



Patient adherence to medication requirements for therapy of type 2 diabetes

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**Patient adherence to medication requirements for therapy
of type 2 diabetes**

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SUMMARY

Type 2 diabetes is a complex and progressive endocrine and metabolic disease that typically requires substantial lifestyle changes and multiple medications to lower blood glucose, reduce cardiovascular risk and address comorbidities. Despite an extensive range of available and effective treatments, < 50% of patients achieve a glycemic target of $HbA_{1c} < 7.0\%$, and about two thirds die of premature cardiovascular disease. Adherence to prescribed therapies is an important factor in the management of type 2 diabetes that is often overlooked. Inadequate adherence to oral antidiabetes agents, defined as collecting <80% of prescribed medication, is variously estimated to apply to between 36% and 93% of patients. All studies affirm that a significant proportion of type 2 diabetes patients exhibit poor adherence that will contribute to less than desired control. Identified factors that impede adherence include complex dosing regimens, clinical inertia, safety concerns, socioeconomic issues, ethnicity, patient education and beliefs, social support, and polypharmacy. This review explores these factors and potential strategies to improve adherence in patients with type 2 diabetes.

Review Criteria

The information for this review was gathered through a series of searches of PubMed and MEDLINE databases for English-language articles published from January 1985 to February 2010 with the following keywords: type 2 diabetes, cardiovascular risk factors, adherence, compliance, persistence, clinical inertia, polypharmacy, and multifactorial intervention.

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Message for the Clinic

Type 2 diabetes typically requires significant lifestyle changes and multiple medications to lower blood glucose, reduce cardiovascular risk factors, and address comorbidities. Adherence to prescribed therapies is a critical factor in the management of type 2 diabetes that is often overlooked. Factors that impede adherence include complex dosing regimens, clinical inertia, safety concerns, socioeconomic issues, ethnicity, patient education and beliefs, social support, and polypharmacy. Strategies to improve adherence are reviewed and discussed.

Introduction

The global diabetes epidemic is predicted to increase from 285 million in 2010 to 439 million by 2030 (1). About 90% to 95% of these patients will have type 2 diabetes, the onset of which will occur at younger ages (1). In the United States, approximately 24 million people (8% of the population) have diabetes with about 18 million diagnosed and 6 million undiagnosed (2,3). It is anticipated that by 2034 the prevalence of diabetes in the United States will increase to 44 million (2).

The long-term complications of diabetes, particularly type 2 diabetes, present a formidable threat that requires comprehensive management of glycemia, and a myriad of cardiovascular (CV) risk factors and comorbidities (4). Although an extensive and effective range of therapies is available to address these issues (4–6), only slightly more than half of patients achieve a HbA_{1c} target of < 7.0%, and about two thirds of patients die of CV disease (3,7). See Table 1 for a list of available drugs with selected properties highlighted. There are also established protocols, guidelines, and algorithms to accommodate the needs of most patients under the majority of circumstances (4,5,8). However, an often neglected issue concerns the number of patients who do (and do not) take their prescribed medications.

This narrative review explores the important subject of adherence in patients with type 2 diabetes. Information was obtained from a search of the PubMed and MEDLINE databases for English-language articles published from January 1985 to February 2010 with the following keywords used in the search: type 2 diabetes, cardiovascular risk factors, adherence, compliance, persistence, clinical inertia, polypharmacy, and

multifactorial intervention. The review examines the extent and clinical impact of poor adherence and potential strategies to address the problem.

Factors affecting adherence to medication regimens for the management of type 2 diabetes

Overview

Compliance, adherence, and persistence are terms commonly used to describe the patient’s response to medical advice or instruction. Compliance is associated with conformity and describes willingness to follow a prescribed course of treatment. Adherence, however, concerns the extent to which the patient achieves an agreed upon treatment without close supervision. Patients achieving > 80% of their prescribed medication (typically calculated as days of medication collected divided by days of medication prescribed) is often accepted as a measure of adherence. Persistence describes the duration of time without default, that is, the time that a patient continues to maintain therapy as a proportion of total time of follow-up. Table 2 lists several well-recognized factors that can impact adherence (9).

Studies to identify the factors affecting adherence have used questionnaires, patient diaries, pill counts at follow-up appointments, prescriptions filled, counting unopened spaces in blister packs, and electronic monitoring. While each of these methods has limitations, it is clear that poor adherence is a common and serious problem among patients with chronic diseases. In a meta-analysis of 569 studies of adherence across a range of medical disorders, the average nonadherence rate was estimated at 24.8% (10). Nonadherence was highest for patients with sleep disorders (34.5%), diabetes (32.5%), and pulmonary disease (31.2%), and lowest for patients with human immunodeficiency

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3 viral infections (11.7%), arthritis (18.8%), gastrointestinal disorders (19.6%), and cancer
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5 (20.9%) (10). This supports the view that conditions perceived as imminently life
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7 threatening, uncomfortable, or painful are more likely to receive better adherence.
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10 Extensive evidence indicates that intensive control of blood glucose is associated
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12 with reduced long-term micro- and macrovascular complications in patients with type 2
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14 diabetes (11–13). One might postulate therefore that greater adherence with treatment
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16 regimens should improve metabolic control outcomes. Indeed, nonadherent patients are at
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18 increased risk for the development of micro- and macrovascular complications,
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20 hospitalizations, and death (14). Also a study of adherence in an indigent population with
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22 type 2 diabetes noted that each 10% decrease in adherence was accompanied by a
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24 +0.14% increase in HbA_{1c} (15). Additionally, the benefits of improved adherence in
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26 patients with type 2 diabetes have been linked to fewer emergency department visits and
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28 fewer inpatient admissions (16).
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36 Clinical inertia

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38 For patients with type 2 diabetes and some other chronic disorders, treatment goals are
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40 well defined, practice guidelines are widely disseminated, and effective treatments are
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42 available (5,17,18). Nevertheless, initiation and escalation of therapy are often delayed
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44 (19,20). This is clinical inertia. Data reported in 1997 from a large hospital diabetes clinic
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46 noted that, over a 3-year period, glucose lowering therapy was only intensified in an
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48 average of 36% of 1051 visits of patients who met the criteria for escalation of treatment.
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50 This was despite an agreed protocol for management of patients with type 2 diabetes
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52 (19,21). A review of practice within the Kaiser Permanente organization found that
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3 between 1996 and 2003 patients with type 2 diabetes who were inadequately controlled
4 (HbA_{1c} \geq 8.0%) on a sulfonylurea were delayed on average for 20 months before
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7 additional or alternative therapy was introduced (20). Recently, the problem of clinical
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10 inertia has been raised by guidelines and standards (4). In a 2009 report, 41% of patients
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12 with sustained hyperglycemia did not receive appropriate care within 6 months of
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14 identification, and 25% had not received appropriate care after 1 year. Interestingly,
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16 appropriate care was often deferred until the HbA_{1c} reached 9.0% or greater (22).
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20 Factors that contribute to clinical inertia include a perceived lack of training and
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22 confusion or lack of focus on glycemic goals (19). However, in the United Kingdom, the
23
24 introduction of financial incentives for general practitioners to have more patients
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26 achieve specific HbA_{1c} targets (the Quality and Outcomes Framework) resulted in rapid
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28 and substantial improvements in glycemic control for patients with type 2 diabetes (23).
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30 While this scheme has its limitations, it is continuing to provide improvements in
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32 glycemic control (24).
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36 Although clinical inertia is customarily directed to physicians, patient
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38 considerations are also relevant (25). Patients with type 2 diabetes are often required to
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40 make significant changes to their behavior and lifestyle to achieve improved glycemic
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42 control. Patient adherence to their medication regimen is strongly associated with the
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44 willingness of the physician to intensify treatment (25). However; physicians are less
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46 likely to intensify therapy in a poorly adherent patient despite an elevated HbA_{1c}. The
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48 reasons for this are not fully appreciated, but it is recognized that patients generally
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50 follow medical recommendations in 2 ways: (a) they return for office/clinic visits; and,
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55 (b) they agree to take medicines as recommended, although they may not take every dose
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(19). Therefore, issues around the level of trust in the relationship impact its influence on motivating the patient to engage in health-promoting behaviors, and the contribution of providers to promote it (25).

Another reason for clinical inertia may be the heavy publicity associated with recent trials of intensive glucose control in patients with type 2 diabetes, notably the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and the Veterans Administration Diabetes Trial (VADT) (26,27). These trials did not show significant reduction in CV event mortality, which could engender reluctance by some physicians and patients to strive for low glycemic targets.

Polypharmacy

While there is no consensus definition of polypharmacy (28), it is well recognized that the treatment of patients with type 2 diabetes is associated with the use of multiple medications, which include not only glucose-lowering therapies but also treatments for accompanying disorders such as dyslipidemia, hypertension, and depression (29–31). Indeed, several studies have suggested that a patient with type 2 diabetes can often expect to take as many as 5 or more medications daily (28,32,33). Irrespective of whether all of their medicines are essential or desirable, it is acknowledged that multiple medications contribute to poor adherence (29–31). Multiple medications are also associated with more adverse events (AEs), drug interactions, and duplications of therapy, as well as extra treatments to address the side effects of some medications (30).

Polypharmacy is commonly considered a marker of poor glycemic control and should serve as a ‘red flag’ leading to assessment of the adequacy of therapy and

adherence (34). The ACCORD study has recently noted that individuals who fail to achieve acceptable glycemic control despite extensive multiple medications are likely to be more vulnerable to AEs (26).

Other medication-related factors

Several medication-related factors can influence adherence in patients with type 2 diabetes. Overall, regimen complexity, including more frequent dosing, impairs adherence. Improved adherence has also been reported with respect to once- and twice-daily dosing of oral glucose-lowering agents (35,36). In addition, the rate of persistence with oral therapy was improved by a once-daily schedule. Since patients treated with once-daily oral antidiabetes drug therapy required more tablets, the authors of the study concluded that dosing frequency has a greater impact on adherence than tablet numbers.

Patient understanding of the drug dosing regimen and its therapeutic value are important for good adherence. In a study that used pharmacist interventions to improve adherence to diabetes care, confusion about dose timing or frequency was a predictor of poor adherence (37). Patients were more likely to adhere to a regimen if they believed that their medications were justifiably indicated, safe, and effective (32). An investigation of polypharmacy and adherence in patients with type 2 diabetes, found that patients were poorly adherent if they were not convinced that the medicine was effective or indicated—a situation common in asymptomatic diseases (32). Among a type 2 diabetes cohort receiving a median of 7 medications, patients reported that they had very limited knowledge about indications and virtually no appreciation of treatment risks (38).

Other factors impairing adherence

Depression significantly impairs adherence to treatment in patients with type 2 diabetes and the degree of adherence worsens with the depth of the depression (9,39). Since depressed patients are less likely to report that they have not been adherent, impaired glycemic control might be falsely attributed to ineffective treatment and additional drugs unnecessarily added to the regimen (9). However, forgetting to take medications is not solely a feature of affective disorders. In a study of medication usage in a real-world, cross-sectional population of patients with type 2 diabetes treated for ≥ 10 years, 20% of participants reported that they regularly forgot to take their medications without any particular explanation (33).

Racial, ethnic, and socioeconomic factors can also significantly affect adherence. Among patients with type 2 diabetes in the United States, HbA_{1c} appears to be significantly higher in non-Hispanic black women and Mexican American men (40). This may be due to a number of race-identified factors such as difficulties with language, dietary management, failure to self-monitor blood glucose, and lack of regular exercise (41). In addition, there are significant black-Caucasian differences in glycemic control with higher mean HbA_{1c} in the former that are not due to differences in adherence and may be related to genetic or environmental factors ($p < 0.0001$) (42). These issues, including cultural factors, increase the importance of adherence in these racial/ethnic groups because minority ethnic groups in the United States have a higher rate of diabetic complications, even after adjusting for differences in glycemic control (40).

Type 2 diabetes has been described as a growing epidemic among children and adolescents throughout the world (43) and studies of minority youths in the United States

indicate that they are at higher risk of difficulties in achieving glycemic control than their Caucasian counterparts (44). This appears to be significantly related to the effect of lower adherence to dietary recommendations and blood glucose monitoring (45).

Other factors that may impact the adherence in all patients, as well as specific racial/ethnic groups, include paying for medications, obtaining refills, and fear of needles (34,46).

Social support impacts mental and physical health and outcomes by mediating health-related behaviors (47). This is established in families and children with type 1 diabetes. In the Diabetes Control and Complications Trial (DCCT), one of the key elements of successful intensive therapy was the availability of support provided to patients by the healthcare team (48). Social support is also considered to be an important element of adherence in patients with type 2 diabetes. For example, regimen-specific measures of family support for glucose testing, medication-type, diet and exercise have been found to impact the potential for adherence (47). While the number of variables that impact adherence can seem daunting, many can probably be modified by making minor changes in clinical practice.

What clinicians can do

Physicians can institute several elements into their practice to improve adherence outcomes in patients with type 2 diabetes and other chronic diseases. These include improving communication, addressing costs, managing dosing issues, and enhancing education about the potential for AEs and the appropriate responses to perceived AEs.

Improving communications

The most commonly overlooked element to ensure adherence is appropriate evaluation of patient comprehension regarding the need for treatment and the value of the therapeutic regimen (49). In a study of 408 English- and Spanish-speaking adults with type 2 diabetes in public hospitals in San Francisco, > 50% of patients had inadequate or marginal health literacy (50). Inadequate health literacy was characterized as an inability to read common medical items such as prescription bottles, nutrition labels or appointment slips. Marginal health literacy pertained to difficulties with more complex materials such as educational brochures or informed consent documents (50). Taking extra time to ensure that patients have adequate recall and comprehension of the treatment regimens can alleviate this issue (49). A study based on new concepts (e.g. change in medication) found that type 2 diabetes patients of physicians who assessed comprehension and recall had significantly lower HbA_{1c} (odds ratio 8.96; 95% confidence interval, 1.1 to 74.9; $p = 0.02$) (51).

Clarifying the benefits of treatment can also improve adherence. This is particularly important in patients with seemingly asymptomatic diseases such as type 2 diabetes and those with increased CV risk factors. An unambiguous appreciation of the long-term implications of inadequate blood glucose control and the value of therapies to reduce CV risk is paramount. Helping patients recognize the subtle symptoms of chronic hyperglycemia such as fatigue, difficulty sleeping, nocturia, infections and missed school or workdays is also important (49). Adherence was significantly lower when patients did not understand that a treatment will improve their current or future health. Moreover, presentation of a new medicine or alteration in treatment, such as the introduction of

insulin therapy, should be communicated in a manner that is portrayed to be a benefit rather than a punishment for perceived poor adherence. Thus, creating a ‘trusted’ relationship with the patient, fostering shared ownership of the patient’s condition, setting realistic goals in a constructive manner, and creating a continuum of self-management are all accepted features of best practice that are believed to assist adherence (52,53).

Addressing costs

Cost of treatment is a significant concern to both patients and providers and for private health care this requires consideration on an individual basis with every patient. In a survey of adults with type 2 diabetes in the United States, 11% reported that they had limited their medications in the previous 12 months due to costs (54). Signals that may indicate potential cost-related adherence issues include an income < \$20,000/year and medication costs in excess of \$50/month (55). In the United States, patients without health insurance are particularly vulnerable to costs of care. In an attempt to provide benefits to patients, pharmacies of some corporate entities provide 30-day supplies of common generic drugs used to treat type 2 diabetes, cardiac risk factors, and comorbidities of type 2 diabetes for a nominal fee (56). These medications include metformin, statins, angiotensin-converting enzyme inhibitors and other antihypertensives, antidepressants, and common antibiotics.

Financial issues may alter adherence even in patients with adequate insurance. Employers and insurers tier drugs and use copays to control drug expenditures (57). Thus, when a drug is not on a formulary or a cheaper alternative is unavailable, the patient’s out-of-pocket expenses can be significantly higher. It has been demonstrated that

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3 copayments of < \$10 significantly improve first-prescription refills and that higher
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5 copayments predict poor adherence and potential treatment failure (58,59). Research also
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7 indicates that the effect of high copays on adherence is greatest during early phases of
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9 treatment and that higher copays are associated with early termination of medication
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11 usage (57). Furthermore, a strategy of increasing copayments after the first few refills of
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13 a prescription does not promote persistence.
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17 In the United Kingdom, the National Institute for Health and Clinical Excellence
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19 (NICE) and various regional formularies are becoming very cost conscious, and while
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21 this influences treatment choices, there is no evidence of its effect on adherence.
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26 27 **Managing dosing issues**

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29 Because of comorbidities and CV risk factors, many patients with type 2 diabetes are
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31 prescribed complex regimens with multiple medications. Due to the relationship between
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33 polypharmacy and poor adherence, it is preferable that treatment is accomplished with a
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35 regimen that includes the fewest medications and fewest doses per week (49). A major
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37 factor affecting adherence with antidiabetes agents is the daily dosing frequency (60,61).
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39 Adherence and persistence rates improve if goals can be achieved with the fewest number
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41 of tablets per day (35,36,62,63). Also, electronic monitoring indicates that once-daily
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43 dosing is accompanied by a decrease in the number of missed doses (64).
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49 One approach that integrates the need to treat multiple comorbidities while
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51 optimizing dosing is to select a fixed dose combination of the necessary medications that
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53 treat more than one pathophysiologic element (65–67). When administered once daily,
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55 fixed dose combination therapy results in significantly better adherence than 2-tablet
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regimens (68). This can be important when patients who have been managed with monotherapy require a second agent or for patients already receiving 2 separate agents. Currently available fixed dose single tablet combinations include metformin plus a sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, or meglitinide. Other commercial formulations include a variety of combination doses of thiazolidinedione plus a sulfonylurea (69). In studies of patients with type 2 diabetes who previously received monotherapy with an oral glucose-lowering drug, adherence was greater when they were treated with a fixed dose combination versus a combination of separate tablets (70,71). The improved adherence with fixed dose combination therapy is accompanied by better glycemic control than with separate tablet combinations at similar or greater doses (72,73).

Improving education about the potential for AEs

Since potential AEs can negatively impact adherence (32,74), it is necessary to frame this within the context of the benefits and risk of medications, and of supporting patient preference where possible (49). However, patients with type 2 diabetes may be willing to accept some AEs in exchange for improved glycemic control, but the potential for specific AEs is not weighted equally. In a survey of 407 patients with type 2 diabetes in the United States and the United Kingdom, glycemic control was selected as the most important property of the medication. Patients preferred to avoid medications that produced weight gain (75). The potential for weight gain of 9.0 kg decreased likely adherence by 30%, while the potential to increase the risk of heart attack by 1% decreased potential adherence by 16.5% (75). Mild and transient gastric distress did not

significantly influence medication preference, but persistent stomach problems were identified as a negative medication feature. Interestingly, the potential for mild to moderate hypoglycemia did not affect potential adherence unless this was likely to occur more than twice a month (75).

Latinos and African Americans were significantly more likely than Caucasians to worry about the effect of potential AEs on quality of life and potential medication dependency (76). In addition, certain ethnic minorities may be candidates for fixed dose combination therapy as initial treatment since they are more likely to express a reluctance to add medications to their current regimen (76). The potential for drug interactions should also be considered as a factor that impacts adherence in patients with type 2 diabetes. In a study of 139 patients (average age 74 years) with polypharmacy discharged from the hospital and receiving home health care services, 38.8% of the subjects were considered to be at potential risk for drug interactions (28).

Conclusions

Type 2 diabetes is a chronic condition and typically requires varied and complex treatment programs. Substantial evidence indicates adherence and persistence with therapy are limiting factors in the drive to achieve and maintain desirable management goals. Factors that impede adherence include treatment choices, administration regimens, clinical inertia, communication deficits, and barriers of trust and belief. Therefore, it is important that these issues are addressed within the process of disease management.

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Author contributions

CJ Bailey and M Kodack contributed to drafting, editing, data analysis/interpretation, and critically reviewing this manuscript.

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Table 1 Drugs available for the management of patients with type 2 diabetes with selected properties highlighted*

Type of agent	Main mode of action	Decrease in HBA _{1C}	Body weight	Problems	Warnings and precautions
Oral					
Metformin	<ul style="list-style-type: none">• Decrease insulin resistance^a• Reduce hepatic glucose output• Increase peripheral glucose utilization	~1–2%	↓/–	Lactic acidosis (rare) GI intolerance	Renal impairment, any hypoxemic condition
Sulfonylureas	<ul style="list-style-type: none">• Increase insulin secretion^b• Stimulate pancreatic β-cells by closure of K⁺-ATP channels	~1–2%	↑	Hypoglycemia	Selection restricted by severe liver or renal disease, or porphyria
Meglitinides	<ul style="list-style-type: none">• Increase insulin secretion^{b,c}• Usually administered pre-meals: rapid onset, short duration of action• Stimulate pancreatic β-cells by closure of K⁺-ATP	~0.5–1.5%	↑/–	Lesser risk of hypoglycemia (fewer and less severe than sulfonylureas)	Liver or severe renal disease

	channels				
Gliptins (DPP-4 inhibitors)	<ul style="list-style-type: none"> • Increase insulin secretion^b • Inhibit DPP-4, allowing increased t_{1/2} for incretins, which potentiate nutrient-induced insulin secretion 	~0.5–1.5%	–	Small risk of hypoglycemia (seldom severe), mostly when used with other antidiabetic agents	Substantial renal or liver disease
Thiazolidinediones (glitazones)	<ul style="list-style-type: none"> • Increase insulin action^a • Stimulate PPAR_γ • Increase adipogenesis • Alter glucose-fatty and cycle 	~1.0–1.5%	↑	Heart failure, edema, anemia, fractures	Cardiac disease, fluid retention, severe liver or renal disease
α-glucosidase inhibitors	<ul style="list-style-type: none"> • Slow carbohydrate digestion^d 	~0.5–1.0%	–	—	Intestinal diseases, severe kidney disease
Bromocriptine	<ul style="list-style-type: none"> • Not established^a 	~0.5–0.8%	–	Fibrotic reactions, hypotension	Psychotic disorders
Colesevelam	<ul style="list-style-type: none"> • Uncertain, may increase GLP-1 secretion^b 	~0.5–0.8%	–	Bile sequestrant	Intestinal diseases

Type of agent	Main mode of action	Decrease in HBA _{1C}	Body weight	Problems	Warnings and precautions
Parenteral					
GLP-1 receptor agonists ^e	<ul style="list-style-type: none">• Increase insulin secretion^b• Resistant to degradation by DPP-4• Potentiate nutrient-induced insulin secretion	~0.5–2.0%	↓	Risk of hypoglycemia when used with other antidiabetic agents, nausea	Not to be used in severe renal or gastrointestinal disease (e.g. gastroparesis) Discontinue if pancreatitis is suspected
Pramlintide ^{e,f}	<ul style="list-style-type: none">• Decrease gastric emptying• Decrease glucagon, satiety^e• Indicated only as add-on to insulin therapy	~0.3–0.6%	↓	Risk of hypoglycemia when used with insulin	Contraindicated in gastroparesis or hypoglycemia unawareness
Insulins ^e	<ul style="list-style-type: none">• Decrease hepatic glucose production• Increase peripheral glucose uptake, storage, and utilization• Decrease lipolysis	Variable, as required	↑	Hypoglycemia	Substantial lifestyle adjustments and glucose monitoring

*Consult full prescribing information for individual agents for complete details on indications, contraindications, warnings and precautions. Most agents have rarely caused hypersensitivity reactions. ^aEfficacy requires presence of circulating insulin. ^bEfficacy requires presence of a functional β -cell mass. ^cTaken with meals prandial, less severe hypoglycemia. ^dTaken with meals rich in complex carbohydrate. ^eSubcutaneous injection. ^fPramlintide is an amylin analogue. DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1, glucagon-like peptide-1; K⁺-ATP = Kir 6.2 inwardly rectifying potassium channel; PPAR γ = peroxisome proliferator-activated receptor gamma; \uparrow increase; \downarrow decrease; \sim approximately; – no change. Developed from the American Diabetes Association, Nathan et al, Bailey et al. (4,5,8)

Table 2 Barriers to medication adherence

Patient factors	Treatment regimen factors
Fear	Complexity of regimen
Knowledge and skill	Frequency of dosing
Self-reliance	Cost
Health beliefs	Adverse events
	Interference with lifestyle
Depression	
Lack of confidence in immediate or future benefits of the medication	
Remembering doses	

Adapted with permission from Odegard et al. (9)