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Medications affecting glycemic control

Ghazwa B Korayem*

Pharmacy Practice Resident, College of Pharmacy, University of Arizona, Banner University Medical Center, Tucson, AZ, USA

Abstract

Introduction: Review non-diabetes management medications that are commonly associated with either serious hyper- or hypoglycemia, or both, outline their mechanisms, and provide strategies for limiting these undesirable glycemic effects.

Methods: Literature search of Pub-Med for studies in which drugs induced hyperglycemia or hypoglycemia. The primary outcome for this review was the incidence and occurrence of hyperglycemia and or hypoglycemia

Results: Both hyperglycemia and hypoglycemia are associated with negative outcomes. Blood glucose variation was significantly associated with mortality in non-diabetic greater than diabetic patients. Medications may contribute to this glycemic variation manifested as either hyperglycemia or hypoglycemia. Many medications have been associated with aggravating hyperglycemia in diabetes mellitus patients, causing new hyperglycemia or outright diabetes in previously non-diabetic individuals. Steroids, immunosuppressive agents, antipsychotics and many other medications are commonly associated with hyperglycemia. On the other hand, hypoglycemia is an uncommon adverse effect associated with some antimicrobials and other medications. The risk may be increased, however, when such medications are used concomitantly with anti-diabetic agents. Benefits of these medications associated with hyper- or hypoglycemia may offset the potential adverse effects of abnormal glycemic control making overall management of the patient a challenge.

Conclusion: Hyperglycemia, hypoglycemia, and glucose variation have been shown to contribute to negative outcomes. Therefore, it is imperative for clinicians to be aware of medications that may adversely affect glucose control. Withholding these medications may be justified in certain situations; however, any decision to avoid a medication based on glycemic effects must be carefully weighed against their benefit as well as the risks and benefits of alternative therapies.

Introduction

Hyperglycemia, hypoglycemia and blood glucose variability are associated with negative outcomes, including increased mortality in both individuals with or without diabetes mellitus (DM) [1-3]. Some medications alter glycemic hemostasis which manifests as either hyperglycemia or hypoglycemia [2]. Inconsistent caloric intake, stress, infections, organ failure, advanced age, intensive inpatient insulin regimens or inadequate glycemic therapy and polypharmacy also contribute to glucose alterations [4,5]. Therefore, controlling blood glucose (BG) in hospitalized or acutely ill patients is a challenge. Hormones involved in glucose hemostasis, such insulin, glucagon, catecholamines (CA), growth hormone, and cortisol, are also affected by some medications. This article aims to review non-DM medications medications that are commonly associated with either serious hyper- or hypoglycemia, or both, and discusses their mechanisms, as well as providing strategies for limiting or avoiding the undesirable glycemic effects.

Hyperglycemia

Drug-induced diabetes is a global issue that is frequently overlooked. Medications can either aggravate diabetes-associated hyperglycemia, or may cause new hyperglycemia episodes or outright DM in previously non-DM individuals. The American Diabetes Association (ADA) classify drug induced DM under "monogenic diabetes syndromes," a specific type of DM that is drug- or chemical-induced [6]. Older age, high body mass index, or family history may increase the risk of medication induced hyperglycemia and impaired glucose tolerance (IGT) [5]. Regardless of the cause, the first step in managing patients with IGT, hyperglycemia or DM, should be preventing or mitigating modifiable risk factors through lifestyle modification including weight loss, maintaining a healthy diet, adequate physical activity and patient education. Clinical judgment along with continuous assessment of the patient's clinical status, illness severity, nutritional status, and concomitant medications potentially affecting glucose concentration should be incorporated into decisions to avoid, hold or continue therapy [7]. If DM develops, it may be appropriate to consider management with anti-diabetic agents.

Atypical antipsychotic

Second generation or atypical antipsychotics (AAP) are widely prescribed for the management of schizophrenia, other psychotic disorders and conditions with severe behavioral disturbance. Both typical antipsychotic (TAP) and AAP use may lead to metabolic abnormalities including hyperglycemia [8]. In addition, it should be recognized that schizophrenia itself may represent an inherent risk for developing type 2 DM [9]. Increased weight and concomitant use of valproic acid, selective serotonin reuptake inhibitors, or buspirone may also exacerbate hyperglycemia [10]. Antipsychotic-associated hyperglycemia occurs early in therapy but risk of new onset diabetes

Correspondence to: Ghazwa B Korayem, Pharmacy Practice Resident, College of Pharmacy, University of Arizona, Banner University Medical Center, Tucson, AZ , 0202, 1295 N, Martin Ave, AZ 85721, USA, Tel: +1(520)694-2265; E-mail: korayem@pharmacy.arizona.edu

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mellitus (NODM) increases with chronic use [8,11]. AAP are associated with a higher risk of developing DM and more severe hyperglycemia compared to TAP [12]. AAP-associated hyperglycemia can be extreme and associated with ketoacidosis or hyperosmolar coma or death [11,12]. Therefore, in 2004 the Food and Drug Administration (FDA) issued a new warning on all APP drug labels regarding the increased risk of hyperglycemia and NODM [13]. Clozapine and olanzapine appear to have the highest risk and are also associated with a significantly higher risk of weight gain, impaired glycemic homeostasis and NODM [14,15]. Data on quetiapine is inconsistent; although minimal effect on glycemic control has been reported with ziprasidone, as well as aripiprazole [15-17] proposed mechanisms behind antipsychotic-induced DM, include drug-induced weight gain and insulin resistance. Potential mechanisms for weight gain include blocking serotonin 2C (5HT2C) or histamine (H1) receptors, resulting in inhibited insulin secretion, insulin resistance, or impair glucose utilization [18,19]. Elevation of serum leptin or hyperprolactinemia may also induce insulin resistance [18,19]. In some cases, discontinuing the APP may resolve hyperglycemia; however, medication is generally required to prevent psychotic relapse and deterioration [9,19]. Both DM and schizophrenia are serious illnesses that require diligent management. Depending on patient and disease characteristics, it may be possible to substitute with a less diabetogenic APP. Fasting blood glucose (FBG) is recommended at baseline, 3 months, then annually for all patients, more frequently for those at higher risk of developing DM [20]. If patients develop hyperglycemia during treatment, injectable or oral anti-diabetic treatment may be initiated despite discontinuation of the suspect drug.

Beta blockers (βB)

βB are commonly used for their cardiovascular benefits. However, Increasing FBG, NODM, and increasing hemoglobin A1c (A1C) have been linked to βB use [21]. The overall magnitude of FBG increase appears to be minor (0.6 mmol/L for pooled endpoint FBG) based on a meta-analysis of data from 1889 patients with DM [21]. Non-selective βB had a greater effect than selective βB (1.3 mmol/L and 0.15 mmol/L increases, respectively) in this meta-analysis although the literature as a whole is inconsistent [10,21-24]. Data are also inconsistent for NODM with βB use. Reanalysis of the NAVIGATOR study data showed a non-significant increase in NODM; valsartan was used as the βB and all participants met criteria for impaired glucose tolerance at study entry [25]. In contrast, a large meta-analysis evaluating NODM in participants without DM at randomization found an increased risk of NODM in patients prescribed βB as initial therapy for hypertension [22]. The extent to which βB-associated glycemic effects may diminish the known cardiovascular benefits of βB is uncertain. Therefore, it is recommended to prescribe or continue βB in DM patients as indicated while closely monitoring their BG and adjusting therapy for glucose management, if necessary [21].

Epinephrine (EPI)

EPI is a widely used vasopressor It contributes to stress-induced hyperglycemia and susceptibility of DM patients to the adverse metabolic effects [26,27]. When EPI is given as a drug, it acutely decreases insulin sensitivity and secretion, in individuals with or without DM [28,29]. The effect on glycogenolysis rapidly wanes; thus the EPI induced hyperglycemia is short lived. Notably, chronic use of EPI and other β2 agonists improves cellular glucose uptake and metabolism [30]. EPI has contradictory roles. While it may raise blood glucose, in some circumstances, it is associated with lowering glucose [26]. It is very difficult to isolate the causality on EPI as a vasopressor on glycemic control from other hyperglycemia contributing factors in critically ill patients. In patients who have stress- or EPI-induced hyperglycemia, it is more appropriate to manage the patient's glucose than avoiding or withholding essential vasopressor therapy.

Niacin

Nicotinic acid (niacin) is commonly used alone or in combination to increase high-density lipoprotein cholesterol and lower triglycerides. Deterioration of glucose tolerance, elevation of FBG concentrations and development of NODM have been reported with niacin use [31-33]. Birjmohun et al found the incidence of niacin-induced hyperglycemia to be around 2.3% in a meta-analysis including 30 trials with 4749 participants randomized to niacin or placebo [32]. Immediate release formulations showed the highest prevalence of hyperglycemia [33]. A review of consensus guidelines, published RCT, and non-RCT, concluded that increases in FBG are usually 4%-5% with niacin doses ≤ 2.5 g daily, although increases may be greater in patients with DM [34]. Effects on A1c were nil to modest and reversible [33]. In contrast, another large meta-analysis with 26,340 non-diabetic participants followed for an average of 3.6 years found the risk of NODM was increased by 34% with niacin [35]. Niacin-associated hyperglycemia may develop due to modestly decreased insulin sensitivity [36,37]. Although doses of niacin currently used may result in minor deterioration of glycemic control in patients with DM; those patient may experience a dose-related increase in their glucose intolerance [38]. It is generally recommended to defer niacin therapy while attempting to improve glycemic control in patients with impaired FBG or IGT, and withdraw therapy or reduced dose in patients with niacin induced NODM [34]. The cardiovascular benefits of niacin may offset the potential adverse effects on glycemic control as shown in ADMIT study [33]. Niacin-induced NODM is an infrequent adverse drug effect that warrants niacin treatment withdrawal or dose reduction. Thus, niacin can be safely used in patients with DM while BG levels may be closely monitored during the first few months of use [33].

Octreotide

Octreotide, a somatostatin analogue, is used for numerous conditions because if its effects on gastrointestinal (GI) hormones and blood flow. The pharmacologic effects of octreotide on the counter-regulatory hormones, insulin, glucagon, and growth hormone [39]. Resulting in hyperglycemia in 16% and hypoglycemia in 3% of treated patients with acromegaly, the only condition for which data are available [40]. Hyperglycemic effects can be mild or aggressive with overt DM developing through the inhibition of insulin release [41]. Due to direct effects on insulin secretion, octreotide may be useful for preventing rebound hypoglycemia in the management of sulfonylurea (SU) and dipeptidyl peptidase-4 (DPP-4) inhibitor overdoses [42,43]. Endocrine Society guidelines recommends monitoring bedside point of care (POC) glucose for at least 24 to 48 h after octreotide initiation, even in patients who were previously normoglycemic [44]. If POC levels are persistently above 7.7 mmol/L, therapeutic intervention to reduce BG should be considered [44].

Pentamidine

Most patients receiving pentamidine are immune-compromised and require treatment or prevention of Pneumocystis jiroveci (carinii) pneumonia (PJP). Intravenours and aerosolized pentamidine use has been associated altering glucose heamostasis [45]. Retrospective studies indicate 9%-32% of patients treated with pentamidine develop

hyperglycemia; mean onset is approximately 52 days after initiating therapy [46]. Pentamidine induced hyperglycemia is attributed to either hyperamylasemia causing an increase in glucagon release or decreased insulin release, especially after a meal [47]. In vitro studies found that pentamidine induces irreversible β cell damage, secretory defect and necrosis precipitating the development of DM [48-50]. Risk factors associated with hyperglycemia include higher cumulative or single pentamidine dose and renal impairment [46]. Dysglycemic effects of pentamidine can be delayed. Hyperglycemia and DM, with or without preceding hypoglycemia, can occur up to several months after cessation of therapy [46,47]. Therefore, patients should be educated on signs and symptoms of both hyper- and hypoglycemia, as well as their management and the importance of regular BG monitoring [47].

Protease inhibitors (PIs)

PIs are a critical component of the antiretroviral therapy for managing HIV and AIDS. However, many metabolic complications have been associated with PIs. The FDA issued a Public Health Advisory in 1997 describing post-marketing surveillance reports of NODM, exacerbation of preexisting DM, IGT and hyperglycemia in patients receiving PIs [57]. The incidence of hyperglycemia ranges between less than 1% to 6% and occurs as early as two weeks after initiation of PI therapy [52,53]. Overt DM was reported in 6% to 13%, most commonly with indinavir, and was more frequently detected later in therapy [51-54]. Ritonavir and saquinavir, or concomitant medications affecting glucose control, such as GC or pentamidine, increase the risk of DM [52,55]. PIs induce IGT by either induction of peripheral insulin resistance or by reduction of β-cell function [53]. Although, metabolic adverse effects of PIs may not be serious enough to warrant discontinuation and may be resolved on discontinuation [56]. The International AIDS Society-USA Panel and the Panel on Antiretroviral Guidelines suggest avoiding PI-based regimens as initial therapy in patients with a concern of metabolic toxicity, preexisting abnormalities of glucose metabolism or with the first-degree relative with DM [55,57]. When a PI-based regimen cannot be avoided, routine monitoring of glucose and A1C is appropriate. Treatment with insulin or oral anti-diabetic agents should be considered if DM develops.

Statins

HMG-CoA reductase inhibitors, commonly referred to as 'statins', are widely used in the primary and secondary prevention of cardiovascular diseases to lower serum cholesterol. Mixed results have been reported for effects of statins on glucose control; however, in 2012 the FDA requested a safety label change on all statins to include risk of increased A1C and FBG concentrations [58]. Data supporting this statement showed a 5-25% increased risk of NODM or DM treatment in patients receiving statin [59,60]. However, a recent cohort study showed no increase in NODM with statins [61]. Onset of initiating DM treatment or NODM reported as early as 6 months up to years after starting statin [61,62]. The risk of DM may increase with statin dose, intensity and is greater in individuals with pre-existing metabolic syndrome or prediabetes [61-63]. An observational study evaluating the effect of statins on FBG over a 2 year follow up period reported a statin-associated increase of 0.5 mmol/L in patients with DM and 0.2 mmol/L without DM [63]. The precise mechanism(s) for statin-induced DM remains unclear, although hypotheses include statin induced insulin resistance, inhibited β cell insulin secretion and synthesis, and decreased insulin-mediated cellular glucose uptake [64-66]. Based on current literature, the long-term CVD benefit of statins outweigh the risk of DM. Therefore, withholding statins in those at high risk of CVD is not recommended for the relatively minor concern of progression to DM [64].

Thiazide

Thiazide diuretics are indicated as adjunctive therapy in congestive heart failure-associated edema and hypertension. However, they have been linked to IGT, hyperglycemia more than NODM [61-69]. Hydrochlorothiazide or chlorthalidone have been reported to cause hyperglycemia more often than other diuretics, and a higher incidence of NODM was reported with chlorthalidone in the ALLHAT trial after 2 and 4 years follow-up [68]. The exact mechanism of thiazide-induced hyperglycemia remains unclear. One of the proposed mechanisms is through thiazide-induced hypokalemia, resulting in decreased insulin secretion and/or reduced insulin sensitivity [67,70]. On the other hand, a subgroup analysis of the PEAR study found no correlation between thiazide-induced changes in potassium and FBG levels [71]. Restoration of normoglycemia has been observed after thiazide discontinuation [72]. Nonetheless, avoiding or holding diuretics in patients with DM or hyperglycemia may be inappropriate since thiazide is usually necessary to provide symptomatic relief or achieve cardiovascular goals. Starting with a low dose and optimizing serum potassium concentrations is recommended when initiating thiazide in patients with DM [73].

Transplant-associated hyperglycemia

Medications for post-transplant immunosuppression (IS) account for 74% of new onset diabetes after transplant (NODAT); Glucocorticoids (GC) are the major cause [74]. Calcineurin inhibitors (CNI) are also implicated. Other NODAT risk factors include hypomagnesemia, which may decrease insulin sensitivity, and hepatitis C infection recipients [75]. Worsening of hyperglycemia in individuals with known pretransplant DM and hyperglycemia without pre-existing DM have been reported within the first 72 hours after transplant [76,77]. NODAT shares many similarities with type 2 DM but in some cases may be reversible [78,79]. β-cell dysfunction is thought to be the main factor in the pathogenesis of NODAT [80,81].

Calcineurin inhibitors (CNI)

Cyclosporine (CsA) and tacrolimus (Tac) remain a cornerstone of maintenance IS after transplant impaired glucose metabolism remains an issue associated with CNI-containing regimens despite the GC reduction allowed by CNI [78]. Toxic effects of CNI on the pancreas may contribute to insulin resistance and reduction in insulin secretion [82].

DIRECT study results indicate a significantly lower risk of NODAT with CsA regimens versus Tac in the first six months posttransplant [83]. Risk of NODAT increases with Tac trough concentrations >15 ng/mL during the first month after transplantation [84]. Tac's profound diabetogenic effect may be due to Tac specific binding to FKBP-12 which is preferentially located in β-cells, resulting in Tac concentrating there [85]. CsA specifically binds to cyclophilin which is preferentially located in the heart, liver and kidneys [85]. Reducing the target for Tac trough concentrations below 10 ng/ml,Tac dose, or switching from Tac to CsA may lower the incidence of NODAT or be effective in managing NODAT [84,86]. Conversely, reducing GC doses or switching from Tac to sirolimus (Sir) does not appear to improve glycemic control; insulin resistance may even worsen with Sir [87,88]. Sir itself impairs pancreatic β –cells responses and insulin production [89,90]. Ability to reduce IS doses or modifying IS regimen is often limited by other side effects of these medications and the risk of acute

organ rejection [78]. All transplant patients need ongoing monitoring of FBG and periodic evaluation of A1C throughout the post-transplant period [86,89]. Management of patients with NODAT should follow a step-wise approach, similar to that followed for patients with type 2 DM [89].

Glucocorticoids (GC)

GC are widely prescribed for their significant anti-inflammatory and IS benefits. However, they are associated with hyperglycemia in individuals with or without DM and with development of NODM [88-91]. Hyperglycemia may occur within 24 hours of receiving greater than physiologic doses, which is more than 10 mg of prednisone daily or equivalent [90,92]. The risk of glucocorticoids induced hyperglycemia (GIH) varies depending on GC duration of therapy, potency, dose, route of administration [93,94]. An intermediate duration GC administered once daily will predominantly cause post-prandial hyperglycemia with a gradual decline toward normal overnight [88,91]. BG is more likely to be high throughout the day with multiple GC doses per day [91]. Increased insulin resistance occurs with GC-induced DM, similar to type 2 DM [88]. GCs antagonize the metabolic effects of insulin, particularly in the postprandial state through effects on reduced postprandial insulin secretion, promoting gluconeogenesis, increasing lipolysis and enhancing the effects of counter-regulatory hormones [94-96]. GC may also cause β cell dysfunction affecting insulin sensitivity and release. The treatment of choice for GC-induced hyperglycemia will vary depending on the GC used, frequency, duration of action, duration of therapy and current anti-diabetic regimen, if any (Table 1). Basal-bolus insulin (BBI) may be initiated with either neutral protamine Hagedorn (NPH) or glargine insulin for hospitalized patients on GC with persistent hyperglycemia above or equal 11.1 mmol/L [7,97]. Both types of insulin have been shown to be are equally effective in small retrospective studies [7,97]. Any of 3 approaches are acceptable for insulin dosing: weight based insulin regimen, steroid dose based regimen or focused prandial insulin therapy [88]. Oral anti-diabetic agents may be considered for outpatient management, when hyperglycemia is mild, or for short-term GC use [81]. Unfortunately, the risk of hypoglycemia may increase with most oral agents due to their slow onset and prolonged duration of action, as well as lack of selectively for postprandial hyperglycemia [81]. Shorter acting agents might be more appropriate, but exenatide is the only agent studied for GIH (Table 2) [88]. Exenatide targets postprandial hyperglycemia and has been shown to prevent prednisone induced glucose intolerance [98].

Hypoglycemia

Severe hypoglycemia has been associated with increased risk of adverse events including mortality and prolonged hospitalizations [99,100]. Several medications have been reported to increase the risk of hypoglycemia. Most commonly reported offending agents included trimethoprim-sulfamethoxazole, βB, quinolones, pentamidine, quinine, angiotensin- converting enzyme inhibitors (ACEI), angiotension receptor blockers (ARB) and insulin-like growth factor [101,102]. However, A systematic review showed that stronger evidence supported the associations between quinolones, quinine, pentamidine and hypoglycemia as discussed below [101]. Certain anti-diabetic agents are at higher risk of hypoglycemia when used as monotherapy compared to other classes. Patients with renal dysfunction, liver disease, malnutrition, or advanced age are particularly at higher risk of medication-induced hypoglycemia [103,104]. Although medication induced hypoglycemia may be uncommon, precautions are necessary because failure to recognize hypoglycemia can be fatal. A standardized hospital-wide and nurse-initiated hypoglycemia treatment protocol should be in place to address hypoglycemia [2].

Fluoroquinolones (FQ)

FQ are frequently prescribed antibiotics. Increased use of these drugs has raised concern regarding rare but severe dysglycemia that may be fatal [105,106]. FQs have higher rates of both hyperglycemia and hypoglycemia compared to macrolides [107]. Higher risk of hypoglycemia was noted in patients concomitantly receiving antidiabetic agents in a nationwide cohort study [107]. Hypoglycemia has also been reported in patients without DM or not on hypoglycemic medication. Episodes occurred mostly at the beginning of FQ therapy and most occur after several days [108,109]. Moxifloxacin has been associated with the highest risk of hypoglycemia, followed by levofloxacin and ciprofloxacin [107]. FQ may cause hypoglycemia by increasing the release of insulin via a blockade of ATP-sensitive K+ channels in a dose-dependent manner and FQ itself may enhance the glucose-induced insulin secretion [110]. Therefore, careful monitoring of blood glucose is recommended when FQ are used, especially if co-administered with anti-diabetic agents.

Table 1. Properties, dosing equivalents, effect on glucose and suggested insulin regimens of systemic corticosteroids.

Glucocorticoids	Equivalent dose (mg)	Relative glucocorticoid activity	Peak action (hr)	Duration of action (hr)	Effect on glucose	Initial insulin regimen options
Short Acting						
Hydrocortisone	20	1	1-4	8-12	Short episodes of hyperglycemia & associated with higher glycemic variability [99].	Basal-bolus insulin 0.3 to 0.5 Units/kg per day [45].
Cortisone	25	0.8	1-4	8-12		
Intermediate Acting						
Prednisone	5	4	4-6	12-36	Single dose: hyperglycemia during the afternoon and night without effect in fasting glucose [89,100]. Divided doses: persistent hyperglycemia	-Basal-bolus insulin 0.3 to 0.5 Units/kg per day [45]. -Once daily oral regimen dose; NPH once daily at the time of steroid dose [97,101]; NPH 0.5 units/mg glucocorticoid (range 0.25–1.0 units) daily administered at the time of the GC dose [7] -Twice or more dosing: NPH twice a day [101]; NPH 0.5 units/mg GC (range 0.25–1.0 units) in divided doses twice daily [7]
Prednisolone	5	4	4-6	12-36		
Methylprednisolone	4	5	4-6	12-36		
Triamcinolone	4	5	4-6	12-36		
Long Acting						
Dexamethasone	0.75	30	1-2	36-72	Hyperglycemia that lasts >24 h, with a slight decline during an overnight fast [81].	-Basal-bolus regimen using long acting insulin [97,101] -In patients already on BBI regimen; use 140–150% of BBI [7] -Start NPH 3 units/mg of dexamethasone or equivalent in divided doses twice daily [7]
Betamethasone	0.6	30	?	36-72		

Table adapted but modified from Liu D *et al.,* 2013 [138]; Furst *et al*., 2012 [139]. BBI: Basal-Bolus insulin, hr: hours

Medications	Class effect	IGT	Hyperglycemia/FBG	NODM	Increase A1C	Time to occur	May be reversible on dis-continuation	Hypo-glycemia	Time to occur
AAP	No [8]	Yes [8]	Yes [12]	Yes [8]	Yes [8,10]	late [8-10]	Yes [9,18]	No	NA
β-blockers	No§ [20]	Yes [17]	Yes [20]	Yes [21]	Yes [20]	Late [68]	-	Yes / [29,30]	
CNI	Yes [78]	Yes [77]	Yes [77]	Yes [78]	Yes [76,123]*	Early & late	Yes [75]	No	NA
Epinephrine	-	Yes [28]	Yes [28]	No [28]	-	Early [28]	Yes	No	NA
FQ	Yes	-	Yes [116]	-	-	Late: days [117]	Yes	Yes [115]	Early [117]
Niacin	-	Yes [31]	Yes [31]	Yes [31]	No [38]	Late; weeks- months [36]	Yes [34]	No	NA
Octreotide	-	Yes [130]	Yes [39,40]	Yes [39,40]	-	Late [39,40]	-	Yes [39]	Early
Pentamidine	-	Yes [47]	Yes [47]	Yes [47]	-	Late [47]	No	Yes [120]	Early
PI	Yes [53]¶	Yes [51]	Yes [51]	Yes [51]	Yes [124]	Late	Yes [56]	No	NA
Steroids	Yes [89,90]	Yes [89,90]	Yes [89,90]	Yes [89,90]	Yes [80,90]	Early	Yes	No	NA
Statins	Yes [61] ∞	Yes [64]	Yes [63]	Yes [60,61]	Yes [63]	Late [63]	-	No	NA
Thiazide	Yes [67]	Yes [67]	Yes [67]	Yes [67]	Yes [72]	Late [67]	Yes [72]	No	NA

AAP: Atypical antipsychotics, CNI: Calcinueurin inhibitors, FBG: Fasting blood glucose, FQ: Fluroquinolones, IGT:Impaired glucose tolerance,NODM: new onset diabetes mellitus, PI: Protease inhibitors. Late: > 14 days of initiation, *NODAT not specifically CNI induced, **§:** Studies suggested that some non-selective vasodilating βB may have favorable effects on glycemic control, but another meta analysis reported that the effect of non-selective βB on FBG significantly more than those of selective βB [20-24], /: βB themselves do not induce hypoglycemia, but mostly mask hypoglycemia or delay hypoglycemia recovery. **¶:** Risk is higher with indinavir, sequinavir and ritonavir [51-55],∞: Risk is higher with high-intensity statins [61-63], - : No date , NA: None Applicable.

Pentamidine

Both hypoglycemia and hyperglycemia have been observed with pentamidine. Hypoglycemia occurs in 7%-38% of patients receiving pentamidine, either parentally or inhaled [45,111]. Onset of hypoglycemia may appear within hours to days after the first dose [47]. Early, sudden, sever and fatal hypoglycemia preceding hyperglycemia has also been reported [47,112]. Hypoglycemia may be attributed to an early excessive insulin leakage from β-cells and the absence or poor response of β-cells to glucagon [46]. Pentamidine induced nephrotoxicity and kidney dysfunction may prolong insulin action and contribute to hypoglycemia [47]. Patients should be educated about signs and symptoms of hypoglycemia and frequently monitor BG while on therapy.

Quinines

Parenteral quinine is no longer commercially available in the U.S [113]. Both quinine and quinidine including hydroxychloroquine may cause or aggravate hypoglycemia by stimulating insulin secretion, but quinine's effect is more potent [113,114].

Conclusion

Hyperglycemia, hypoglycemia and glucose variation contribute to negative outcomes in DM and non-DM patients. Medications may play a significant role in glucose hemostasis with multiple mechanisms potentially contributing to dysglycemia. Knowing the mechanism(s) by which a medication induces hyperglycemia or hypoglycemia could help guide therapy and determine if the clinical benefit of the medication outweighs dysglycemic risks. Medications that pose higher risk of hyperglycemia or hypoglycemia may be avoided when therapeutic alternative exist while highly beneficial medications are appropriately selected despite their effect on glucose homeostasis.

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