

Practical Insights Into Improving Adherence to Metformin Therapy in Patients With Type 2 Diabetes

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IN BRIEF Adherence to metformin-based treatment regimens for type 2 diabetes is currently suboptimal due to a complex array of patient-, treatment-, and physician-related barriers, including physical and psychological swallowing difficulties associated with large tablets and gastrointestinal disturbances. Patients often avoid discussing these issues with their primary care providers, and delays in addressing them can lead to reduced glycemic control. This article reviews the issues commonly responsible for poor adherence to metformin and presents strategies to improve compliance, including shared decision-making and the use of different metformin formulations, including liquid metformin.

The rapidly increasing prevalence of type 2 diabetes is regarded as one of the most important health care emergencies of the 21st century. At least 425 million adults worldwide are estimated to have diabetes, a figure equivalent to 1 in every 11 adults, more than 90% of whom have type 2 diabetes (1). Although patients may initially be able to manage their condition with diet and lifestyle changes, the progressive nature of type 2 diabetes dictates that all patients will eventually require medication to maintain adequate control of their blood glucose levels.

Strict self-management of type 2 diabetes is required throughout a patient's lifetime to maintain blood glucose levels as close to normal as possible and to reduce the risk of long-term diabetes-related complications affecting the heart, circulatory system, eyes, nerves, and kidneys. A good partnership between patients and their health care providers (HCPs) is vital to optimize long-term health outcomes, and good adherence to prescribed medication regimens is vitally important to ensure that treatment is as effective as possible (2).

However, numerous patient-related barriers—both psychological and physical—prevent good adherence to diabetes therapeutic regimens (3), and adherence rates to oral anti-diabetic drugs are suboptimal (4,5). Poor adherence and persistence lead to less effective control of blood glucose, early progression of the disease, and increased complication rates, which are associated with higher health care costs (2). Patients with diabetes who have better adherence also have better glucose control and less health care resource utilization (6).

The aim of this review is to examine barriers to adherence to and persistence with metformin, the first-line oral antidiabetic medication recommended by the American Diabetes Association (ADA) for patients diagnosed with type 2 diabetes (7), and to discuss ways in which metformin adherence can be improved.

Metformin: First-Line Antihyperglycemic Therapy

Metformin is a biguanide that is highly effective at lowering both basal and prandial glucose levels by reducing hepatic glucose production, increas-

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ing intestinal glucose absorption, and improving insulin sensitivity (8). In addition to being an effective first-line antihyperglycemic therapy for newly diagnosed patients, metformin is well tolerated and inexpensive (7,9), making it ideally suited as a long-term treatment. Moreover, metformin is widely regarded as the “foundation” of antidiabetic therapy, to which other drugs are added as second- or third-line therapies if adequate glucose control is not achieved with metformin alone. Current recommendations advise that if the A1C target is not achieved after 3 months of metformin monotherapy, addition of a second glucose-lowering drug should be considered, provided that the patient does not have atherosclerotic cardiovascular disease (7). If such treatment intensification is required, the ADA recommends combining metformin with an agent from one of six preferred drug classes: sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, or basal insulin (7).

Approved by the U.S. Food and Drug Administration (FDA) in 1995 (10), metformin remains the most widely used initial antihyperglycemic therapy today (11). It is at least as effective as newer agents in reducing A1C levels and does not result in weight gain (9). It also has benefits beyond glucose control, including a protective effect on cardiac and vascular metabolism and function (11), an effect shown to result in a clinically significant reduction in the risk of cardiovascular events and cardiovascular mortality (9,12). These clinical study findings are supported by a recently published, large, nested case control study of more than 80,000 new metformin users that showed for the first time that long-term adherence to metformin is associated with a significant reduction in all-cause mortality (13). There is also emerging evidence that metformin therapy may offer patients with diabetes some protection from cancer. Patients with type 2 diabe-

tes have a greater risk of cancer than individuals without diabetes—mainly cancers of the pancreas, liver, and endometrium (14). A meta-analysis of published data showed that taking metformin reduces cancer incidence in patients with type 2 diabetes by 31% overall compared to other antidiabetic drugs and significantly reduces the risks of hepatocellular and pancreatic cancers, specifically (15). It is the author’s opinion that the collective effects of metformin—including both antihyperglycemic effects and pleiotropic effects beyond diabetes control—strongly suggest that metformin should be prescribed as a lifelong treatment for patients with type 2 diabetes.

Given the importance of metformin therapy for individuals with type 2 diabetes, good adherence to treatment is vital. Poor compliance with dosing regimens (i.e., missed doses), nonadherence (i.e., not following the recommendations of an HCP for medication or lifestyle management), and poor persistence with medication (i.e., discontinuation of treatment) are widespread problems in diabetes management and very difficult to assess in real-world clinical practice.

A high proportion of patients do not take their medication as prescribed, and physicians may be unaware of the extent to which patients miss doses or stop treatment (4,5). Despite the importance of adherence to oral antidiabetic drugs, studies consistently report adherence levels that are suboptimal. In prospective electronic monitoring studies, adherence rates have ranged from 67 to 85% (4); retrospective, observational studies have reported an even wider range of rates, from 36 to 93% (4). A meta-analysis of studies that examined persistence, adherence, and discontinuation rates for oral antidiabetic drugs reported a mean adherence rate of only 67.9% (5).

Adherence to and persistence with prescribed diabetes medications are strongly influenced by the class

of medication prescribed (16,17). Metformin was recently shown to be associated with a higher level of persistence than other classes of oral antidiabetic drugs (17), but persistence with metformin therapy remains less than optimal (4,5,16,18). In one study, only 58.6% of patients had good persistence with metformin, defined as compliance with medication purchase for at least 9 months (18).

The immediate consequence of poor adherence to antihyperglycemic treatment is inadequate glycemic control (i.e., treatment failure). Patients who adhere poorly to their treatment experience less improvement in glycemic control than do patients who are fully compliant (19,20). Over the longer term, poor adherence is associated with increased risks of micro- and macrovascular diabetes complications, a greater likelihood of early mortality, increased health care costs, and reduced quality of life (3,17).

Barriers to Metformin Therapy Adherence

Metformin is administered as an oral therapy, usually in tablet form. Oral antidiabetic medications are usually well accepted by patients and present fewer patient-related barriers to adherence than do injectable treatments such as basal insulin. However, many factors may affect patients’ willingness or ability to adhere to metformin-based treatment regimens (Table 1).

Patients may not fully understand the clinical benefits of their metformin-based therapy because of inadequate HCP-patient communication, perhaps due to language, social, and cultural barriers, and patients’ denial of the seriousness of their condition is not uncommon, particularly in nonsymptomatic patients (2). Patients may also skip doses or stop treatment because they dislike the side effects of treatment; symptomatic hypoglycemia in patients taking metformin with a sulfonylurea is associated with nonadherence

TABLE 1. Barriers to Optimal Adherence to Metformin

Patient-Related Barriers	Practitioner-Related Barriers	Treatment-Related Barriers
<ul style="list-style-type: none"> • Difficulties in understanding the rationale for long-term metformin treatment • Physical impairment such as difficulty swallowing; psychological difficulty swallowing tablets • Memory problems (e.g., in older patients) • Socioeconomic factors (e.g., medication costs, lack of support during treatment) • Cultural attitudes and beliefs 	<ul style="list-style-type: none"> • Poor health care team–patient relationship • Lack of time for in-depth communication with patient • Lack of awareness of problems with treatment adherence 	<ul style="list-style-type: none"> • Regimen complexity, especially in patients with multiple comorbid conditions • Large size of or rough coating on metformin tablets • Inflexible treatment regimens • Gastrointestinal side effects

and reduced treatment satisfaction, despite providing effective glucose control (21). Gastrointestinal side effects are common in patients taking immediate-release (IR) metformin, particularly during the initial dose titration phase, and lead to discontinuation of treatment in 5–10% of patients (8). Poor adherence can also result from poor understanding of the rationale for the metformin treatment regimen, particularly if the patient is managing several other comorbid conditions and needs to remember to take many different medications every day, with different timings and doses (2). Another patient-related barrier to compliance is the cost of treatment. Although metformin is an inexpensive drug, newer metformin formulations are more expensive (discussed below), and patients may also struggle to pay for supplies needed for regular blood glucose monitoring and for transportation to clinic visits. Lack of social support and cultural barriers also affect adherence to oral antidiabetic medications (2).

It is the author’s opinion that patients starting metformin treatment may also experience difficulties swallowing capsules or pills that are large or that have a rough surface coating. Patients of all ages complain about the size or the surface texture of metformin pills. Often, patients want to crush or cut the tablets to help swallow them. If patients cannot break the tablets, they simply stop taking

them. Crushing or cutting the pills may alter the absorption of the medication, change the dose, or increase the risk of gastrointestinal disturbances, thus discouraging long-term compliance. In addition, swallowing a large pill can cause the sensation of a pill stuck in the throat, even when this is not so, and can lead patients to seek emergency care for removal of the perceived foreign body, thus resulting in unnecessary and unacceptably increased use of emergency health care services.

Metformin tablet size is also an issue for patients with type 2 diabetes who have physical swallowing difficulties (dysphagia). Although this difficulty can occur at any age due to short- or long-term illness, elderly patients are particularly prone to swallowing problems because of an age-related reduction in saliva production or reduced swallowing strength (22). Comorbid conditions that reduce swallowing strength, narrow the esophagus, or reduce saliva production also have a negative effect on compliance with oral treatment, and such conditions (e.g., dementia, Parkinson’s disease, and stroke) are common among elderly patients with type 2 diabetes (22). Moreover, many older patients with comorbid conditions take a plethora of other medications, such as diuretics, beta-blockers, anticholinergic agents, and prostate medications that may cause dry mouth, reduced saliva pro-

duction, or esophageal irritation. This situation often leads patients to skip their medications to ease their discomfort. In the author’s experience, given the size of the tablets, metformin is usually the first medication that patients will remove from their treatment regimen in such situations.

Polypharmacy, which is common among patients with type 2 diabetes and multiple comorbidities, can also reduce compliance with antidiabetic therapy regimens (4). Following current ADA recommendations, physicians add other oral antidiabetic medications to metformin to improve glucose control (7), yet there is evidence that increasingly complex oral antihyperglycemic treatment regimens do not increase glucose control to the extent expected (23), and patient compliance may suffer (4).

Metformin is now available in fixed-dose combination tablets with most classes of oral antidiabetic drugs (e.g., dipeptidyl peptidase-4 inhibitors) in a range of different combination formulations. Although these combination products simplify multi-agent regimens and may improve compliance (24), many health insurance providers do not reimburse for them. Nevertheless, in the author’s experience, many HCPs and their patients are often financially incentivized with manufacturers’ coupons to start treatment with combined formulations, but when the subsidy or vouchers run out, patients

may discontinue both drugs in the combined tablet. Disease control then worsens until, perhaps many months later, the nonadherence is identified and addressed by the patients' health care team.

Discontinuation of oral antidiabetic medications may also arise when patients who are taking many medications for comorbid conditions, including diabetes, are asked to temporarily stop taking certain medications during illness or before medical procedures. Metformin is the medication most commonly stopped in such cases because it interferes with the contrast dye used in almost all imaging studies and radiological interventions. It is the author's opinion that patients then often forget or become confused about which medications they should stop taking and when to resume treatment. Confusion may also arise when patients are hospitalized and asked by the hospital health care team to change some component of the combination medication to accommodate a change in their disease status. Often, such an instruction comes from someone other than a patient's usual HCP, who is unaware of the patient's current specific medicine.

Although the patient's usual health care team would be expected to become aware of this situation and advise the patient during medication reconciliation at the point of care in the pharmacy, patients rarely use only one pharmacy for all their prescriptions, often switching pharmacies to maximize their cost savings. Thus, pharmacists' ability to safely reconcile changes in medication regimens and counsel patients appropriately may be compromised (author's opinion).

Strategies to Improve Adherence to Metformin

Patient Education and Counseling

Several strategies can be used to improve adherence to diabetes medications. Patient education initiatives and counseling aimed at improving

patients' understanding of the chronic, progressive nature of type 2 diabetes and the importance of sustained glycemic control and adherence to prescribed antihyperglycemic medication are valuable, particularly when such interventions consider patients' cultural perspectives and attitudes regarding their treatment (2).

It is also important for HCPs to regularly engage patients in discussions about their medication regimen to highlight any unidentified changes in the regimen that may have inadvertently arisen. How patients take their medications can evolve over time; they may simply forget or omit an instruction, and that simple mistake quickly becomes a habit. For example, a patient originally asked to take all medications in the evening goes on vacation and decides to shift pill-taking to the morning. Experiencing more side effects, the patient lowers the dose to obtain symptom relief. By the time the vacation is over and the next appointment with the health care team is due, the patient has entirely forgotten about the change to the regimen and does not mention it. In the author's experience, unless a member of the health care team specifically asks about any possible medication changes at every clinic visit, months or even years may elapse before a patient is discovered to be not taking the metformin as prescribed.

eHealth Interventions

Electronic monitoring of patient adherence by using medication-event monitoring systems such as electronic pill-bottle caps can be useful to improve adherence and guide clinical decision-making (25). One study (25) used the Micro Electronic Monitoring System (MEMS; Aardex Group, Sion, Switzerland) pill bottles to assess adherence to metformin therapy and to identify patients with poor adherence (<80%). In that study, 4 months of cue-dose training (i.e., beep reminders at the time doses were due) improved adherence to metformin by 15–20%. Electronic monitoring of patients'

pill-taking behavior using MEMS adherence data also showed that true adherence to treatment was significantly lower than patients' self-reported adherence (25), emphasizing the importance of improving patient education and increasing awareness of the importance of the treatment regimen.

In this regard, eHealth approaches that use technology such as smartphone apps and text reminders to support patients during their treatment can be very useful. Such tools are particularly useful when patients are initiating or changing treatment regimens, as well as to help improve physician-patient communication. Smartphone technology is also now being used to log and send data on patients' self-monitored blood glucose levels to diabetes care teams (26), and in the future, alerts or reminders could be built into software of this type to maintain awareness of medication compliance. Future studies are needed to evaluate the effects of available eHealth interventions on patient health outcomes and economic burden.

Physician-Patient Communication

As discussed earlier, it is often easy for practitioners to assume that their patients understand the long-term need for, and dose schedule of, metformin therapy and to forget to regularly check that patients understand the correct way to take their medication and the clinical benefits that sustained adherence brings. In this context, shared decision-making through open, two-way communication between patients and their health care team is a useful strategy. Although not a new concept, shared decision-making is vital in the management of chronic diseases such as diabetes. Nonadherence to treatment may have negative psychological implications and cause distress to the patient, disrupting the relationship between patient and practitioner. However, it is the author's belief that if practitioners can engage their patients in regular,

neutral, nonjudgmental conversations about their diabetes treatment, the practitioner-patient relationship can improve and result in a more appropriate treatment regimen.

Many patients feel guilty when they cannot comply with medication orders even though they would like to be able to do so. This awareness of their own nonadherence may lead them to progressively omit this information during clinic discussions. For example, patients may be asked to take their metformin tablets daily but find themselves unable to swallow the pills. They do not initially share this information with their practitioner, but instead crush, chew, or split the tablets to allow them to comply with treatment, which may have repercussions on dosing and glucose control. Owing to feelings of frustration about the reasons for their noncompliance, these patients may also reveal nothing of their difficulties during follow-up appointments. Such patients may not mention the problem until their practitioner expresses concern that they are not meeting health goals and raises the need to add additional therapies. More commonly, patients internalize the failure to reach target control as their own failure and may stop returning for clinic visits until they feel that they have resolved the problem on their own. More drastically, patients may switch to another clinic to avoid facing a difficult topic.

Real conversations that arise during carefully managed patient consultations can identify seemingly trivial but nonetheless crucial daily issues or hurdles that may influence patients' adherence to metformin therapy. For example, although some older patients may experience memory problems that affect their ability to take metformin as prescribed, support with MEMS or another cue-training approach may resolve the issue easily. As another example, in the early dose-titration phase of metformin therapy, patients often experience the need to pass stools more frequently or urgently, with unpredictable timing,

causing embarrassing social situations and limiting daily activities. In such situations, asking about daily activities can lead to an eye-opening discussion about patients' experiences with trying to find and use public bathrooms. This experience can clearly compromise patients' willingness to adhere to treatment, but it could potentially be resolved if discussed at the initial clinic visits by adjusting the dose or switching to an extended-release (ER) metformin formulation.

Recognizing patients' feelings of guilt about noncompliance is important to identifying resolvable barriers to metformin adherence. Engaging in regular discussion and shared decision-making will allow practitioners to identify which medications their patients are comfortable taking and would be most likely to adhere to.

Older patients who understand the importance of taking metformin but cannot swallow the tablets may feel ashamed and therefore may not discuss the issue with their practitioner unless coaxed. Such patients could be prescribed liquid metformin (27), which is often prescribed for children or young patients. Currently, adults—including older patients—are expected to swallow large pills or capsules, which may cause social pressure and feelings of frustration.

In addition, although metformin is generally well tolerated and interacts with few drugs, gastrointestinal side effects can develop in up to 25% of patients taking IR formulations of metformin and lead to discontinuation of treatment (8). However, metformin is also available as an ER formulation, which is often associated with fewer gastrointestinal side effects (24). Despite the various tablet options, which can be beneficial for patients who can tolerate the tablets, many patients crush their metformin pills or tablets to make them easier to swallow. This should not be done with ER tablets, which must be taken whole to maintain the controlled release.

Current and Novel Metformin Formulations and Their Impact on Adherence

Increasing practitioners' awareness of differences in metformin formulations and what these differences mean for their patients can improve medication adherence. The standard formulation of metformin is IR metformin, available as pills or tablets taken two or three times daily. Several ER formulations of metformin are also licensed, and a liquid formulation (Riomet, Sun Pharmaceuticals, Ltd.) is available (27). Additionally, both IR and ER formulations are now available as combination tablets with a range of other oral antidiabetic medications (24).

Extended-release formulations include Glucophage XR and Fortamet (Table 2). The Glucophage XR formulation uses a proprietary GelShield Diffusion System technology that comprises a polymer matrix that slowly releases the active drug when it becomes hydrated, allowing the drug to dissolve upon exposure to gastrointestinal fluids (28). The Fortamet formulation comes as a tablet with laser-drilled ports on the membrane, allowing permeability to water but not to body fluids of higher molecular weight. When ingested, water is taken up through the membrane, where it dissolves the drug and excipients, which are subsequently released through the membrane ports (29).

The dosing schedules and advantages and disadvantages of the different metformin formulations are summarized in Table 2. Metformin is almost completely absorbed from the upper gastrointestinal tract; the ER formulations of metformin have been designed to slow the absorption of the drug from the upper gastrointestinal tract by using a controlled-release delivery system to maximize absorption (8,24). The slower release of metformin from ER tablets is associated with a lower incidence of gastrointestinal side effects than with IR metformin, and this improves tolerability for some patients (28,30). The combination

TABLE 2. Dose Schedules, Advantages, and Disadvantages of Different Metformin Formulations

Metformin Formulation	Year of FDA Approval (10,33–36)	Starting Dose (27,29,31,32)	Generic Dose (if Available)	Approximate Cost (\$/Month)	Advantages	Disadvantages
IR tablets						
Glucophage 500, 850, or 1,000 mg	1995	500 mg orally twice daily or 850 mg once daily with meal ^a	500, 850, or 1,000 mg	7 (generic)	<ul style="list-style-type: none"> Low cost Available in combination with other oral antidiabetic drugs 	<ul style="list-style-type: none"> Large tablet size or rough texture makes swallowing difficult May cause gastrointestinal side effects (especially in early titration phase)
ER tablets						
Glucophage XR 500 or 750 mg (32)	2000	500 mg once daily with the evening meal ^b	500 or 750 mg	10 (generic)	<ul style="list-style-type: none"> Low cost of generic metformin ER (similar to IR) 	<ul style="list-style-type: none"> Tablets cannot be broken or crushed
Glumetza 500 or 1,000 mg (31)	2005	500 mg once daily with the evening meal ^c	500 or 1,000 mg	750	<ul style="list-style-type: none"> Fewer gastrointestinal side effects (improved tolerability) 	<ul style="list-style-type: none"> Higher cost of Glumetza and generic Fortamet compared with generic IR metformin (~100 and ~35 times the cost, respectively)
Fortamet 500 mg or 1 g (29)	2004	500 mg once daily with a full glass of water and the evening meal ^d	250 (generic)		<ul style="list-style-type: none"> Available as combination formulations with other oral antidiabetic drugs 	
Liquid						
Riomet 500 mg/5 mL (27)	2003	Once daily or twice daily with meals ^e		555 ^f	<ul style="list-style-type: none"> Easy to administer Can be taken by patients with physical (dysphagia) or psychological swallowing problems 	<ul style="list-style-type: none"> Prescribing physicians have relatively limited experience with the formulation

^aAdult dose; increase the dose in increments of 500 mg weekly or 850 mg every 2 weeks up to a maximum dose of 2,550 mg per day, given in divided doses. ^bAdult dose; increase the dose in increments of 500 mg weekly up to a maximum of 2,000 mg once daily with the evening meal. ^cIncrease the dose in 500-mg increments every 1–2 weeks if a higher dose is needed and there are no gastrointestinal adverse reactions up to a maximum of 2,000 mg daily. ^dGradual dose escalation if needed; not to exceed 2,500 mg daily. ^eDosing must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose. The maximum recommended daily dose of Riomet is 2,550 mg (25.5 mL) in adults and 2,000 mg (20 mL) in pediatric patients (aged 10–16 years of age). ^fEstimated based on an 8.5 mL twice-daily dose.

of ER metformin formulations with other oral antidiabetic drugs in a single pill reduces pill burden and simplifies therapeutic regimens to improve adherence (24). However, the fact that ER metformin tablets must be swallowed whole may present a barrier to their use by patients who have a swallowing difficulty and are used to breaking up tablets to aid swallowing or for dose flexibility (8). In addition, the inert tablet matrix from ER formulations may be eliminated as a soft mass in the stool, which is harmless, but may alarm some patients (29,31,32). A delayed-release metformin formulation currently in clinical development is designed to maximize the gastrointestinal mechanism of action of metformin and reduce systemic exposure, thus giving it the potential to be used in patients with chronic kidney disease (24).

The liquid formulation of metformin offers a number of potential advantages, and there are many reasons why a patient may need or prefer a liquid formulation. Whether it be due to dry mouth, esophageal strictures, psychological trauma, or dose flexibility, patients' needs must be taken into consideration when they are being prescribed oral medication that comes in tablets as large as the typical metformin tablet. Liquid metformin can be administered straight from the bottle without further dilution, so it is easy for patients to take. In the author's experience, adherence is usually better if patients need to perform only a single action to take their medication rather than having to dissolve or mix a medication or remember to take the medication with a drink or with or after food. Liquid metformin can also be taken in alternative dosing regimens. For example, patients who have significant gastrointestinal concerns while on metformin could take liquid metformin diluted in another liquid and ingested slowly throughout the day. Although this is an off-label dosing regimen, patients appreciate its use as an alternative means to comply with

their treatment. Such an approach returns control of dosing to the patient and can improve a patient's positive feelings through shared decision-making.

Conclusion

Adherence to and persistence with metformin are currently suboptimal, thus exposing many patients with type 2 diabetes to the short- and long-term risks associated with inadequate blood glucose control, including disease progression, diabetes-related vascular complications, and a shortened life span. Adherence to metformin therapy can be improved through several different strategies. Understanding the specific barriers to treatment compliance and the complex attitudes and needs of individual patients is crucial. In this regard, shared decision-making through regular practitioner-patient dialogue is vital to identifying the reasons for nonadherence and proactively developing potential solutions. Prescribing the most appropriate metformin formulation may be an effective means of improving adherence in specific situations. The newer ER and delayed-release formulations of metformin offer the potential to improve adherence through better gastrointestinal tolerability and simplified regimens for many patients. The new liquid formulation of metformin may be of benefit to several specific patient groups, including older patients, children, and patients who have difficulties swallowing large tablets.

Duality of Interest

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