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DPP- 4 Inhibitors in the Management of Type 2 Diabetes Mellitus

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KEY WORDS

Antihyperglycemic drug, Clinical trial, Diabetes, DPP-4 inhibitor, Glucagon Like Peptide -1 and Incretin

INTRODUCTION, HISTORY AND EVOLUTION OF INCRETINS

Dipeptidyl peptidase-4 (DPP- 4) inhibitors or Gliptins are a class of antihyperglycemic agents used in treatment of type 2 diabetes mellitus (T2DM). They reversibly inhibit DPP- 4, a serine protease enzyme which degrades incretins like Glucose dependent Insulinotropic polypeptide (GIP) and Glucogan like peptide 1 (GLP-1) from intestine. Hence biological active levels of Incretins are increased that control the levels of fasting and postprandial glucose concentration within minutes through its pleotropic mechanism.[1] Incretins stimulates insulin secretion and suppresses glucagon in a glucose dependant manner along with decreased hepatic glucose production and gastric emptying. Although metformin is preferred for T2DM, insulin, sulfonylureas and thiazolidinediones are recommended as second line drugs to optimize glycemic control.[2] Nevertheless, intensive use of these therapies, they were associated with multiple risk factors like hypoglycemia, bone fracture, weight gain, cardiovascular, renal and other comorbities. This led to a new modality of treatment like incretin based therapy with specific interest on DPP-4 inhibitors. Table 1 gives the historical perspective of incretins.

Glucagon-like peptide -1 Receptor (GLP-1R) agonists and DPP IV inhibitors were the two classes of incretin based therapies approved for T2DM. They either promote weight loss (GLP-1 Receptor agonist) or do not affect body weight (DPP –IV inhibitor) and cause no risk of hypoglycemia. Hence Incretin based therapy offers a good treatment option for T2DM.[3]

DPP IV INHIBITORS ADDRESSING THE KEY PATHOGENIC DEFECT IN T2DM

The key pathological defects in type 2 diabetes occurs due to impaired insulin secretion through progressive

Table 1: Historical perspectives of Incretins and Evolution of Incretin based therapy

Year	Development
1902	Mechanism of Pancreatic Secretion by William M Bayliss, Ernest H Starling
1932	La Barre et al coined the term Incretine (Incretin) and defined its effect
1964	Incretin effect (Significant Insulin release on oral ingestion than Intravenous injection) demonstrated through radio Immunoassay by Elrick et al, Mcintyre et al.
1966	DPP –4 enzyme first described
1970	GIP discovered
1973	GIP demonstrated
1985	GLP 1demonstrated
1995	GIP & GLP 1 were demonstrated to be degraded by DPP-4 enzyme
2002	GLP 1 – Exendin -4 extracted
2005	Exenatide introduced
2006	Sitagliptin introduced for the use of T2DM
2007	Vildagliptin
2009	Saxagliptin
2010	Alogliptin
2011	Linagliptin
Recent GLP 1 R agonist	Liraglutide (2010), Albiglutide(2014), dulaglutide (2014) Taspiglutide semaglutide are under investigation
Recent DPP IV inhibitors	Anagliptin,Gemigliptin, Teneligliptin in 2012; Evogliptin, Omarigliptin and Trelagliptin in 2015.

DPP-4: Dipeptidylpeptidase-4, GIP: Glucose dependent Insulinotropic polypeptide, GLP-1: Glucagon-like peptide -1, T2DM: Type 2 Diabetes Mellitus.

Table 2: Comparison of action of DPP-4 inhibitors and GLP-1 receptor agonists

Action	DPP-4 inhibitors	GLP-1 receptor agonists
Insulin secretion	Increased	Increased
Glucagon Secretion	Decreased	Decreased
PPPG	Reduced	Reduced
Appetite	No effect	Suppressed
Satiety	No effect	Induced
Gastrointestinal adverse effects	Rare to none	Often Nausea
Gastric emptying	No effect	Slowed
Body weight	Neutral	Reduced

DPP-4: Dipeptidylpeptidase-4, GLP-1: Glucagon-like peptide -1

deterioration of pancreatic β-cell function and increased insulin resistance in peripheral tissues (in both liver & skeletal muscle) which results in elevated fasting and postprandial glucose levels leading to hyperglycemia.[4] Dysregulation in the incretin effect characterized by reduced GLP-1 secretion and impaired responsiveness to GIP is another major defect in T2DM.

Glucagon-like peptide 1 and GIP are intestinal incretin hormones released in response to food ingestion. GLP-1, secreted from intestinal L cells, is an incretin derived from the transcriptional product of the proglucagon gene. GIP is derived from K cells, a 153-amino acid proprotein encoded by the GIP gene and circulates as a biologically active 42-amino acid peptide. Both GLP-1 and GIP enhance meal-related insulin secretion and promote glucose tolerance, a phenomenon called 'incretin effect'.[5] Besides insulin secretion enhancement via cAMP-dependent signalling pathways, GLP-1 also suppress glucagon secretion from pancreatic alpha cell in highly glucose-dependent manner, and glucagon secretion is inhibited under hyperglycaemic conditions and even increased under hypoglycaemia. In addition GLP-1 regulates glucose homeostasis through its beneficial effects such as slowing of gastric emptying which decreases the entry of glucose into the circulation after meals, a reduction in appetite, and earlier induction of satiety, leading to weight reduction. GLP-1 also promotes beta-cell regeneration and reduces beta-cell apoptosis, which provide hope for preservation of beta-cell functions in T2DM patients.

However upon secretion, GLP-1 and GIP are rapidly degraded and inactivated by dipeptidyl peptidase 4 (DPP-4) enzyme (also known as CD26), a 110-kDa trans membrane glycoprotein constitutively expressed as a dimer on epithelial cells of the liver, hepatocytes, kidney and intestinal tissues, as well as in some endothelial cells, fibroblasts and lymphocytes. Endogenously released GLP-1 has a short biological half-life of 1.5–5 min and the serum half-life of GIP is 5–7 min. In order to prevent degradation of endogenously released GLP-1 and GIP, and to extend their half-life, led to the proposal of development of DPP-4 inhibitors.

DPP-4 INHIBITORS (INCRETIN ENHANCERS) VERSUS GLP-1 RECEPTOR AGONISTS (INCRETIN MIMETICS)

GLP-1 receptor agonists and DPP-4 inhibitors has been compared head-to-head in few long-term clinical trial, it is difficult to identify the patient population most likely to respond optimally to these two groups of drugs.[6] DPP IV inhibitors are small molecular weight drugs generally well tolerated and are effective orally. When used either as monotherapy or in combination with metformin, sulphonylureas or a combination of both, they are relatively easy to use and can be used in elderly, frail or vulnerable, renal and hepatic impairment patients. They are also associated with lower rates of hypoglycemia , reduction in HbA_1c levels (0.6 to 0.7 %), and have also been shown to be weight neutral. Because they do not cause hypoglycaemia, they do not require dose titration and can be taken at any time of day, independently of meal times. They are also generally free of drug–drug interactions and can mostly be used with other medications without the need for dose adjustment of either agent. Neither the pharmacokinetic profiles of nor exposure to other commonly used medications, including drugs which alter the activity of the CYP system [e.g. ketoconazole, rifampicin (rifampin) and ritonavir] or the P-glycoprotein transporter (e.g. cyclosporine) are affected in a clinically relevant manner by DPP-4 inhibitors. DPP-4 inhibitors may, therefore, be useful in conditions such as tuberculosis or HIV, which often present with diabetes as a side effect of the disease.

In contrast Incretin mimetics or GLP1 R agonists are peptide based drugs administered as subcutaneous injection to avoid degradation by gastrointestinal hormones. Compared to DPP IV inhibitor they are more effective in reducing HbA_1c levels due to its increased concentration (6 to 10 fold) after injection. GLP-1 receptor agonists are associated with high rates of nausea due to gastric slowing, causes significant weight loss, especially in very obese patients, whereas DPP-4 inhibitors are weight neutral agents.

The main patient-perceived difference between DPP-4 inhibitors and GLP-1R agonists is likely to be their mode of administration and convenient once-daily oral dosing that promote patient adherence and improve health outcomes.[7, 8] Although it is believed that patients generally oppose injectable therapies, evidence suggests that this is not always the case, especially if the injectable therapy has greater efficacy. A comparison of the actions of the DPP-4 inhibitors and GLP-1 receptor agonists in patients with T2DM is provided in Table 2.

DPP-4 INHIBITORS

Dipeptidyl peptidase-4 inhibitors can be broadly divided into peptidomimetics (i.e., sitagliptin, gemigliptin, teneligliptin, vildagliptin, saxagliptin, and anagliptin) and non-peptidomimetics (i.e., alogliptin and linagliptin). Both are competitive reversible inhibitors of the DPP-4

Table 3: Comparison of different properties of available DPP-IV inhibitors

	Alogliptin	Anagliptin	Evogliptin	Gemigliptin	Linagliptin	Omarigliptin	Saxagliptin	Sitagliptin	Teneligliptin	Trelagliptin	Vildagliptin
Approval date	2010	2012	2015	2012	2011	2015	2009	2006	2012	2015	2007
Peptidomimetic	-	+		+	-		+	+	+		+
Pharmacodynamics											
IC50 for DPP-4 inhibition (nmol/L)	7	3.8		6.31	1		0.5	18	0.9-1.8		3.5
DPP-4 selectivity (vs DPP-8 and 9)	>14000	59000, 100000		27728, 23373	>10000		390, 77	4777, 10926	703, 1460		135, 8
% Inhibition of plasma DPP-4 activity	75-93			>80	>70		>70	>80			>80
Fold increase in active GLP-1 level	3-4			1.8-2.8	2-3		1.5-2	2			2-3
Reduction in HbA1C (%)	0.5-1.2										
Pharmacokinetics											
Oral bioavailability (%)	100	73			29.5		75	71-88	58-83		84-85
Volume of distribution (Vd, L)	417				368-918		151	198	106.8		70.5
Fraction bound to plasma proteins (%)	20				70		<10	38	77.6-82.2		9.3
Half-life (hr)	21.1	4.37		17-21	120-184		2.2-3.8	8-14	16-20		2.8
Renal excretion (%)	63.3-76	73.2		63.4	5		75	75-87	35.8		85

substrate acting extracellularly.

In 1990s kinetic properties and substrate specificity of DPP-4 enzyme inhibitors were studied which provided knowledge for the basis of DPP – 4 inhibitor concept and was used in developing several DPP – 4 inhibitors which were identified in drug discovery programmes based on structure-activity profiling.

DPP-4 inhibitors differ widely in their chemistry and pharmacokinetic, pharmacodynamic clinical characteristic and safety profiles.[9] (Shown in Table -3)

Sitagliptin was the first member of DPP-4 inhibitors launched in 2006, with new drugs continuing to be approved (Anagliptin,Gemigliptin, Teneligliptin in 2012; Evogliptin, Omarigliptin and Trelagliptin in 2015), and the class is now an established therapy. Intense research activities towards these inhibitors have resulted in seventeen gliptins. Out of these, eleven DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, anagliptin, teneligliptin, trelagliptin, omarigliptin, evogliptin, and gemigliptin) are currently approved for clinical use in various countries while others are advancing into pre-registration/phase 3 and looking forward for approval. DPP-4 inhibitors are widely used in various combination regimens because of their robust efficacy, good tolerability, and overall favorable safety profiles.[10]

CURRENT STATUS OF CARDIOVASCULAR SAFETY OF DPP IV INHIBITORS

The effects of glucose-lowering agents on the incidence of cardiovascular AEs have been extensively debated in recent years so that the cardiovascular safety and potential protection of antidiabetic agents is currently a major issue. T2DM is associated with increased risk of micro and macrovascular complication leading to increased athero-thrombotic events which results in cardiovascular morbidity and mortality. DPP-4 inhibitors may increase the circulating numbers of bone-marrow derived stem cells that repair injured vascular endothelial cells, this phenomenon led to investigation of clinical trials.[11]

Currently DPP-4 inhibitors are the first antihyperglycemic agent which undergoes comprehensive investigation of clinical trials for assessing its cardiovascular safety. DPP-4 inhibitors control blood pressure via regulation of natriuresis independent of its glucose reduction action, especially in individuals with salt-sensitive hypertension. A recent study provided the first evidence for a complex interactive hemodynamic effect of DPP-4 and angiotensin-converting enzyme (ACE) inhibition in humans.DPP-4 inhibitors (Sitagliptin) reduced postprandial plasma levels of triglyceride rich lipoproteins of both intestinal and hepatic origin. This effect is most likely mediated by increasing incretin hormone levels, reducing circulating plasma free fatty acid concentrations and improving insulin sensitivity and B-cell function. Reductions in hsCRP, soluble vascular cell adhesion molecule and microalbuminuria have also been observed with the use of gliptins.[12] In T2DM, microalbuminuria is not only

Table 3: Comparison of different properties of available DPP-IV inhibitors is given in table

	Alogliptin	Anagliptin	Evogliptin	Gemigliptin	Linagliptin	Omarigliptin	Saxagliptin	Sitagliptin	Teneligliptin	Trelagliptin	Vildagliptin
Approval date	2010	2012	2015	2012	2011	2015	2009	2006	2012	2015	2007
Faecal excretion (%)	10-13	26		27.1	85		22	13-21	33.3		2-4.5
% Excreted unchanged	95	50		90	90		24	79	40.9		22.6
Metabo-lism	Cyp3A4, Cyp2D6	Unknown			Cyp3A4		Cyp3A4	Cyp3A4, Cyp2C8	Cyp3A4, Cyp2D6, FMO1, FMO3		No
Active metabolites	M-I (3% of parent drug activity; M-II not active)	No			No		Hydroxyl-ated metabolite (50% activity of parent drug)	No			No

considered as a marker of early nephropathy, but also as a marker of widespread endothelial dysfunction. Therefore, disappearance of microalbuminuria, when possible, may also reflect improvement of endothelial function with DPP-4 inhibitors reducing macrovascular disease as well. Results of a recent meta-analysis of 18 trial has shown that overall use of DPP-4 inhibitors was associated with a lower risk of adverse CV effects [risk ratio (RR) = 0.48, 95% CI = 0.31–0.75, p = 0.001] and a lower risk of nonfatal myocardial infarction or acute coronary syndrome (RR = 0.40, 95% CI = 0.18–0.88, p = 0.02) compared to placebo or other oral hypoglycemic agents.[13]

DIFFERENT CLINICAL TRIAL PROGRAMMES OF DPP IV INHIBITORS

Following concerns about the uncertainty regarding the cardiovascular profile of glucose lowering agents regulatory agencies in both Europe and the United States issued guidance requesting the assessment of cardiovascular safety of new antidiabetic medications during the early stages of their marketing authorization. Some of the trials which is ongoing or completed to assess the safety outcome of DPP IV inhibitors are "The EXAMINE (NCT00968708; Alogliptin), CARMELINA (NCT01897532; Linagliptin), OMNEON (NCT01703208; Omarigliptin), SAVOR-TIMI (NCT01107886; Saxagliptin) and TECOS (NCT00790205; Sitagliptin) trials compare DPP-4 inhibition against placebo and CAROLINA (NCT01243424; Linagliptin) with glimepiride as the active comparator".[9] Trial results of DPP-IV inhibitors shows neutral effect on all cause and cardiovascular mortality, acute coronary syndrome, stroke and less risk of heart failure. SAVOR-TIMI-53 and EXAMINE trials had a composite primary outcome of CV death, nonfatal MI, and nonfatal stroke. HF hospitalization was an adjudicated secondary outcome for SAVOR-TIMI-53 & EXAMINE. The CAROLINA study, a large prospective cardiovascular safety trial comparing linagliptin with glimepiride may be expected to shed further light on cardiovascular safety for which the results are expected in 2018.[14]

CAN DPP-4 INHIBITORS BE USED IN COMORBID CONDITIONS ?

Patients with type 2 diabetes mellitus frequently have comorbidities (elderly, renal and hepatic impairment patients) that complicate the management of their disease.[15] The particular decision to use antidiabetic agent is based on risk and benefits of each treatment decision in light of the patient's glycaemic control, cardiovascular status, efficacy, cost, effects on weight, comorbidities and patient preferences.

1. Elderly people

   Age is not a co-morbid disease condition per se but usually a constellation that increases the likelihood of comorbid diseases. In elderly patients with T2DM, reductions in HbA_1c after treatment with a DPP-4 inhibitor were not significantly different from those in younger patients and the use of DPP-4 inhibitors was associated with a low risk of hypoglycemia and also weight neutrality. The efficacy and safety of DPP-4 inhibitors in elderly patients with T2DM have been demonstrated in RCTs with sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin.[16, 17]

2. Renal impairment

   With reduced glomerular filtration rate (GFR), toxicity of the oral drugs increases as the drugs tend to accumulate in the body. Except linagliptin every gliptin dose has to be reduced in case of moderate to severe renal impairment (RI) (Table 4). Sitagliptin has shown reduction of HbA1c in case of moderate/severe RI and in end-stage renal disease (ESRD) patients who are undergoing dialysis. It can also be given after kidney transplant and reduces albuminuria. Saxagliptin dose has to be reduced to half in moderate-severe RI. Trial results shows after 52 weeks the reduction in HbA_1c was greater with saxagliptin than with placebo in the subgroups of patients with moderate and severe RI, but not in the subgroup with ESRD on hemodialysis. In pooled analysis, it has been found that vildagliptin is also safe and effective in case of mild/moderate RI. No dose adjustment is necessary for linagliptin.[18]

3. Hepatic impairment

   Only mild changes in pharmacokinetic characteristics of sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin were observed in patients with different degrees of hepatic impairment, presumably without major clinical relevance. No significant changes in liver enzymes were reported with DPP-4 inhibitors alone or in combination with various other glucose-lowering agents, in clinical trials up to 2 years. Warning against a potential risk of hepatotoxicity of alogliptin has been reported by the FDA but overall the set of available data from RCTs and real-life condition provides reassurance and if present the risk of liver injury appears very low. Except vildagliptin, all the gliptins are recommended in case of hepatic insufficiency.

SAFETY OF DPP-IV INHIBITORS

All oral glucose-lowering agents have some adverse effects: gastrointestinal intolerance and risk of lactic acidosis with metformin, allergic reactions and severe hypoglycemia with sulfonylureas, bone fractures, fluid retention and heart failure (and possibly bladder cancer for pioglitazone) for thiazolidinediones and increased risk of mycotic genital infections and urinary tract infections associated with SGLT-2 inhibitors. Commonly reported adverse reactions in clinical trials were nasopharyngitis, upper respiratory tract infection, hypersensitivity and headache.[19] Pancreatitis has been reported with use of DPP-4 inhibitors and warnings exist on all labels – specifically, they should not be prescribed to patients with a history of pancreatitis. Treatment should be discontinued if signs and symptoms arise, and in this

Table 4: Use of Different DPP-I inhibitors based on renal and hepatic impairment

DPP-IV Inhibitor	Renal impairment Mild (Crcl >50ml/min) Moderate (Crcl >30 <50 ml/min) Severe- (Crcl <30ml/min)	Hepatic impairment	Renal & Liver function monitoring	Use with other drugs (Dose reduction with sulphonyl urea & Insulin)
Sitagliptin	50 mg – moderate - OD 25 mg – severe - OD	Yes	Yes	-
Vidagliptin	50 mg – Moderate & Severe - OD	No	Yes	Dose reduction (50mg once daily) when used with sulphonylurea
Saxaglitpin	2.5 mg OD	Yes	Yes	Dose reduction (2.5mg once daily) when used with strong CYP3A4/5 inhibitors (e.g. ketoconazole, ritonavir)
Alogliptin	12.5 mg –moderate-OD 6.25 mg –severe-OD	Yes	Yes	-
Linagliptin	Yes	Yes	No	Efficacy may be reduced if used with CYP3A4 inducer (e.g. rifampin)
Gemigliptin	Yes with caution	Presently not recommended	-	May require dose reduction when used with drugs which alter CYP3A4 activity
Teneligliptin	Yes	Yes with care	No	-

regard, it is important to educate patients on the signs and symptoms of pancreatitis. Therapy should not be resumed if pancreatitis is confirmed. Hypoglycemia is infrequent and severe hypoglycemia is rare when using DPP-4 inhibitors.

CURRENT PLACE OF DPP IV INHIBITORS IN THE MANAGEMENT OF TYPE II DM

In clinical trials, all available DPP-4 inhibitors have been shown to improve glycemic control, with clinically meaningful reductions in HbA_1c. Furthermore, they are well tolerated, are associated with a low risk of hypoglycemia, and have a favorable weight profile. As evidence accumulates for their effectiveness, the DPP-4 inhibitors have been incorporated into numerous guidelines available for the management of patients with T2DM. A consensus statement and algorithm issued by the American Association of Clinical Endocrinologists (AACE) in 2016 describes several options for monotherapy and variations of combination therapy. The DPP-4 inhibitors are placed among monotherapy options for patients with an entry level HbA_1c of < 7.5%. As with American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommendations, metformin is recommended as the first-line choice where not contraindicated. The AACE algorithm also places DPP-4 inhibitors as an option for the second component of initial dual or triple therapy in patients with entry HbA_1c levels of ≥7.5% or ≥9%, respectively. The DPP-4 inhibitors may also be considered as the first component of dual or triple therapy for patients for whom metformin is contraindicated. The detailed AACE guidelines issued in 2016 noted that DPP-4 inhibitors, along with metformin, sulfonylureas, glinides, and thiazolidinediones, are all approved for use in combination with insulin.

RATIONALE OF COMBINING DPP IV INHIBITORS WITH METFORMIN OR SGLT2 INHIBITORS

The progressive deterioration of β-cell function in T2DM often necessitates the use of combination therapy in order for individuals to reach their glycaemic goals; however, the use of anti-hyperglycaemic agents in combination may lead to an increase in the risk of adverse events, including weight gain and hypoglycaemia, which occur with sulphonylureas and thiazolidinediones.[20, 21]

The rationale for combining metformin with DPP-4 inhibitors is its complimentary mechanism of action, metformin acts primarily by reducing hepatic glucose output and improving insulin sensitivity in liver and muscle whereas DPP-4 inhibitors act by increasing GLP-1 levels and thereby stimulating insulin secretion and inhibiting glucagon secretion. The two strategies therefore have the potential to improve different mechanisms, which are defective in type 2 diabetes and therefore an additive or synergistic action when used in combination is anticipated. In addition, metformin has been shown to increase GLP-1 levels and DPP-4 inhibition to some extent which would be a potential for an additional synergistic action with DPP-4 inhibitors. Another important information is that when combined metformin and DPP-4 inhibitor their pharmacokinetic properties remain unchanged which further indicates the feasibility of the combination.[22]

In contrary to DPP-4 inhibitors, Sdium-glucose co-transporters-2 (SGLT 2) inhibitors (canagliflozin, dapagliflozin and empagliflozin) acts completely by different mechanism;[23] They reduces reabsorption of

glucose from the glomerular filtrate independant of insulin and induce excretion of glucose into the urine (i.e. Glycosuria). In response to glycosuria, SGLT2 inhibitors enhance glucagon secretion, which may in turn increase glucose production in the liver and elevates blood glucose levels. Although this effect helps reduce the risk for hypoglycemia, it may contribute to an increase in blood glucose levels. However, this effect is counteracted by combining it with DPP-4 inhibitor and possibly further reduce blood glucose levels. In addition to improvements in glycemic control, SGLT2 inhibitors provide other effects such as weight loss and moderate reductions in systolic blood pressure. The combination of DPP-4 inhibitors and SGLT2 inhibitors also has the potential to exert beneficial effects on the kidney. Both classes have been reported to lower urinary albumin excretion, a risk factor for renal disease. In addition, drug–drug interactions of these inhibitors had no clinically relevant effect on the pharmacokinetics of either agent; therefore can be co-administered without dose adjustments.

CONCLUSION

DPP-4 inhibitors have become potential therapeutic agent for the treatment of T2DM. Overall, the DPP-4 inhibitors appear to be very well tolerated, with fewer side effects, do not inherently cause hypoglycaemia, they are weight neutral with decreased cardiovascular risk and generally not different to other antidiabetic agents. They are preferable agents in certain patients, including vulnerable individuals or those with occupational/social activities where avoidance of hypoglycaemia is important. Medication costs clearly influence drug of choice in some geographic regions (due to economics and/or healthcare provider systems), but this may become less relevant in the future, when generic DPP-4 inhibitors may be readily available. Ultimately, the decision of which drug to use should take into account differences, both within and between drug classes, and be made according to the individual patient needs.

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