some tangible sense that the prescribed medication is contributing to some positive and relatively immediate outcomes.[33] Indeed, in numerous studies across a wide variety of chronic illness conditions, there is a consistent finding that medication adherence is associated with perceived need.[34] The more firmly the patients believe that the prescribed medication is actually necessary, the more adherent they are likely to be. Consider, for example, that among 477 patients with T2D starting on any new class of diabetes medication, self-reported medication adherence over 6 months was associated with greater weight loss (≥3 kg: 29.9% adherent vs 24.2% poorly adherent) and with a greater likelihood of attaining HbA1c goal (<7.0%: 47.5% adherent vs 32.7% poorly adherent).[35] These data may suggest that realization of patients that improvement is occurring (and that this may be due, at least to some extent, to their medications) contributes to their willingness to continue with their medications in a more reliable manner.

2. Hypoglycemia: A cross-sectional study of patients with T2D treated with metformin and a sulfonylurea agent found that patients reporting moderate or worse symptoms of hypoglycemia had poorer medication adherence vs those with no or mild hypoglycemia (MPR >80%: 46% vs 67%, $P<0.01$).[36] Among T2D participants in a recent survey, 56% had experienced hypoglycemia and had higher HbA1c levels than in those with no reported hypoglycemia (Figure 3).[37] Finally, a claims database was used to evaluate the impact of hypoglycemia-related events on costs and discontinuation rates among 212,000 patients with T2D.[38] During a 6-month interval, the risk for medication discontinuation was significantly ($P<0.0001$) greater among those with a hypoglycemic event vs those with no reported hypoglycemia. It is noteworthy that even a single hypoglycemic event may contribute to greater fear of hypoglycemia in patients with T2D,[39] and hypoglycemic fear, in turn, may contribute to poorer medication adherence as the patient chooses to keep his/her blood glucose levels in a higher range where further hypoglycemic events will be less likely.[40] The choice of medication(s) will, of course, have a major impact on the risk of hypoglycemia. However, even in the case of sulfonylureas, the actual likelihood of hypoglycemic problems may be influenced by the dosage prescribed, prescription errors, and/or how well or poorly the patient understands and follows medication directions.

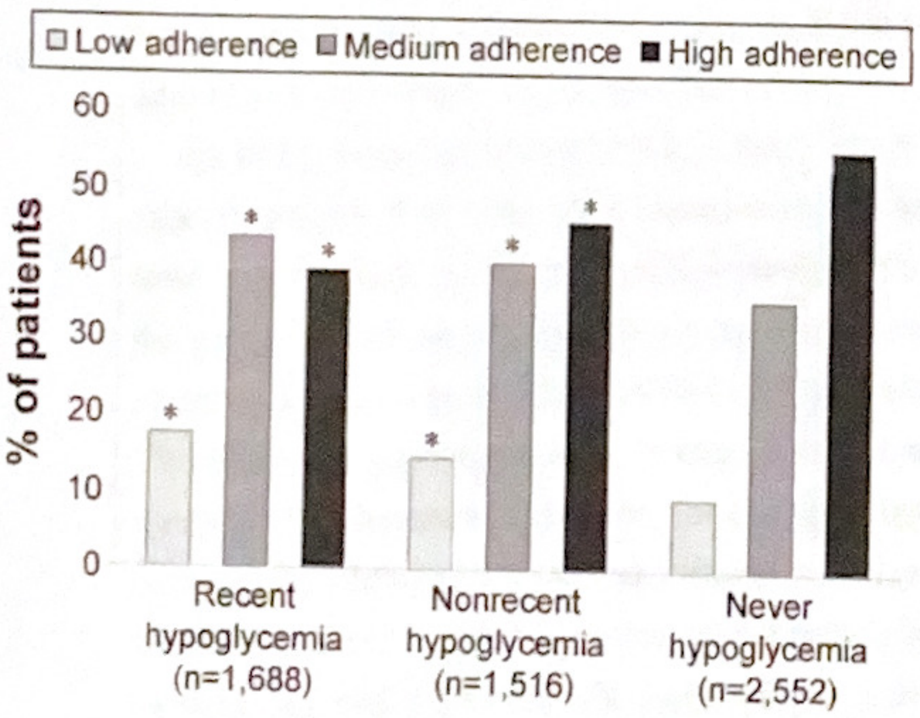

Figure 3 Percentage of patients with low, medium, or high adherence to antidiabetic medication based on the MMAS score according to the occurrence of recent hypoglycemic episodes.
Notes: *$P<0.05$ vs never hypoglycemia. Data from a previous study.[37]
Abbreviation: MMAS, Morisky Medication Adherence Scale.

3. Treatment complexity and convenience: Not surprisingly, medication adherence and persistence become more challenging when the treatment itself is perceived as more difficult, onerous, or burdensome.[41] In their comprehensive review of 76 studies, Claxton et al[42] found that the prescribed number of doses per day was inversely associated with medication adherence; indeed, the mean adherence across studies decreased progressively from 79% with a once-daily dose to 51% with a four times daily dose. Several recent reviews have confirmed these findings, with adherence rates for patients with chronic diseases, including T2D, found to be significantly lower for any medication regimen requiring more than once-daily dosing (79%–94% once daily vs 38%–67% three times daily; $P<0.05$).[43,44] Beyond the influence of dosing schedules, recent data suggest that the overall complexity of the T2D medication regimen predicts adherence, with greater complexity contributing to poorer adherence.[45] Similarly, the convenience or complexity of medication delivery devices can influence adherence. For example, in retrospective analyses of insulin pen vs vial and syringe use in T2D samples, improved persistence and adherence, improved glycemic control, and lower rates of hypoglycemia were reported in the insulin pen groups.[46–49]
4. Cost of treatment. Out-of-pocket costs for medications have been consistently associated with problematic adherence across treatment conditions.[50] Higher out-of-pocket costs for antidiabetic medications in particular are linked to poorer adherence.[32,51] To illustrate, patients with T2D receiving a low-income subsidy for Medicare Part D were found to have lower out-of-pocket costs and

better medication adherence than those not receiving the subsidy.[52]

5. Medication beliefs: Many patients hold markedly negative or highly skeptical beliefs about their prescribed medications, often fearing that the long-term risks outweigh any likely benefits.[26,53] Numerous studies have examined the impact of this "necessity-concerns framework"; although – as noted above – while believing that one's medications are necessary is associated with adherence, there is a consistent finding across the studies to date that patients' concerns about their medications are more strongly linked to adherence than their beliefs in the necessity of those same medications.[54] In patients with T2D, such concerns about the possible negative impact of medications are associated with poor adherence[55] as well as reluctance to initiate new medications, both orals[56] as well as injectables.[57,58]
6. Physician trust: Adherence to hypoglycemic medications[59] as well as antidepressant medications[60] has been linked to patients' trust in their physicians. In a conceptually similar vein, Kerse et al[61] found that primary care patients' sense of "concordance" with their physician (feeling that their needs during medical visits had been heard and addressed) predicted medication adherence over time. In a large multinational survey, Polonsky et al[62] found that ratings of patients with T2D on the overall quality of communication with their physicians at the time of diagnosis were linked to adherence to current hypoglycemic medications. To highlight the potential influence of physician trust, a small study by Piette et al[63] reported that the association between medication adherence and out-of-pocket costs is minimized among those patients who report high trust in their physicians.

Of note, while the available data focus solely on the critical value of trust in the physicians, it seems likely that trust in other key health care professionals with whom the patients have ongoing contact may also be similarly potent in influencing medication attitudes and behaviors. Therefore, we hope to see future research examining how medication adherence is affected, for example, by trust in community pharmacists (whose clinical practice role in the US has been expanding in the recent years) and trust in nurse specialists in the UK (who play a central role in the diabetes care system of National Health Service).

In summary, these data suggest that modifiable factors influencing T2D medication adherence fall into two broad categories: treatment burden (eg, complexity and convenience, out-of-pocket costs, and hypoglycemia risk) and treatment-related beliefs (eg, perceived treatment efficacy, medication beliefs, and trust in one's health care providers). To address problematic adherence, it would therefore seem likely that effective strategies might target one or both of these domains. However, what is known about what really works?

Interventions to address poor medication adherence

While numerous methods to address poor medication adherence across disease states have been developed and tested, including educational programs, disease management programs, intensive behavioral support, medication reminders, and special packaging, long-term, sustained reductions in the rates of poor adherence have been difficult to achieve.[64,65] Recent literature reviews focusing specifically on T2D-specific medication adherence interventions have led to similarly disappointing conclusions; in those cases where benefits are apparent, the magnitude of intervention effects is typically small and/or of limited duration.[66–70] A closer examination of the wide variety of intervention contents revealed no single form of intervention to be consistently effective for improving adherence,[71] though multifaceted interventions were found to be more effective than single-strategy approaches,[66] and as observed in one recent review, interventions targeting medication side effects might be of particular value.[67]

Descriptions of the specific T2D interventions are often inexact, making it difficult to determine which of the key modifiable factors, if any, are being targeted. For example, educational and/or behavioral support interventions are described as central pillars in the majority of adherence interventions, especially in the complex interventions consisting of multiple strategies, but exactly how these operate or what obstacles are being targeted are typically not specified.

In total, we speculate that most interventions to date have focused within the broad category of reducing treatment burden – focusing primarily on the problem of medication behavior rather than medication attitudes. Indeed, we know of no study that has directly examined the potential impact of addressing dysfunctional medical beliefs, perceived treatment efficacy, or any other aspect of patients' treatment-related beliefs. One of the keys to future advances in addressing problematic medication adherence, especially primary medication adherence, may be through better physician communication regarding benefits and risks of treatment, addressing patients' treatment concerns, engaging in shared decision-making, and providing and/or supporting self-management training.[26]

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Finally, it must be noted that the inability to draw firm conclusions regarding interventions is partly, perhaps largely, due to methodological limitations. To date, measures of adherence across studies vary widely, hard outcomes (eg, changes in glycemic control) are often lacking, interventions may not be clearly explained, and duration of follow-up is often inadequate.[70] Research into the causes and management of medication adherence will require improved study designs that can explore the feasibility of long-term interventions, development of more objective adherence measures, and the inclusion of sufficient numbers of patients to detect improvements in clinical outcomes.[65] A key element is the need for greater consistency when measuring medication adherence, which require better instruments and tools for assessment.[20]

Future developments

Novel treatment approaches are in development that may address many of the treatment burden factors (eg, treatment complexity, hypoglycemia, and side effects) as well as treatment belief factors (eg, perceived treatment efficacy). While drugs that are administered daily or even weekly for T2D have not shown substantial benefits with respect to improved adherence and persistence, new products will soon become available that are administered at monthly or longer intervals, potentially addressing some of the barriers to maintaining good medication adherence. One approach is sustained delivery of a therapeutic agent that has demonstrated efficacy, safety, and improved outcomes. Optimally, for treatment of diabetes, this agent should deliver sustained reduction in HbA1c levels, result in weight loss, and have a favorable side-effect profile to minimize the chance of discontinuation. One such product, ITCA 650 (Intarcia Therapeutics, Inc., Boston, MA, USA), provides continuous delivery of exenatide for up to 1 year via a subcutaneous osmotic mini pump. Phase III trials in patients with T2D have shown robust efficacy, tolerability consistent with the glucagon-like peptide-1 class, and 100% adherence.[72,73]

In addition, drug combinations may provide another valuable approach by simplifying the dosage regimen with fixed-dose formulations. A retrospective analysis of patients with T2D taking fixed-dose combinations versus individual dose combinations showed significantly ($P<0.001$) greater adherence (57.0% vs 50.7%) and persistence (32% vs 27%) with the fixed-dose combination.[23] A number of fixed-dose combinations of oral antidiabetic agents and insulin formulations are now available, and recently, insulin degludec combined with liraglutide was approved in Europe and is pending for approval in the US. A number of other combinations of oral and injectable antidiabetic agents are either approved or in late-stage clinical development (ClinicalTrials.gov). However, the benefit–risk ratio of fixed-dose combinations needs to be demonstrated, and to date, little evidence is available to demonstrate improvements in adherence with these or other combinations.

In total, by providing new approaches that can make the process of taking medication less burdensome (or, as in the case of ITCA 650, even less apparent or noticeable) while simultaneously providing favorable outcomes (especially, long-term glycemic control and weight loss), there is a likelihood that patients may begin to weigh the hassles/risks of medications vs the benefits quite differently, leading to a greater sense of perceived treatment efficacy and an enhanced sense of engagement with their own diabetes self-management.[33]

Summary and conclusion

Medication adherence in T2D remains poor despite the availability of many new classes of medications and increased efforts toward patient education and targeted interventions that address adherence. New nonpharmacologic and pharmacologic approaches are needed that will have a clinically significant and sustained long-term impact on adherence. Innovative strategies for addressing treatment burden as well as patients' problematic beliefs about their medications are needed. Toward this end, novel drugs or delivery systems that remove the need for daily, weekly, or even monthly dosing should be available in the near future, offering the potential for greatly increased adherence accompanied by markedly improved glycemic control, reduced complications of diabetes, and lower health care costs and resource use.

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