. The special considerations that apply when using other drugs in patients with diabetes and in the presence of specific diabetic complications are also discussed.

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Drugs that raise blood glucose concentrations

Drug-induced diabetes is now recognized as a distinct etiologic category, and diabetogenic drugs are discussed in detail in Chapter 16. The main culprits are shown in Table 26.1. Most of these drugs – notably glucocorticoids (a common and important cause of iatrogenic diabetes), contraceptive steroids and β-adrenoceptor antagonists – act by inhibiting insulin action. By contrast, insulin secretion is inhibited by diazoxide, while pentamidine can cause permanent β-cell damage. In recent years, antipsychotic drugs, HIV protease inhibitors and the fluoroqui-

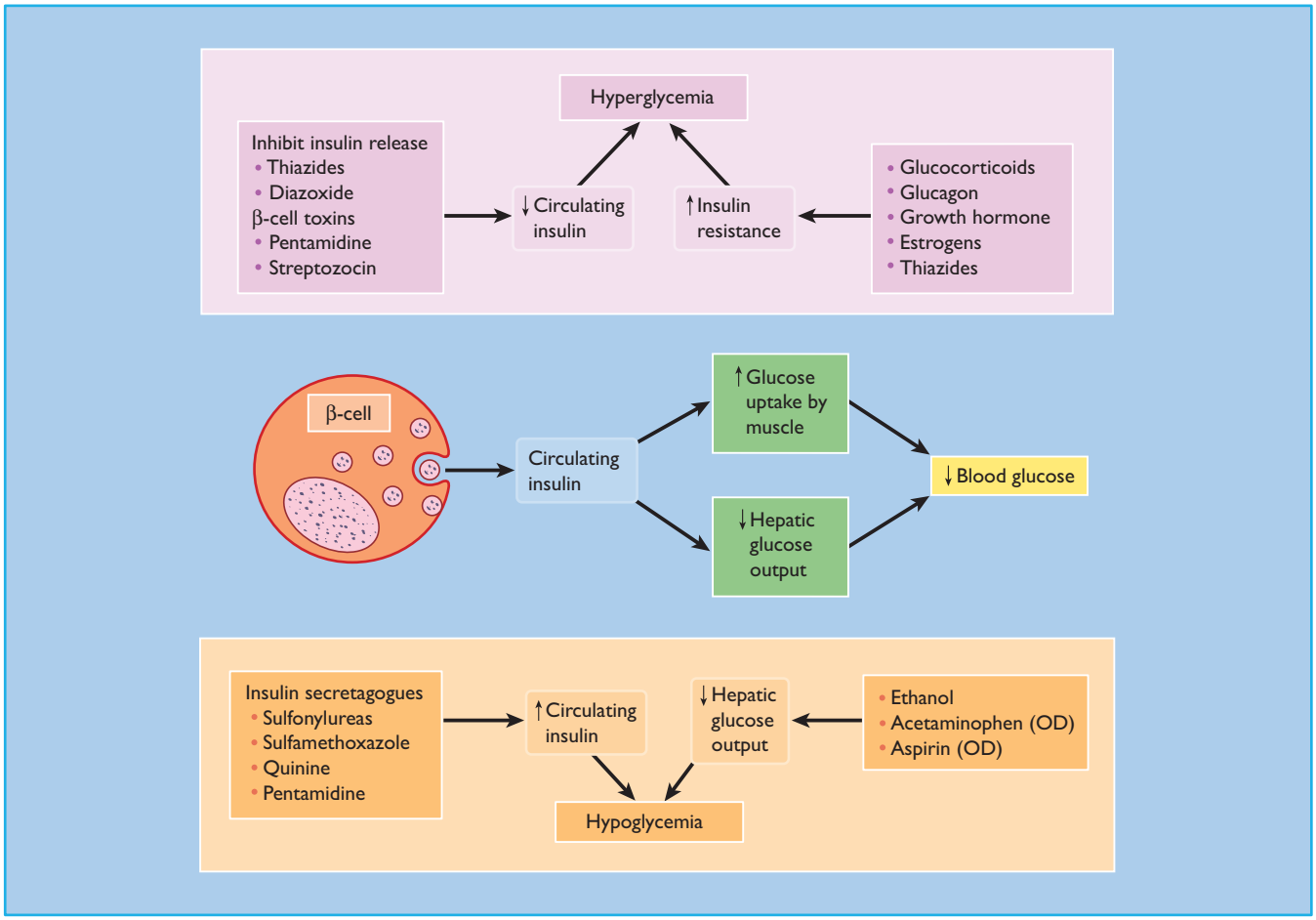

Figure 26.1 General mechanisms of drug-induced hyperglycemia and hypoglycemia. OD, overdose.

nolone antibiotic gatifloxacin have emerged as important causes of hyperglycemia.

Drugs that lower blood glucose concentration

Many drugs can cause hypoglycemia (Table 26.2) [1–10]. These include some that interact with and enhance the action of glucose-lowering drugs. Others act in their own right as insulin secretagogues, or to enhance or mimic the effect of insulin in suppressing glucose production by the liver and stimulating glucose uptake into peripheral tissues. Some drugs (e.g. non-selective β-adrenoceptor antagonists) specifically block the warning symptoms or the neuroendocrine counter-regulatory responses that are normally triggered by hypoglycemia, and so can prolong and intensify hypoglycemic episodes.

Drugs should always be suspected whenever patients with previously well-controlled diabetes experience unexplained hypoglycemic episodes, or if dosages of insulin or oral hypoglycemic agents decline. As well as prescription drugs, patients should be asked about herbal, traditional and other alternative medicines. These are now widely used by people with diabetes – up to one-third of patients in one study [11] – and some products may contain naturally occurring or synthetic glucose-lowering agents (Table 26.3).

Sulfonylureas

Sulfonylureas are an important and sometimes unrecognized cause of symptomatic hypoglycemia (see Chapter 33). They are also affected by numerous interactions with other drugs (Figure 26.2).

The long-acting sulfonylureas glibenclamide and chlorpropamide are especially troublesome. In one outpatient survey, 20% of patients treated with glibenclamide reported symptoms of hypoglycemia within the previous six months [12], while other surveys suggest that tolbutamide is much less likely to cause severe hypoglycemia (i.e. requiring hospital admission) than either glibenclamide or chlorpropamide [13,14]. A Swiss study [15] defined the risk of severe hypoglycemia as two episodes per 1000 persons per year in those given glibenclamide, over twice as high as in those taking shorter-acting sulfonylureas such as tolbutamide, gliclazide or glipizide. The novel sulfonylurea, glimepir-

Table 26.1 Drugs that may cause or exacerbate hyperglycemia.

Potentially potent effects	Minor or no effects
Glucocorticoids	Oral contraceptives
Oral contraceptives	Progestogen-only pills
High-dose oestrogen	Levonorgestrel in combination pills
Thiazide diuretics (especially high dosages)*	Loop diuretics
Non-selective β-adrenoceptor antagonists	Calcium-channel blockers
β_2-Adrenoceptor agonists	α_1-Adrenoceptor antagonists
Salbutamol	Growth hormone (physiologic doses)
Ritodrine	Somatostatin analogs†
Antipsychotics	Androgen deprivation therapy for prostate cancer
HIV protease inhibitors	Selective serotonin reuptake inhibitors
Indinavir, nelfinavir, ritonavir and others	Nicotinic acid
Others	Lamivudine
Pentamidine	Isoniazid
Gatifloxacin	
Streptozotocin	
Diazoxide	
Cyclosporine (ciclosporin)	
Tacrolimus	
Temsirolimus	
Interferon-α	
L-Asparaginase	

* "High" dosages of thiazides correspond to ≥5 mg/day bendroflumethazide.
† Somatostatin analogs may induce hyperglycemia in type 2 but not type 1 diabetes.

Table 26.2 Drugs that may cause or exacerbate hypoglycemia.

Antidiabetic drugs
Insulins
Sulfonylureas, e.g. glimepiride
Repaglinide
Drugs that interact to enhance the actions of sulfonylureas (Table 26.4)
Quinolone antibacterials: Levofloxacin, gatifloxacin [4]
Corticosteroids, including inhaled corticosteroids (when withdrawn may lead to adrenal insufficiency) [5,6]
Other drugs
Aspirin (in overdosage)
Cibenzoline
Disopyramide
Doxycycline [7,8]
Etanercept
Ethanol
Hydroxychloroquine
Imatinib
Mefloquine
Non-selective β-adrenoceptor antagonists
Paracetamol (in overdosage)
Pentamidine
Quinidine
Quinine
Sulfamethoxazole (in co-trimoxazole)
Valproate (in neonates exposed *in utero*) [9]
Venlafaxine (in overdosage) [10]

ide, is said to carry a relatively low risk of hypoglycemia because it binds to a different site on the sulfonylurea receptor from classic sulfonylureas and also has distinct pharmacokinetic properties. None the less, the rate of hypoglycemia is still substantial, with 10–20% of patients experiencing at least one mild episode each year [16].

Several factors other than the individual drug per se can increase the risk of hypoglycemia from sulfonylureas, notably increasing age and renal impairment [13,14,16–18]. Reduced food intake during intercurrent illness can also contribute [17,18]. Drug interactions that enhance the action of sulfonylureas are considered below.

Not all those who have sulfonylurea-induced hypoglycemia are patients with type 2 diabetes (T2DM): "bystanders" have included toddlers who ate a grandparent's tablet [19], nursing-home residents given the treatment of other patients [20] and people whose prescriptions for other drugs have been misread [21].

Sulfonylurea-induced hypoglycemia can be profound and prolonged, and difficult to manage. Patients with sulfonylurea-induced hypoglycemia may require admission and treatment with glucose until the effect of the sulfonylurea has worn off although caution is needed as indicated in the case report below.

Insulin hypersecretion induced by sulfonylureas can be suppressed effectively with either diazoxide (which opens the β-cell K_{ATP} channel that is closed by sulfonylureas) [22,23] or by the somatostatin analog octreotide [24].

Case report: Severe relapsing sulfonylurea-induced hypoglycemia

A 62-year-old woman was admitted with acute confusion and became unresponsive 2 hours after admission. She had type 2 diabetes with impaired renal function (serum creatinine 176 μmol/L) and had been taking 40 mg gliclazide twice a day. Her blood glucose concentration was 1.8 mmol/L. The hypoglycemia was reversed with an intravenous bolus of 50 mL 50% glucose but subsequently she had repeated episodes of hypoglycemia and required continuous intravenous glucose infusion for 3 days. A blood sample taken when she was hypoglycemic showed raised serum insulin and C peptide concentrations, indicating increased insulin secretion. This patient had impaired renal function. It is likely that this caused gliclazide to accumulate, leading to hypoglycemia. Intravenous glucose restored consciousness, but also stimulated further insulin secretion, leading to further episodes of hypoglycemia.

Adapted from Langford *et al. Postgrad Med J* 2003; **79**:120.

Table 26.3 Some herbal medicinal products and food supplements that can potentially interact with antidiabetic drugs to affect blood glucose concentrations. Data from Ernst E. *The Desktop Guide to Complementary and Alternative Medicine. An Evidence-Based Approach*. Edinburgh: Mosby, 2001.

Name	Effect on blood glucose	Name	Effect on blood glucose
Alfalfa	↓	Ginseng, *Eleutherococcus*	↓
Aloe vera	↓	Ginseng, *Panax*	↓
Basil	↓	Gotu kola	↑
Bee pollen	↑	Guar gum	↓
Bitter melon	↓	Horehound	↓
Burdock	↓	Hydrocotyle	↑
Celandine	↓	Juniper	↓
Celery	↓	Licorice	↑
Coriander	↓	Marshmallow	↓
Cornsilk	↓	Melatonin	↓
Damiana	↓	Myrrh	↓
Dandelion	↓	Myrtle	↓
Devil's claw	↑	Nettle	↓
Elecampane	↑	Night-blooming cereus	↓
Eucalyptus	↓	Onion	↓
Fenugreek	↓	Sage	↓
Figwort	↑	St. John's wort	↑
Garlic	↓	Tansy	↓

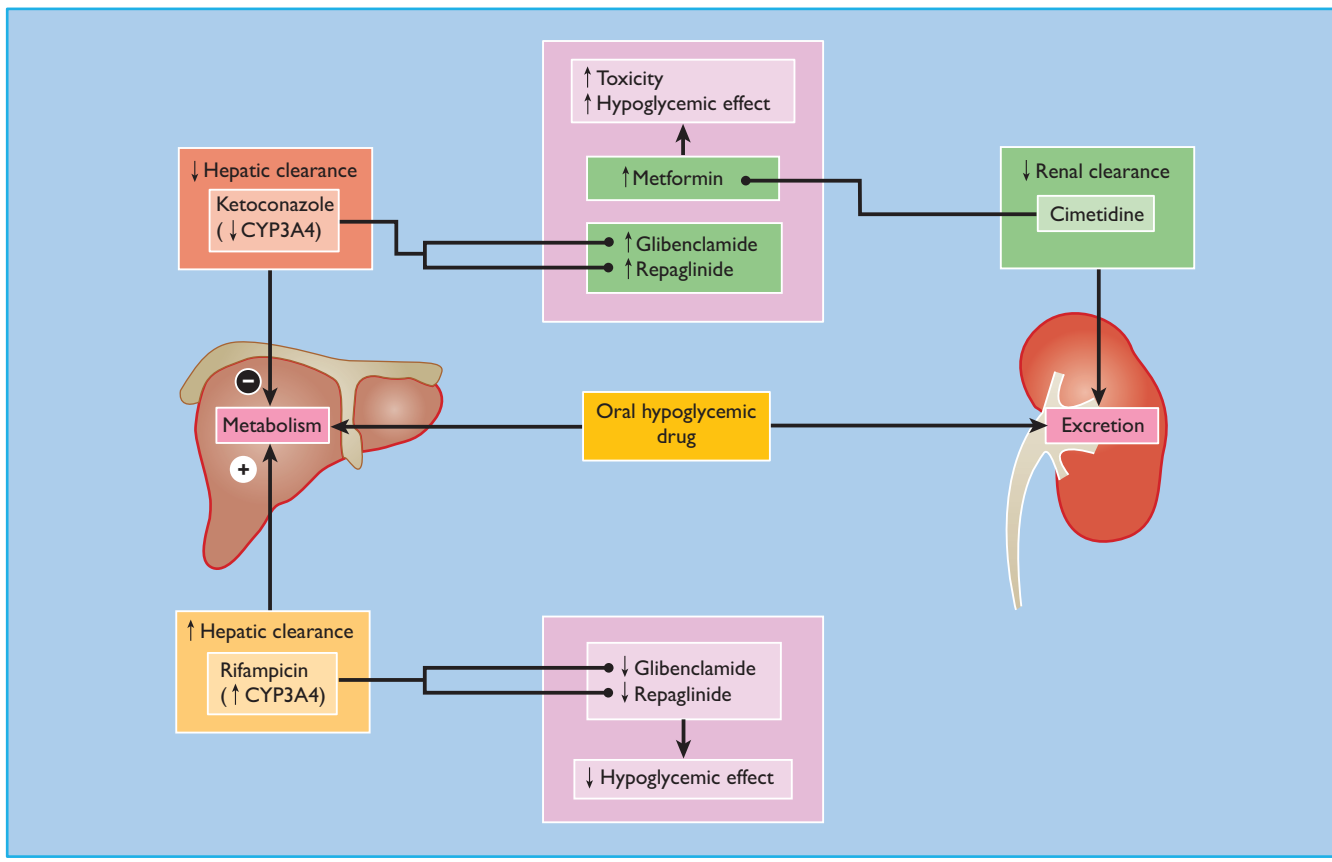

Figure 26.2 Interactions between oral hypoglycemic agents and other drugs.

Other antidiabetic agents

These are described in Chapter 29.

• *Metformin* used alone is not expected to cause hypoglycemia in therapeutic use; but instances of "hypoglycemia" were reported by the UK Prospective Diabetes Study (UKPDS) during metformin treatment [25]. They were not generally confirmed by blood glucose measurements.

• *Thiazolidinediones* (e.g. rosiglitazone and pioglitazone) potentiate the peripheral actions of insulin. They do not induce hypoglycemia in their own right, but can enhance hypoglycemia caused by sulfonylureas or insulin when used in combination with them.

• *Repaglinide* stimulates insulin release by a mechanism distinct from that of the sulfonylureas and so causes hyperinsulinemic hypoglycemia. A case of factitious hypoglycemia from repaglinide has been reported [26].

• *Acarbose* inhibits intestinal disaccharidase, and so reduces the hydrolysis of sucrose and thus glucose absorption. It does not cause hypoglycemia when used as monotherapy. Acarbose-treated patients who develop hypoglycemia from other glucose-lowering drugs should be warned that oral glucose, not sucrose, is needed to treat the episode.

• *Exenatide* and *liraglutide* are incretins, that is, peptide hormones that enhance the pancreatic insulin response to glucose in the gut. They are agonists of the glucagon-like peptide-1 (GLP-1) receptor. They slow down stomach emptying and stimulate insulin secretion. Unlike insulin, they do not tend to cause hypoglycemia. They also increase pancreatic β-cell mass and promote weight loss. The major disadvantages are nausea, the need for subcutaneous injections, and the high cost relative to sulfonylureas.

• *Gliptins* increase the circulating levels of incretins by inhibiting dipeptidyl peptidase 4 (DPP-4), the enzyme that breaks down incretins and other peptides. The oral route of administration is an advantage, but the long-term effects of DPP-4 inhibition remain unknown. Exenatide and gliptins are indicated for glycemic control as alternatives to thiazolidinediones or acarbose in patients with T2DM on metformin therapy in whom a sulfonylurea is not tolerated or inappropriate.

• *Inhaled insulin preparations* deliver insulin by the pulmonary route, and have a value in patients who have a phobia of needles. Because of poor sales and safety concerns, the first inhaled insulin marketed has been withdrawn. There could be a revival of interest in inhaled insulin if long-acting formulations become available.

Other drugs

Antimicrobials

• *Quinine and quinine derivatives*. Patients with falciparum malaria are often extremely ill, and may have hypoglycemia because of the effects of cytokines and malnutrition, both of which diminish hepatic gluconeogenesis. In this context, it is easy to overlook quinine-induced hypoglycemia, which can be profound, especially in children [27,28]. It is caused by insulin hypersecretion, as quinine has insulin secretagogue activity [29]. Octreotide (a long-acting somatostatin analogue) has been used successfully to inhibit insulin release and raise blood glucose concentrations under these conditions [30]. Quinidine and mefloquine may occasionally cause hypoglycemia, while chloroquine does not [28].

• *Sulfamethoxazole*, which is combined with trimethoprim in co-trimoxazole, has a sulfonylurea-like action and can stimulate insulin secretion; several cases of severe hypoglycemia have been described [31]. This tends to be long-lasting, perhaps because excessive amounts of glucose solution are infused; this may paradoxically worsen hypoglycemia by further stimulating insulin secretion. Elderly patients receiving high dosage, and patients in renal failure (which causes the drug to accumulate) are at particular risk [32], as are patients infected with HIV who receive high doses of co-trimoxazole to treat *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii*) [33].

• *Pentamidine*, a drug used to treat and prevent *P. jirovecii* pneumonia, can also damage pancreatic β-cells. This initially leads to the passive leakage of insulin out of secretory vesicles, causing hypoglycemia, but diabetes may develop subsequently [34]. In two series of patients with HIV treated with pentamidine, 25% [35] and 14% [36] developed symptomatic hypoglycemia; they invariably developed renal damage from the drug as well. Even inhaled pentamidine can cause hypoglycemia [37].

• *Doxycycline* has been suggested to cause hypoglycemia, but the reaction is infrequent and no mechanism has been identified [38].

• *Quinolones*, particularly gatifloxacin, can cause hypoglycemia (and also hyperglycemia). A case–control study defined an adjusted odds ratio for hypoglycemia with gratifloxacin treatment of 4.3 (95% confidence interval [CI] 2.9–6.3) compared with macrolide treatment [4]. There was a small increase in risk with levofloxacin.

Miscellaneous drugs

• *Disopyramide* and *cibenzoline* (*cifenline*), class Ia antiarrhythmic agents, can rarely cause symptomatic hypoglycemia; this can occur either with or without hyperinsulinemia [39], suggesting that peripheral effects contribute. In normal subjects, disopyramide produces a small but statistically significant fall in fasting glucose concentration [40]. In a Japanese case–control study, cibenzoline treatment was associated with an eightfold increase in the risk of hypoglycemia; disopyramide did not significantly increase the overall risk, but the confidence intervals were wide [41]. The effect of disopyramide appears to be dose-dependent. In one case, a man developed severe hypoglycemia while taking disopyramide only after starting treatment with clarithromycin for an intercurrent infection [42]; clarithromycin inhibits the hepatic microsomal enzymes that metabolize disopyramide and so greatly increases serum disopyramide concentrations.

• *Antidepressants*, including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and nefazodone, have been reported to reduce blood glucose concentrations [43].

Drugs in overdose

• *Acetaminophen* (*paracetamol*), in overdose, can cause hypoglycemia as a complication of acute hepatic necrosis. Overdosage

of *aspirin* and other salicylates inhibits hepatic glucose production and also increases peripheral glucose utilization, leading to hypoglycemia, especially in children. Paradoxically, and for unknown reasons, hyperglycemia can be encountered in adults.

• *Ethanol* inhibits gluconeogenesis; consequently, it can cause hypoglycemia in children or fasting adults and exacerbate hypoglycemia from another cause even when consumed in relatively modest amounts (see Chapter 24). Results of experimental studies are unclear: modest concentrations of ethanol impaired the growth hormone response to insulin-induced hypoglycemia in volunteers with type 1 diabetes (T1DM), but did not affect glucagon response [44]. The same dose of ethanol impaired glucagon, although not growth hormone (GH), response to the same degree of hypoglycemia in patients with diet-treated T2DM [45]. Rebound hypoglycemia can follow 2–3 hours after drinking alcohol with a glucose load in the form of sweet drinks or foods – so-called "gin-and-tonic hypoglycemia" [46]. Alcohol ingestion also increases the risk of severe brain damage or death in people who take an intentional overdose of insulin [47].

Non-pharmacopoeial drugs

Some "herbal," "traditional" and "folk" remedies contain compounds with glucose-lowering properties that are generally weak [48]. Some preparations, however, have caused severe hypoglycemia and have been found on analysis to contain an undeclared sulfonylurea [49].

Drug interactions that affect blood glucose concentrations

Several potential mechanisms underlying drug interaction cause hyperglycemia or hypoglycemia. Pharmacokinetic interactions can influence the effective concentrations of a glucose-modifying drug; examples are the increased concentrations of disopyramide following co-administration of clarithromycin, as described above, and the large number of drugs that increase or decrease circulating concentrations of sulfonylureas (see below).

Pharmacodynamic interactions occur when the observed action of one drug is modified by the action of another, without a change in the circulating concentration of either. The drugs can act at the same site (e.g. sulfamethoxazole is a ligand at the SUR-1 sulfonylurea receptor) or at different sites. Examples of the latter include β-adrenoceptor antagonists and other drugs that influence the physiologic response to hypoglycemia, and so alter the duration or severity of hypoglycemia from another cause.

Drugs that interact to enhance the actions of insulin secretagogues

Many drugs have pharmacokinetic or pharmacodynamic interactions with sulfonylureas that can cause clinically important disturbances in glycemic control. Some of the more important examples are shown in Table 26.4 and Figure 26.2. The most common outcome is hypoglycemia, brought about by reduced metabolic or renal clearance. Transient effects from displacement of protein-bound drug may occasionally also be important. Major dangers include the potentiation of the effects of tolbutamide, and possibly of chlorpropamide, glibenclamide and glipizide, by azapropazone (apazone), oral chloramphenicol and fluconazole. Miconazole interacts with glibenclamide and glipizide as well as tolbutamide. All these interactions are secondary to the inhibition of the metabolism of sulfonylurea in the liver. Similarly, ciprofloxacin increases the plasma concentrations and therefore enhances the hypoglycemic action of glibenclamide, apparently by inhibiting the hepatic CYP2C9 enzyme that metabolizes glibenclamide [50].

Table 26.4 Drugs that interact with sulfonylureas.

Drugs that may enhance the hypoglycemic effect of sulfonylureas
Azapropazone, phenylbutazone
Salicylates
Probenecid
Sulfonamides
Clarithromycin
Nicoumalone
Fluconazole, ketoconazole, miconazole, voriconazole
Drugs that may reduce the hypoglycemic effect of sulfonylureas
Rifampicin
Chlorpromazine

By contrast, rifampicin reduces the action of glibenclamide by inducing CYP2C9 and enhancing the hepatic clearance of sulfonylurea. Chlorpromazine also decreases the glucose-lowering effect of sulfonylurea, possibly by inhibiting insulin secretion.

Another important interaction with chlorpropamide (and, to a much lesser extent, with other sulfonylureas) is the cutaneous vasodilatation of the face and occasionally the trunk that is induced by ethanol, the chlorpropamide–alcohol flush (see Chapter 29).

Clarithromycin has been reported to interact with glibenclamide and glipizide, leading to hypoglycemia [51].

Some patients may be more susceptible to drug-induced hypoglycemia than others. For example, a Japanese case–control study suggested that patients taking levothyroxine and who also had liver disease were at substantially increased risk of mild hypoglycemia, with an odds ratio of 14.7 (range 1.6–137) [52].

Several oral hypoglycemic agents, including glimepiride, glipizide, glibenclamide, tolbutamide and nateglinide, are metabolized by CYP2C9, and a study suggests that among other factors, individuals with genetically determined low CYP2C9 activity are at an increased risk of sulfonylurea-associated severe hypoglycemia [53].

A meta-analysis confirms the impression that hypoglycemia is more likely with glibenclamide than other insulin secretagogues (relative risk 1.52 [95% CI 1.21–1.92]) [51].

Surreptitious ingestion of sulfonylureas such as glibenclamide in alternative medicines can cause hypoglycemia [54].

Interactions with metformin

Metformin has a high renal clearance. Cimetidine reduces the renal clearance of metformin, and causes it to accumulate (Figure 26.2). Drugs that impair renal function, such as non-steroidal anti-inflammatory agents and aminoglycosides, should be used with care, as they can also raise metformin concentrations, increasing the risk of lactic acidosis. Metformin should be stopped 24 hours before prolonged fasting (e.g. before surgery) and 48 hours before procedures requiring intravenous radiocontrast media. Patients on metformin are advised to avoid alcohol or to drink in moderation as hepatic damage poses a risk of hypoglycemia and lactic acidosis.

Interactions with other antidiabetic agents

- *Rosiglitazone* is metabolized by the hepatic microsomal enzyme CYP2C8, raising the theoretical possibility of interaction with other agents metabolized by the same enzyme. These include cerivastatin, now withdrawn in the USA and the UK, and paclitaxel [55], but no clinically significant interactions have yet been reported.
- *Repaglinide* is metabolized by CYP3A4, which also breaks down glibenclamide and several other important drugs, and is then excreted in the bile. Clarithromycin, an inhibitor of CYP3A4, has been reported to increase repaglinide concentration and the risk of hypoglycemia [56]. Rifampicin, which induces the same enzyme, reduces the effective concentrations of repaglinide by 25% in healthy volunteers, and could potentially worsen glycemic control in patients with T2DM [56]. Repaglinide is also metabolized by CYP2C8, and its plasma concentration is greatly increased by gemfibrozil, an inhibitor of CYP2C8. This interaction can result in hypoglycemia [56].
- *Glimepiride* is broken down by CYP2C9, and its metabolism is significantly inhibited by fluconazole, thus potentially enhancing its hypoglycemic action [57].

Hazards of general drugs when used in patients with diabetes

The presence of diabetes can influence the choice of agent for treating several important conditions. Drugs to treat cardiovascular diseases – hypertension, angina, arrhythmias and heart failure – and hyperlipidemia are of particular importance, because these conditions are common in people with diabetes.

Drugs with cardiovascular actions

β-Adrenoceptor antagonists

These are useful in the treatment of hypertension, angina, arrhythmias and in some cases of heart failure. There is also evidence that β-adrenoceptor antagonists (beta-blockers) are effective cardioprotective agents that reduce mortality following myocardial infarction in subjects both with and without diabetes [58,59]. β-Adrenoceptor antagonists are indicated in patients with chronic heart failure as they improve left ventricular function and reduce mortality [60]. The β-adrenoceptor antagonists should be started in stable patients, at a very low dose which should be escalated gradually.

β-Adrenoceptor antagonists can, theoretically at least, interfere with several aspects of glucose homeostasis (Figure 26.3). In the islets, insulin secretion is enhanced by β_2-adrenoceptor stimulation, while the β_2-adrenoceptor-mediated response to hypoglycemia in the liver promotes hepatic glycogenolysis and increases hepatic glucose output, a crucial part of the counter-regulatory response that restores blood glucose to normal.

Long-term treatment with β-adrenoceptor antagonists, especially in combination with high-dose thiazide diuretics, has been shown to be diabetogenic. This is discussed further in Chapter 16. β-Adrenoceptor antagonists were used in combination with thiazide diuretics in most of the early large clinical trials in patients with hypertension. In clinical trials testing a β-adrenoceptor antagonist on its own, its effect on stroke was less favorable than comparative drugs. This led to its relegation to fourth line treatment in the fourth British Hypertension Society guidelines [61]. In people with diabetes, their effect on insulin resistance may make them a less suitable choice than angiotensin-converting enzyme (ACE) inhibitors for example. People with diabetes, however, have a more stringent blood pressure target (130/85 mmHg), which necessitates the use of multiple classes to control blood pressure. In such instances, a beta-blocker could be added. People with diabetes frequently have ischemic heart disease, which is another indication for β-adrenoceptor antagonists.

β-Adrenoceptor stimulation is responsible for major hypoglycemic symptoms: the pounding heart and palpitation are secondary to β_1-adrenoceptor-mediated increases in heart rate and contractility, while tremor and sweating are both β_2-mediated (sweating also has a cholinergic component) (Figure 26.3). Non-selective β-adrenoceptor antagonists that antagonize both β_1- and β_2-receptors can therefore delay recovery from hypoglycemia and also reduce the patient's awareness of hypoglycemia.

Cardioselective β_1-adrenoceptor antagonists are less likely to interfere with awareness of or recovery from hypoglycemia, and so are preferable in patients treated with insulin or sulfonylureas. Even low doses of cardioselective β_1-adrenoceptor antagonists can modify some of the symptoms and signs of hypoglycemia (e.g. tachycardia), while other symptoms that are robust indicators of hypoglycemia (e.g. sweating) are unchanged or even more pronounced in the presence of β_1-blockade [62,63]. Overall, cardioselective β-adrenoceptor antagonists rarely impair recognition of hypoglycemia. The incidence of hypoglycemia is not increased during treatment with β_1-selective adrenoceptor antagonists, even in patients prone to the condition [64,65]. By contrast, the non-selective drugs can impair recovery from hypoglycemia [62,66,67].

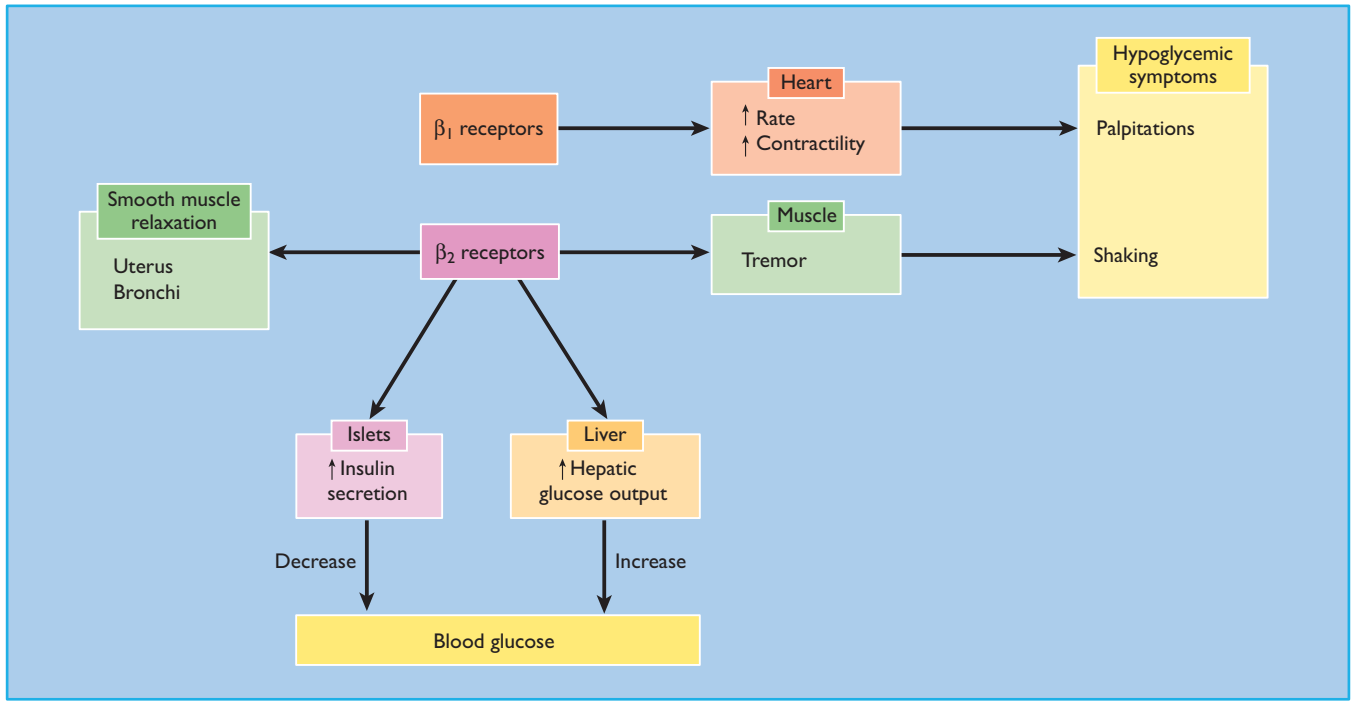

Figure 26.3 Effects mediated by β-adrenoceptors.

Concerns about the adverse metabolic effects of β_1-selective adrenoceptor antagonists have probably been exaggerated and the potential benefits of their cardioprotective effects underplayed [58]. Moreover, studies in heart failure have now provided extensive data showing that low-dose β-adrenoceptor antagonists are relatively safe in older, vulnerable patients [68].

Calcium-channel blockers

In vitro and *in vivo* studies have suggested that calcium-channel blockers may impair glucose metabolism, possibly because of impaired insulin secretion. Very few cases of clinically significant hyperglycemia, however, have been reported, and most of these were associated with excessive dosages of the drugs. When used appropriately, calcium-channel blockers are as safe in patients with diabetes as in people without diabetes (see Chapter 40). In people of Asian or African origin, calcium-channel blockers are relatively more efficacious in lowering blood pressure. This is especially relevant in populations that have a high incidence of stroke.

Angiotensin-converting enzyme inhibitors

ACE inhibitors are now widely used to treat hypertension and heart failure in both people with and without diabetes. The evidence of benefit of ACE inhibition after myocardial infarction, in systolic ventricular dysfunction and chronic heart failure is strong [69–71]. Similarly, ACE inhibitors reduce proteinuria and the endpoint of doubling of serum creatinine, or the need for dialysis or transplantation [72]. This protective effect on the kidney is encouraging their use in normotensive patients with early nephropathy (see Chapter 37). By contrast, the use of ACE inhibitors in patients with coronary heart disease without systolic ventricular dysfunction remains controversial. Two large randomized controlled trials showed reductions in cardiovascular events [73,74], but this was not confirmed in a third trial [75].

ACE inhibitors do not cause hyperglycemia, and neither do they adversely affect lipid metabolism [76,77]. Indeed, there is some evidence from the HOPE study that ACE inhibitors may reduce the likelihood of new-onset diabetes [78]. The DREAM study, which specifically addressed this issue, did not confirm this. In comparison with diuretics and beta-blockers, the effect is striking. ACE inhibitors can improve insulin sensitivity and lower blood glucose concentrations, occasionally causing severe hypoglycemia [79,80]. Case–control studies in the Netherlands and Scotland have demonstrated a threefold increase in the risk of severe hypoglycemia (requiring hospital admission) in patients with diabetes who were taking ACE inhibitors [81,82].

In people with and without diabetes, ACE inhibitors are contraindicated if the renal arteries are stenosed because of the high risk of renal impairment, which is usually reversible but sometimes permanent. There may be significant renal artery stenosis in up to 20% of patients with both hypertension and T2DM [83].

Angiotensin receptor blockers

Like ACE inhibitors, angiotensin receptor blockers (ARBs) are also indicated for hypertension, heart failure, post-myocardial infarction and diabetic nephropathy [84]. One study showed a marked reduction in stroke and mortality in patients with diabetes on an ARB-based regimen [85]. There is also evidence that ARBs reduce the risk of new-onset diabetes [86].

There are no trials demonstrating that ARBs are superior to ACE inhibitors in terms of outcome, and they are currently more expensive. On the other hand, ARBs do not cause the characteristic dry cough associated with ACE inhibitors.

Combining an ACE inhibitor and an ARB has no demonstrable value in coronary heart disease or diabetic nephropathy, other than reducing urinary albumin excretion further [87,88]. Furthermore, it may be associated with significant hyperkalemia.

α_1-Adrenoceptor antagonists

α_1-Adrenoceptor antagonists are effective hypotensive agents. They are generally thought to have beneficial metabolic effects, including improved insulin sensitivity, with falls in blood insulin, glucose and lipid concentrations [89–91], although one report [92] has suggested that the use of doxazosin may worsen glycemic control in patients with diabetes. Despite their potential advantages, these drugs are not currently in extensive use, perhaps because of the side effect of postural hypotension. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the α-blocker arm of the study was prematurely terminated because of an increased incidence of congestive heart failure compared to the diuretic arm [93]. This probably reflects the benefit of diuretics in treating the symptoms of heart failure rather than induction of heart failure by α-adrenoceptor antagonists.

Thiazides and other diuretics

Thiazides

It has become unfashionable to use thiazide diuretics in patients with diabetes, even though they are generally well tolerated, inexpensive and at least as effective as newer agents in preventing stroke and myocardial infarction. The concerns are the reversible impairment of glucose tolerance that can occur with thiazides, unfavorable changes in serum lipid profile and the worry that they may make men impotent [94–111]. Many of these concerns stem from old trials in which high doses of thiazide diuretics (e.g. 5 mg bendroflumethiazide) were used.

The diabetogenic potential of the thiazides is discussed in detail in Chapter 16. The consensus is that low dosages (e.g. 2.5 mg bendroflumethiazide), which are just as effective as higher dosages in lowering blood pressure, cause little if any deterioration in glycemic control [112]. The effects on lipids of low dosages are minor, and outweighed by the benefits of blood pressure reduction [109,110,113]. Finally, one large study (Treatment of Mild Hypertension Study) found no excess of impotence attributable to thiazide treatment among middle-aged hypertensive men, who had a high baseline incidence of this complaint [111]. Overall, the thiazides have a useful place in the treatment of hypertension in people with diabetes [114].

Loop diuretics

Loop diuretics, such as furosemide, ethacrynic acid and bumetanide, seem to have less impact on glucose homeostasis than thiazide diuretics, although several reports suggest that they can cause hyperglycemia [115,116]. Recent *in vitro* studies have shown that furosemide inhibits enzymes in the glycolytic pathway [117], so leading to poor glucose utilization and hyperglycemia. In practice, however, few problems are encountered in using loop diuretics in people with diabetes; it has been argued that any insulin resistance and hyperglycemia are not actually drug-induced, but instead are the consequence of the conditions that require potent diuretic therapy.

Antihyperlipidemic agents

The relationship between diabetes mellitus and dyslipidemia is discussed in detail in Chapter 40. Hypertriglyceridemia is often ameliorated by the effective treatment of hyperglycemia; conversely, some evidence indicates that lowering lipids (including free fatty acid concentrations) can improve blood glucose control. In practice, drugs are often prescribed independently for diet-resistant hyperglycemia and hyperlipidemia, so interactions between agents used to treat the conditions are potentially important.

Statins

Statins (hydroxymethyl-glutaryl coenzyme A inhibitors) seem to pose few problems in this respect. Meta-analysis has shown that people with diabetes treated by a statin enjoy the same relative risk reduction in major cardiovascular events as people without diabetes [118]. In general, people with diabetes have a higher absolute risk of myocardial infarction and stroke; their annual cardiovascular risk is comparable with that in non-diabetic patients with a history of myocardial infarction. Therefore, diabetes is regarded in many guidelines as an indication for lipid lowering therapy.

Fibrates

Early studies suggested that clofibrate could improve glycemic control in patients with poorly controlled T2DM taking sulfonylureas [119] or metformin [120]. More recently, similar benefits have been reported with bezafibrate [121], although these observations have not been widely pursued.

Nicotinic acid and its derivatives

Nicotinic acid (niacin) has recently been confirmed as an effective treatment for dyslipidemia in patients with diabetes; it does not appear to interact with antidiabetic therapy, and may be an alternative to fibrates or statins in those who are unable to tolerate them [122]. It can, however, cause hyperglycemia [123] and unpleasant flushing. A slow-release formulation that causes less flushing is now available. Acipimox is an analog of nicotinic acid that does not cause hyperglycemia (see Chapter 16) [124].

Anion-exchange resins

Anion-exchange resins such as cholestyramine could theoretically reduce the absorption of antidiabetic drugs from the gut, although clinically significant interference has not been reported. By contrast, ezetimibe does not have this effect.

Combined statin and fibrate therapy

This is sometimes indicated for dyslipidemia that is refractory to treatment with single agents. Myalgia and more serious muscle damage (with rhabdomyolysis and myoglobinuria) are rare but well-established complications of both statins and fibrates, and the risks are substantially increased by co-administration.

Other drugs

The UK Summaries of Product Characteristics of many products contain contraindications to using the product in patients with diabetes, or diabetic complications. Some of the less obvious examples are oxymetazoline hydrochloride nasal spray and verruca gels containing salicylic acid [125]. In addition, there is a wide range of warnings that medicines should be used with caution in diabetes; for example, oral rehydration solutions and ribavirin [125].

Special precautions in diabetic complications

Some drugs are relatively or absolutely contraindicated in the presence of certain diabetic complications. These include oral contraceptives or hormone replacement therapies in women with diabetes and severe vascular disease, the antiplatelet agents abciximab and cilostazol, and growth hormone in patients with proliferative retinopathy, and propranol by injection in patients prone to hypoglycemia [125]. Important examples are shown in Table 26.5.

Table 26.5 Drugs requiring caution in specific diabetic complications.

Complication and drug	Problem	Action to be taken
Nephropathy		
Sulfonylureas	Accumulate in renal failure; increased risk of hypoglycemia and toxicity	Use insulin or a sulfonylurea not cleared through the kidneys (e.g. gliquidone, gliclazide)
Metformin	Accumulates in renal failure; increased risk of lactic acidosis	Avoid
ACE inhibitors or ARBs	Initial rise in plasma creatinine; risk of hyperkalemia	Use with caution and appropriate monitoring of renal function
NSAIDs or COX-2 inhibitors	Further compromise renal function	Avoid if possible
Radiocontrast media	Reduce renal function	Adequate hydration before procedure
Cardiovascular disease		
β-Adrenoceptor antagonists	Accentuate hypoglycemia May cause modest VLDL elevation	Consider alternative antihypertensive, antianginal or antiarrhythmic drugs (e.g. ACE inhibitors, calcium-channel blockers)
Thiazide diuretics (high dose)	Worsen glycemic control in type 2 diabetes Exacerbate hyperlipidemia	Reduce dose, or use loop diuretic or alternative antihypertensive drugs
Retinopathy		
Mydriatics (eyedrops or systemic atropinic drugs)	In patients with rubeosis or previous eye surgery, glaucoma may be precipitated	Seek ophthalmologic advice before dilating pupils
Anticoagulants	May predispose to vitreous hemorrhage in patients with proliferative changes	Avoid if possible
Abciximab	May predispose to vitreous hemorrhage in patients with proliferative changes	Avoid if possible
Somatropin	Can worsen proliferative retinopathy	Avoid
Autonomic neuropathy		
Phosphodiesterase inhibitors (e.g. sildenafil)	Aggravates postural hypotension	Avoid, especially in the elderly and those taking nitrates
Ganglion-blocking agents and vasodilators	Aggravate postural hypotension	Use with caution
Impotence		
Ganglion-blocking agents β-Adrenergic blockers Clonidine α-Methyldopa	Aggravate erectile failure	Use alternative antihypertensive drugs (e.g. ACE inhibitor, calcium-channel blocker or α-adrenergic blocker)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COX, cyclo-oxygenase; NSAID, non-steroidal anti-inflammatory drug; VLDL, very low density lipoprotein.

There has been controversy about the risks of inducing vitreous hemorrhage with thrombolytic treatment (e.g. streptokinase) for myocardial infarction in patients with proliferative retinopathy. Current advice is to give thrombolytic drugs according to the usual indications, as the likely benefits far outweigh the potential threat to vision.

Drug interference with monitoring of diabetic control

Urine testing for glucose, still favored by many elderly patients, is subject to interference by several drugs [126], including ascorbic acid, which can give false-negative urine glucose readings with glucose oxidase strips (see Chapter 25) [127].

Blood glucose measurements, using dry-reagent glucose oxidase test strips, can potentially be affected by drugs such as aspirin if present in very high concentrations [128]. Readings can also be misleading if fingers are contaminated with alcohol from swabs (which inactivates glucose oxidase) or with glucose (e.g. from sugary drinks) [129].

The complex sugar icodextrin, used as a peritoneal dialysate, can give spuriously high glucose concentrations; this can mask underlying hypoglycemia [130].

Conclusions

Rational prescribing is a difficult task whose success demands the integration of data about the drugs being used, the patient, and the conditions that affect the patient. There are three major areas of difficulty when prescribing for patients with diabetes. First, a large number of drugs affect glucose tolerance. They include important agents, such as oral corticosteroids, which can be lifesaving but confound attempts to achieve euglycemia. Secondly, patients with diabetes are now commonly asked to take several medicines to control glycemia, and to treat the complications of diabetes. The number of potential interactions between pairs of drugs increases rapidly with the number of different drugs prescribed. As the number of prescribed medicines increases from 5 to 10, the number of possible pair-wise interactions increases from 10 to 45 (and the number of three-way interactions from 10 to 120). Thirdly, patients with diabetes are at high risk of other disorders whose management conventionally involves the prescribing of a range of medicines. For example, treatment of patients after myocardial infarction, five times more likely in the presence of diabetes, would commonly involve one or more antiplatelet agents, a statin, an ACE inhibitor, and a β-adrenoceptor antagonist.

Rational prescribers will consider, in consultation with the patient, therapeutic purpose, and the potential benefit and the possible harm of any additional treatment in the individual patient prior to prescribing. They will also review long-standing prescriptions from time to time to revisit previous decisions in the light of changes in the patient, the reason for prescribing, and the pharmacopoeia.

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