Medication Adherence During Adjunct Therapy With Statins and ACE Inhibitors in Adolescents With Type 1 Diabetes

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OBJECTIVE

Suboptimal adherence to insulin treatment is a main issue in adolescents with type 1 diabetes. However, to date, there are no available data on adherence to adjunct noninsulin medications in this population. Our aim was to assess adherence to ACE inhibitors and statins and explore potential determinants in adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS

There were 443 adolescents with type 1 diabetes recruited into the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) and exposed to treatment with two oral drugs—an ACE inhibitor and a statin—as well as combinations of both or placebo for 2–4 years. Adherence was assessed every 3 months with the Medication Event Monitoring System (MEMS) and pill count.

RESULTS

Median adherence during the trial was 80.2% (interquartile range 63.6–91.8) based on MEMS and 85.7% (72.4–92.9) for pill count. Adherence based on MEMS and pill count dropped from 92.9% and 96.3%, respectively, at the first visit to 76.3% and 79.0% at the end of the trial. The percentage of study participants with adherence ≥75% declined from 84% to 53%. A good correlation was found between adherence based on MEMS and pill count ($r = 0.82$, $P < 0.001$). Factors associated with adherence were age, glycemic control, and country.

CONCLUSIONS

We report an overall good adherence to ACE inhibitors and statins during a clinical trial, although there was a clear decline in adherence over time. Older age and suboptimal glycemic control at baseline predicted lower adherence during the trial, and, predictably, reduced adherence was more prevalent in subjects who subsequently dropped out.

Adherence to a medication regimen, defined as the extent to which a person's medication-taking behavior corresponds with the agreed recommendations from a health care provider, is a key determinant of response to therapy and patients' outcomes (1). Adherence is a complex and multifactorial paradigm that varies depending on the disease and treatment regimen and is also influenced by physician- and patient-related factors (1–3).

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**A complete list of the AdDIT Study Group is included in the Supplementary Data online.*

In adolescents with type 1 diabetes, suboptimal adherence to diabetes self-management, including insulin therapy, is a main concern (4,5) and reflects age-related issues as well as the complexity of diabetes management (6,7).

Insulin is the standard treatment for type 1 diabetes, but its doses and timing of administration need to be coordinated daily with the results of blood glucose monitoring, dietary intake, and levels of physical activity, as well as with potential intercurrent illnesses and other factors (6). The burden of adhering to these various behaviors is carried by patients and their families and can affect every aspect of daily life.

Given that glycemic control is often suboptimal during adolescence (8), there is a growing interest in implementing new noninsulin adjunct drug therapies to achieve recommended glycemic targets and to prevent short- and long-term complications (9). International guidelines are also more widely recommending treatments with drugs to lower blood pressure and lipids during adolescence in the presence of cardiovascular risk factors such as dyslipidemia and hypertension (10,11). Understanding how these adjunct medications will be accepted and adhered to by young people is needed, not least to inform potential strategies to improve and maintain treatment adherence after their implementation into clinical practice. Although there is clear evidence for a strong association between adherence to diabetes treatment and glycemic control and, in turn, complication risks (12), there are no available data on adherence to adjunct noninsulin medications in adolescents with type 1 diabetes.

The Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) recruited a contemporary cohort of adolescents with type 1 diabetes from the U.K., Canada, and Australia (13). Trial participants were requested to take two oral medications, ACE inhibitors and statins, or related placebos, daily for 2–4 years. Thus, this trial offers a unique opportunity to look at adherence to medications other than standard insulin treatment. As part of the trial, adherence was assessed with the Medication Event Monitoring System (MEMS), which records the date and time of each opening of a pill container and is currently considered the gold standard for tracking drug dosing history in clinical trials (14,15). Pill count was used as a secondary indirect method to assess adherence. Using data from the AdDIT trial, we aimed to *1*) assess rates of adherence and its changes over time, *2*) compare MEMS and pill count as methods of assessing adherence, and *3*) assess factors predicting adherence in adolescents with type 1 diabetes in the context of a clinical trial.

RESEARCH DESIGN AND METHODS

Study Population

The study cohort included 443 adolescents with type 1 diabetes, aged 10–16 years, recruited into the AdDIT trial. The design and results of the AdDIT trial have been previously reported (13). In brief, AdDIT was a multicenter, double-blind, randomized, placebo-controlled trial conducted at 32 centers across the U.K., Canada, and Australia. AdDIT was designed to explore the potential cardiorenal protection provided by ACE inhibitors and statins in adolescents with type 1 diabetes at increased risk of vascular complications based on an albumin-to-creatinine ratio in the upper tertile of the normal range (13).

The inclusion criteria for the AdDIT trial were age between 10 and 16 years, a diabetes duration of at least 1 year (or a diagnosis within the past year with an undetectable C-peptide level), and an adjusted albumin-to-creatinine ratio in the upper tertile of the screened population. Exclusion criteria were non–type 1 diabetes, pregnancy or unwillingness to adhere to contraceptive advice and pregnancy testing, severe hyperlipidemia or a family history of familial hypercholesterolemia, hypertension unrelated to diabetic nephropathy, previous exposure to the investigational drugs, unwillingness or inability to adhere to the trial protocol, the presence of coexisting conditions (excluding treated hypothyroidism and celiac disease), proliferative retinopathy, and the presence of renal disease that was not associated with type 1 diabetes (13).

Participants were randomized, using a two-by-two factorial design, to receive a variable dose of an ACE inhibitor (quinapril, 5 or 10 mg), a fixed dose of a statin (atorvastatin, 10 mg), combinations of both drugs, or matched placebos. The drugs were given orally as two tablets daily for a minimum of 2 up to a maximum of 4 years. Trial duration varied based on the time when each participant was enrolled during the recruitment timescale.

The trial conformed to the provisions of the Declaration of Helsinki and was approved by the Cambridge University Hospitals and participating local research ethics committees. Parents of the participants provided written informed consent, and the trial participants were asked to provide their written assent if they were not yet at an age when they could provide consent.

Assessment of Adherence

Electronic Monitoring

Quinapril, atorvastatin, and the matched placebos were supplied at each study visit. The tablets were provided in containers with the electronic monitoring caps MEMS (provided by AARDEX, Zug, Switzerland), which recorded the precise date and time of each opening and closing to track adherence (13). Each study participant was provided with two bottles containing the study medications/placebos. Participants were asked to keep the tablets in the bottles provided and not to transfer them to other containers. They were informed that their adherence to both drugs was monitored during the trial, and at each study visit, they were encouraged to take the medications. However, they did not receive any incentives to promote adherence, and no detailed data on adherence to diabetes self-management were collected during the trial.

At each study visit, data from the caps were read by MEMS devices and stored. MEMS adherence was estimated assuming that each cap opening represented a participant taking the correct number of medications from the container during the study period. Participants who did not open their MEMS cap were rated as nonadherent for that day.

Pill Count

At every study visit, unused tablets were brought back and counted.

By both methods, adherence was assessed at 1 month after randomization and then every 3 months. It was calculated as the percentage of days on which a tablet was apparently taken by participants remaining active in the study out of the days in between study visits.

Predictors of Adherence

Potential predictors of adherence were chosen a priori from participants' characteristics assessed at baseline and included in the randomization process (13).

These included chronological age, sex, diabetes duration, age at diabetes diagnosis, baseline glycemic control, as assessed by glycated hemoglobin (HbA_{1c}), method of diabetes treatment (multiple daily injections [MDI] or continuous subcutaneous insulin infusion [CSII]), and country (U.K., Australia, or Canada).

Statistical Analysis

Results are presented as percentages or as median and interquartile ranges (IQRs). A linear mixed model was used to compare adherence rate across the study visits. Mann-Whitney and Kruskal-Wallis tests were used to compare differences in overall adherence between study groups. Linear regression models were used to assess factors associated with overall adherence. Bland-Altman plots were used to assess agreement between the MEMS and pill count methods. Two-sided *P* values of <0.05 were considered statistically significant. Analyses were performed with SPSS 25 software.

RESULTS

Baseline Characteristics of the Study Population

There were 443 adolescents (203 girls and 240 boys; 376 white and 67 from other ethnic groups) randomized into the AdDIT trial at a median age of 13.8 years (IQR 12.6–15.0) and median diabetes duration of 5.0 years (3.2–7.8) across the three countries: Australia ($n = 201$ [45%]), Canada ($n = 124$ [28%], and U.K. ($n = 118$ [27%]). Their baseline median (IQR) HbA_{1c} was 8.3% (7.6–9.3) (67.2 mmol/mol [59.6–78.1]); 266 (60%) were on MDI and 177 (40%) on CSII.

These 443 study participants represented ~43% of the eligible screened population, and their demographic characteristics were similar to those who refused to take part in the study (data not shown).

Study participants were monitored for a median of 2.6 years, and their adherence was assessed starting from 1 month after randomization and every 3 months thereafter, until completion of the trial after 2–4 years.

Adherence Rate Based on MEMS Versus Pill Count

There were no significant differences between adherence to the ACE inhibitor or related placebo and the statin or related placebo (Supplementary Fig. 1). The average adherence for both drugs was used in all analyses. Levels of adherence between the active drugs versus placebo-placebo groups during the whole trial period were similar (81.6% [66.5–92.2] vs. 79.9% [62.9–91.7]; $P = 0.54$).

Overall median (IQR) adherence was 80.2% (63.6–91.8) (mean ± SD 75.0 ± 20.8) based on MEMS and 85.7% (72.4–92.9) (mean ± SD 80.4 ± 17.0) based on pill count. Adherence based on both MEMS and pill count dropped from 92.9% and 96.3%, respectively, at the first visit, to 76.3% and 79.0% at the last visit (*P* for trend <0.001). As shown in Fig. 1, the main decline in adherence occurred during the first 18 months (adherence at 18 months: MEMS, 79.8%; pill count, 83.2%) (*P* for trend <0.001), and after that it remained almost stable (Fig. 1). The sample size, as reported in Fig. 1, decreased over time, mainly due to participants completing the minimum duration of 2 years in the trial. In addition, 78 participants dropped out at different time points, and 37 participants stopped treatment earlier than expected but remained in the study. Adherence during the trial was lower in participants who subsequently dropped out or stopped medications compared with the rest of the trial population remaining active in the trial (72.4% [53.2–90.3] vs. 82.0% [66.2–92.2]; $P = 0.02$). When these nonactive participants are included, with their adherence considered equal to 0 in the analysis, overall adherence during the trial was 4.4% lower compared with the adherence calculated only for participants remaining in the study (Supplementary Fig. 2).

The correlation between MEMS- and pill count–based adherence was 0.82 ($P < 0.001$) (Fig. 2*A*). Bland-Altman plots showed good agreement between the two methods, with a bias of 5.3% (95% CI −28.2; 17.9) (Fig. 2*B*).

Levels of Adherence Over Study Treatment Visits Based on MEMS Data

The data were analyzed using different categories of adherence (≥75%, 50–75%, 25–50%, and <25%), and most participants had a median adherence rate ≥75% during the trial period (Fig. 3). However, the percentage of active participants with adherence ≥75% decreased from 84% at the beginning of the study to 56–58% after 18–24 months and to 53% after 48 months. In parallel, the proportion of participants with adherence rates between 50% and 75%, 50% and 25%, and <25% increased from 13% to 28%, 1.8% to 14%, and 0.7% to 4.6%, respectively.

Baseline Factors Associated With Adherence Based on MEMS Data

Adherence decreased across the 10–12-, 12–15-, and 15–17-year-old age-groups at 81.4% (70.1–93.4) vs. 79.3% (60.8–91.0) vs. 78.9% (60.8–91.7), although the between-group difference reached only borderline statistical significance ($P = 0.07$).

No differences in adherence during the study period were found between participants with a diabetes duration, at the baseline visit, of <5 years (80.6% [65.7–91.8]) compared with those with a duration of 5–10 years (80.4% [66.8–91.8], $P = 0.56$). No differences were found between boys (79.8% [63.4–91.0]) and girls (80.4% [64.3–92.6], $P = 0.63$).

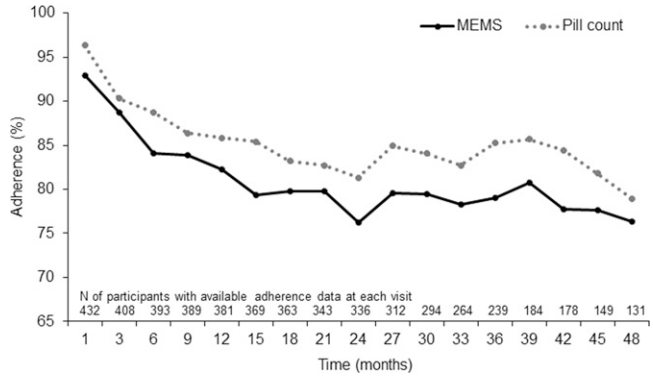

Figure 1—Adherence during the trial period based on MEMS and pill count. Results at each study visit are reported as medians. *N* of participants are those still active at each follow-up study visit with available adherence data. $P < 0.001$ for changes over time for each adherence method.

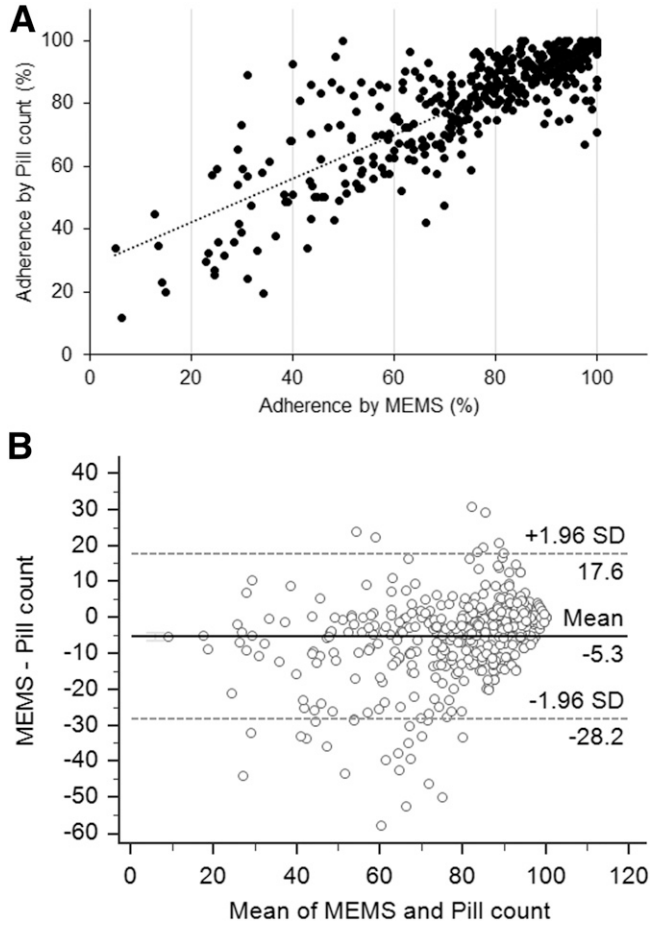

Figure 2—*A*: Scatter plot shows comparison between adherence assessed by MEMS vs. pill count ($r = 0.82$, $P < 0.001$). *B*: Bland-Altman plots of the two adherence methods.

When adherence between the three countries involved in the AdDIT trial was compared, Australia showed a slightly higher median adherence (83.4% [70.1–92.9]) compared with the U.K. (78.9% [61.7–91.6] and Canada (73.8% [56.8–88.3]; *P* for trend = 0.001). However, the decline in adherence during the trial period was observed in all three countries: at the first study visit, median adherence was 93.3% for Australia, 92.9% for the U.K., and 89.0% for Canada, whereas by the last study visit, it dropped to 79.8%, 76.1%, and 73.0%, respectively.

Levels of adherence varied in relation to glycemic control at the baseline study visit, with the lowest adherence (76.9% [56.9–88.8]) in participants with an HbA_{1c} >8.5% (>69 mmol/mol), compared with 81.9% (66.5–91.7) in those with HbA_{1c} 7.5–8.5% (58–69 mmol/mol) and 88.1% (75.2–93.9) in those with an HbA_{1c} <7.5% (<58 mmol/mol) ($P = 0.001$) (Supplementary Table 1 and Supplementary Fig. 3). There were no significant differences in adherence between participants on MDI and those on CSII: 80.2% (60.6–92.2) vs. 80.5% (67.6–91.9; $P = 0.84$).

In univariate linear regression models, baseline factors significantly associated with adherence were chronological age, with a lower adherence in older study participants; country of origin, with the highest adherence in Australia; and glycemic control, with the lowest adherence associated with the highest HbA_{1c} levels (Table 1). In a multiple regression model, HbA_{1c} and country remained independently associated with adherence (Table 1).

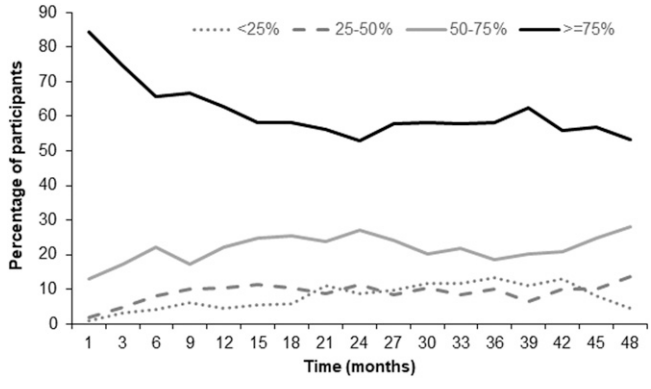

Figure 3—Percentage of participants showing different levels of adherence, from ≥75% to <25%.

CONCLUSIONS

This is the major study providing data on adherence to medications other than insulin in a large contemporary cohort of adolescents with type 1 diabetes, recruited across three countries and enrolled in a clinical trial involving taking two adjunct oral medications daily for a total duration of 2–4 years.

Median adherence to both ACE inhibitors and statins during the AdDIT trial was ~80%, although there was a deterioration in adherence over time. Adherence to medications in adolescents, in clinical practice and in clinical trials, varies widely from 10% to 90%, with most studies reporting rates <50%, particularly in those with chronic rather than acute conditions (16). The physical and psychological changes occurring during adolescence, along with demographic and socioeconomic factors and the intrinsic characteristics of the underlying disease, can all contribute to poor adherence in this age-group (17).

Type 1 diabetes is a good example of a chronic disease where adherence to treatment strategies and self-management can be challenging, particularly during adolescence (18). Current diabetes self-management is based on MDI or CSII, which need to be balanced with frequent blood glucose monitoring, diet, and physical activity, as well as other factors such as intercurrent illnesses (18). Observational studies based on self-reports, questionnaires, HbA_{1c}, and, more recently, on continuous glucose monitoring and insulin

Table 1—Baseline predictors of adherence during the trial

	β-Coefficient	*P* value
Univariate linear regression models		
Sex (girls vs. boys)	−0.04	0.41
Age (years)	−0.10	0.03
Age at diagnosis (years)	−0.007	0.88
Diabetes duration (years)	−0.05	0.34
HbA_{1c} (mmol/mol)	−0.21	<0.001
Diabetes treatment (MDI vs. CSII)	0.05	0.35
Country (Australia vs. U.K. vs. Canada)	−0.18	<0.001
Multivariate linear regression model		
Age (years)	−0.09	0.05
HbA_{1c} (mmol/mol)	−0.20	<0.001
Country (Australia vs. U.K. vs. Canada)	−0.19	<0.001

The dependent variable is median adherence over time; independent variables are as collected at the baseline study visit.

pumps, indicate suboptimal adherence to insulin treatment and other self-management behaviors among children and adolescents with type 1 diabetes (19–24). One of these studies found that adherence to individual components of treatment regimens varied from 29% for dietary recommendations to 52% for insulin administration and 69% for blood glucose monitoring (24). In addition, ~65% of children who wear an insulin pump miss one or more mealtime boluses of insulin per week (20). These data are a concern given that nonadherence to a diabetes regimen can result in suboptimal glycemic control and increased episodes of diabetic ketoacidosis and, in the long term, lead to higher rates of vascular complications and reduced life expectancy (25).

In contrast to these real-life data, AdDIT provides valuable information about adherence to adjunct oral medications in the context of a clinical trial. Although, nonadherence to ACE inhibitors or statins does not have the same impact as nonadherence to insulin in risk for acute complications, understanding factors affecting adherence to these medications is important to maximize their benefit when used in clinical practice. This is important given that use of these drugs from an early age may improve long-term outcomes of young people with type 1 diabetes.

Although overall adherence was better than expected, there was deterioration during the AdDIT trial in adherence to both ACE inhibitors and statins over time: after 2 years of treatment, 58% of participants showed an adherence of at least 75%, and this percentage dropped to 53% after 4 years. This is in line with previous findings from other studies and likely reflects loss of participants' motivation and their feeling of lack of immediate benefits, as well as the age-related factors (5,17,18). Overall, these data highlight the need for strategies to reinforce adherence over time to gain the maximum benefit from any intervention during a clinical trial and in the real-word setting.

The AdDIT trial provides valuable data on how adherence can vary based on the methods of assessment. Several methods can be used to assess adherence, and they are broadly classified as direct and indirect methods (26–28). Direct methods, based on the measurement of the level of the administered drug or its metabolites in biological samples, are the most accurate but are also the most expensive and impractical ways to assess adherence.

In contrast, indirect methods rely on patient self-reports or questionnaires, rates of prescription refills, and pill counts and are considered less precise and more prone to errors (1,28). Pill count is one of the most used indirect methods to assess drug adherence but can be susceptible to misrepresentation and overestimate a patient's adherence (27,28). The MEMS method, which records the date and time of each opening of a pill container, is considered a more accurate indirect method and the gold standard for tracking drug dosing history in clinical trials (14,15). MEMS has been used to investigate adherence in adult populations with various conditions (29) but only in a few clinical trials involving pediatric populations. These were mainly studies with small sample sizes and short periods of exposures to medications, ranging from 1 up to 12 months (30–32).

In the AdDIT population, two indirect methods were used, namely, pill count and MEMS, and this comparison confirmed that pill count tends to overestimate adherence, as previously reported (27,29). This overestimation with pill count occurred even though the study participants were aware that their adherence was being monitored with the MEMS caps. Reasons for this attempt to mislead about adherence may include inadequate knowledge about the aim or benefits of treatment as well as dissatisfaction with treatment (1).

The AdDIT trial also offered the opportunity to assess potential factors associated with adherence in the context of a clinical trial. Adherence to a medical regimen can be affected by caregiver-related factors, patients' characteristics, relationships between health care professionals and patients, social and cultural circumstances, and disease- and treatment-related factors (2,3). Frequently, patients are able to memorize only 50% of discussed issues during clinical visits (33) and may have insufficient knowledge about drug usage, and that could lead to patients not taking the appropriate prescribed doses, missing doses, or discontinuing treatment (1). Another potential main barrier to adherence to prescribed drugs is disbelief related to the diagnosis, fear of adverse effects, high frequency of dosing, number of concurrent medications, routes of drug administration, and long-term treatment (3).

Medication adherence in children and adolescents is generally more complex than in adults, and this is reflected by worse adherence rates reported in pediatric than in adult studies (34). Younger children require involvement of a third party in the management of their medical condition (17), whereas adolescents face a particular life phase characterized by many challenges potentially conflicting with optimal adherence (35).

Adherence in the AdDIT trial was lower in older than younger participants, in line with the results of previous studies suggesting a decline in adherence during the transition from childhood to adolescence (36). This may reflect specific developmental changes occurring during adolescence and less parental involvement in diabetes management (37), which is a known step as children grow up

and express their desire of being more independent.

Surprisingly, we did not find any effect of diabetes duration on adherence rates, in contrast to other studies reporting a decline with longer disease duration (36). Our findings could be explained by the relatively short and narrow range of diabetes duration in our study population.

Despite the implementation of a standardized protocol in the AdDIT trial, there were differences in adherence across countries, with a slightly higher adherence to therapy in Australia than in the U.K. and Canada. Variations in adherence between countries have been previously reported and could be related to sociodemographic and socioeconomic factors, differences in health care systems and medical care, and physician-patient communication (1,2,38).

Suboptimal glycemic control was also associated with lower adherence to the adjunct oral medications during the AdDIT trial, likely reflecting participants' specific characteristics and behaviors that affect adherence not only to insulin regimens but also to any additional treatment strategies. Adolescents with type 1 diabetes face several obstacles to treatment adherence, including psychosocial issues, model of family functioning, communication, and regimen-associated barriers (35). They are also at high risk of depression, anxiety, or other mood or eating disorders (18). All of these factors have previously been associated with poor adherence to insulin treatment (35) and may similarly impact adherence to adjunct oral medications.

The association between suboptimal glycemic control and lower adherence across all randomized groups during the AdDIT trial raises the question about whether more complex treatment approaches, which should be directed mainly toward those patients not achieving recommended glycemic targets, could bring real benefits.

Currently, several adjunct noninsulin treatments are being investigated with the aim of improving glycemic control in people with type 1 diabetes as well as addressing weight control, preserving β-cell function, and inducing vascular protection (9–11). These include use of gliptins and sodium–glucose cotransporter 2 inhibitor agents as well as other drugs to reduce cardiovascular risk factors, such as statins and ACE inhibitors. However, before more complex drug therapies are implemented, strategies examining and overcoming the issues of poor adherence in those adolescents already nonadhering to current insulin treatment regimens are required (3).

Some limitations of the current study need to be acknowledged. Although the study population was demographically well representative of the larger multinational AdDIT screening population of >4,000 adolescents with type 1 diabetes, the adherence data related to a selective group who agreed to participate in a clinical trial and were aware that adherence to the adjunct medications was monitored. This likely resulted in a greater adherence than that observed in daily clinical practice where there is no specific standardized monitoring system in place, and thus the findings are less generalizable to a real-world setting. Participants remained active in the study for a variable duration, from a minimum of 2 to a maximum of 4 years, leading to adherence data available only for ~30% of the study population for the whole 4-year trial duration. Although the MEMS method seems superior to pill count or other indirect methods, it could still have disadvantages, such as misleading the system when opening the container without taking the drug or taking the wrong number of tablets or multiple doses out of the container at the same time (26). In addition, we did not collect data on socioeconomic status or psychosocial factors (family, peers, social support, acceptance/understanding of disease and treatment, mental status, and self-esteem), which have previously been reported to affect adherence in children and adolescents in some although not all studies (39,40). Finally, we were unable to assess the effect of other potential predictors of adherence, such as ethnicity (39), given that the participants were predominantly white.

Conclusion

Overall, AdDIT has provided valuable insights into medication adherence in the context of multiple drug treatment for young people with type 1 diabetes. The AdDIT trial showed an overall good adherence rate in a population of adolescents with type 1 diabetes in a clinical trial setting but also confirmed that deterioration of adherence over time can be an issue. Older age and higher HbA_{1c} at baseline predicted adolescents with lower adherence during the trial, highlighting two targets for strategies aimed at improving adherence both in clinical trials and in daily clinical practice. Although type 1 diabetes is a complex condition, on the basis of the present data, the implementation of adjunct oral therapies in type 1 diabetes in the future seems feasible but will require specific strategies addressing potential barriers to adherence and ways of overcoming them.

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Author Contributions. E.N. was involved in the literature review and in data interpretation and analysis and wrote the first draft of the manuscript. C.L.A. contributed to data acquisition and interpretation and critical review of the manuscript. S.T.C. and T.S. contributed to data acquisition and analysis and critical review of the manuscript. R.N.D., D.D., J.E.D., T.W.J., F.H.M., S.M.M., H.A.W.N., and D.B.D. contributed to the study concept and design, data interpretation, and critical review of the manuscript. M.L.M. contributed to study design and concept and data interpretation, performed statistical analysis, and wrote and reviewed the manuscript. M.L.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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