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Barriers and strategies for oral medication adherence among children and adolescents with Type 2 diabetes

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Abstract

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Aims—Examine barriers for taking glucose-lowering oral medications, associated baseline characteristics, strategies used, and the adherence impact in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study.

Methods—We studied youth prescribed oral diabetes medications over two years (N = 611, 583, and 525 at 6, 12, and 24 months). Clinicians documented barriers (e.g. forgetting, routines, other concerns) in the subsample that reported missed doses (N=423 [69.2%], 422 [72.4%], and 414 [78.9 %] at 6, 12, and 24 months, respectively). Adherence strategies were also assessed (e.g. family, schedule, reminder device) using standard questions. Logistic regression was used to analyze associations with medication adherence.

Results—Those missing doses were not different from the total sample (61.5% female, 13.9 ± 2.0 years, >80% racial/ethnic minorities). No baseline demographic or clinical predictors of barriers to medication adherence were identified. Among those for whom barriers were assessed, “forgetting” with no reason named (39.3%) and disruptions to mealtime, sleep, and schedule (21.9%) accounted for the largest proportion of responses. Family support was the primary adherence strategy identified by most youth (≥50%), followed by pairing the medication regimen with daily routines (> 40%); the latter strategy was associated with significantly higher adherence rates (p=0.009).

Conclusions—Family supported medication adherence was common in this mid-adolescent cohort, but self-management strategies were also in evidence. Findings are similar to those reported among youth with other serious chronic diseases. Prospective studies of multi-component family support and self-management interventions for improving medication adherence are warranted.

Introduction

Little is known about the barriers and adherence strategies associated with taking prescribed oral medications among youth with Type 2 diabetes. Prior research suggests that adherence rates for children and adolescents with chronic medical conditions vary by disease type and treatment complexity [1, 2] and that pediatric patients often take only about 50% of their prescribed medications [3–5]. However, most information about diabetes medication adherence comes from studies of adults with Type 2 [1, 2] or youth with Type 1 diabetes [3, 4].

The TODAY clinical trial was the first to compare different treatments for youth with recent-onset Type 2 diabetes [6] and presented an opportunity to examine barriers to the prescribed glucose-lowering oral medication routine all youth were administered, and the strategies used to improve adherence. Participants were randomized to metformin alone (M), metformin plus rosiglitazone (M+R), or metformin plus an intensive lifestyle program (M +L) with the primary study outcome being failure to maintain target glycemic control (persistent HbA1c ≥ 8%/64 mmol/mm). Almost half of the cohort was unable to sustain adequate glycemic control over the 4-year period of study [7, 8] and eventually required insulin rescue therapy.

A previous study of oral medication adherence rates among TODAY participants documented that a high proportion of youth in this cohort (72%) demonstrated adequate

adherence at the two-month assessment (≥ 80% based on pill count), but that rate steadily declined to 56% by the 4 year visit [9]. No specific baseline characteristics of the sample significantly predicted poor adherence to the oral diabetes regimen at subsequent follow-up visits, except elevated depressive symptoms. Moreover, study analyses failed to show an association between medication adherence rate and metabolic control suggesting that unremitting beta cell decline is characteristic of Type 2 diabetes course in youth, requiring insulin rescue. In addition, emerging data indicates that youth with Type 2 diabetes are at high lifetime risk for cardiovascular disease [10] and a rapid worsening of comorbidities over a period of 2–6 years [11–14] that will require chronic medication self-management. Thus, in this study we sought to learn more about individual barriers and strategies for taking oral glucose medications during the first 24 months of the trial, as an initial step in understanding medication behaviors in this population [15].

The first aim of the current study was to identify the types and frequencies of barriers and strategies for those using glucose-lowering oral medication and to evaluate the relation of baseline demographic and clinical correlates to medication self-management. The second aim was to explore whether reminder strategies utilized by youth with Type 2 diabetes had an impact on regimen adherence rates over time. Because very little is known about barriers and strategies for medication adherence in this population, both aims were considered exploratory.

Participants and Methods

Design, methods, and primary outcomes for the randomized clinical trial have been reported previously [6, 16, 17] and are summarized here. Participants were recruited and studied by a collaborative group of 15 clinical sites, mostly in large pediatric medical centers. Of the 1,211 children and adolescents screened for the study, 927 (76.5%) entered the run-in phase. Between July 2004 and February 2009, 699 (75.4%) youth were enrolled and randomized. Eligible youth were aged 10–17 years, with Type 2 diabetes of less than two years' duration, a body mass index ≥ 85th percentile, and had an adult caregiver who agreed to provide support during the trial. They were required to complete a 2–6-month study run-in to establish glycemic control, receive uniform and high quality diabetes education, and demonstrate their ability to attend visits and initially achieve adequate adherence (≥80%) to study prescribed oral medications (1,000 to 2,000 mg of metformin monotherapy) for at least 8 of 12 consecutive weeks.

Eligible participants were then randomized to either M, M+R, or M+L. The primary outcome, per study protocol, was treatment failure (i.e., loss of glycemic control). This was operationalized as either HbA1c ≥ 8%/64 mmol/mol over a 6-month period, or the inability to wean from insulin therapy within 3 months following acute metabolic decompensation. Upon reaching this primary outcome, metformin was continued, rosiglitazone was discontinued in the M+R group, and insulin was added. After initiation of insulin rescue therapy, participants and clinicians remained masked to the original treatment assignment, but were unmasked to HbA1c. After an average follow-up period of 3.9 years, 319 (45.6%) of all enrolled participants were considered to have failed treatment; M+R was superior to M (P = 0.006) and M+L was intermediate but not different from M.

For the current study, we examined barriers and strategies for those participants, who were being prescribed any glucose-lowering oral medication for their diabetes management (regardless of treatment outcome) at 6, 12, or 24 months from baseline. Barriers and strategies data was not collected at the baseline assessment. Of the 699 originally randomized participants in the TODAY cohort, n= 611 (91%) at the six-month visit, n = 583 (84%) at the 12-month visit, and n = 525 (87%) at the 24-month assessment visit were being prescribed oral diabetes medications. Assessment visits were scheduled every two months during the first year and every three months during the second year. Barriers data was documented during these regular visits, but only among participants who reported having missed one or more doses of the study medication during the prior two- or three-month interval (n = 423 [69.2%], n = 422 [72.4%], and n = 414 [78.9 %] of the enrolled sample at 6, 12, and 24 months, respectively. Strategies data was assessed for all participants on oral medications regardless of adherence.

The study protocol was approved by the Institutional Review Boards of the participating institutions; parents signed informed consent for a minor child and youth signed informed assent consistent with local practice.

Medication Management and Adherence Measurement

Uniform, high quality diabetes education was provided during the study run-in period, which included medication self-management approaches. Participants were instructed to use behavioral strategies such as keeping all supplies in one place, using calendar reminders or sticky note prompts on mirrors, refrigerators and glucose meters, and circling AM/PM pill pictures in a medication diary when doses were taken. If they were not able to take medications within a two-hour window of their usual AM/PM schedule, participants were advised to resume their regular dose at the next scheduled time (and not to “double-up”). Parents were also encouraged to initial youth diaries weekly as a shared responsibility. Finally, participants were instructed to bring all materials and supplies to each clinic visit for review and discussion. If participants demonstrated ≥ 80% adherence for 8 out of 12 weeks, they were randomly assigned.

Dosing instructions included taking 2 pills, twice a day. Masked study drug (M or M+R) was provided in 7-day blister packs separated into the am and pm dose; all pills looked, smelled, and tasted the same. Pill counts and dispensation of study drug occurred at each study visit. Participants were instructed to return all blister packs, and medication adherence was calculated as the percentage of prescribed study drug taken based on pill counts. If pill packs were not returned, adherence rate could not be determined and data was coded as “missing” (5.0%, 6.4%, and 7.0% of the sample in the current study at 6, 12, and 24 months). Study staff discussed the diabetes management experience with participants at each visit and completed a survey that documented barriers to and strategies for medication use. However, a formal medication adherence intervention was not the primary focus of these visits.

Measurement of Barriers to Medication Adherence

Empty pill packs were coded as “no missed doses” and barriers were not assessed. If partial or full pill packs were returned, participants were asked, “What has gotten in the way with

taking study medication as prescribed?" and staff endorsed all that applied from a checklist of 12 barriers, or indicated "other reason" or "no specific reason given". The checklist items were designed by consensus among TODAY clinical research personnel familiar with pediatric diabetes medication self-management.

There were numerous "other reason" write-in responses (n = 120, 96, and 92, at the 6, 12, and 24 month visits respectively). These responses were examined by an expert panel of TODAY clinical diabetes educators, nurse specialists, behavioral scientists, and study physicians, blinded to all identifying information about the participants. The panel recoded the "other" responses per the original barrier checklist, by consensus. Only one new barrier category was derived and labeled "negative perception of medication and diabetes" (e.g., the statement "I'm sick and tired of taking pills").

Measurement of Strategies to Improve Adherence

Staff queried all participants, including those with 100% adherence based on pill counts, about strategies they found helpful in remembering to take oral medication as directed. The original checklist included 5 strategies but strategy 1 ("taking pills at a scheduled time") and strategy 2 (taking pills at the same time as another activity (e.g., brushing teeth or meals") were collapsed to form one category labelled "uses schedule or routine".

Statistical Analysis

Descriptive statistics were reported as mean ± SD, or percentages. T-test or chi-square tests were used to compare baseline participant characteristics by number of oral medication barriers and strategies reported at study visits categorized as 1, 2, or 3+ barriers and as 0,1, or 2+strategies. Barriers and strategies were rank ordered by the percentage of participants for whom they were reported and were not mutually exclusive. Logistic regression models for repeated measures were used to examine changes in the number of barriers/strategies reported over time. Similar logistic regression models were used to evaluate the relationships between the number of barriers and strategies reported and adherence to oral medication adherence (classified as ≥ 80% vs <80%). Results presented should be considered descriptive and exploratory with $P<0.05$ considered to be statistically significant. The Statistical Analysis Software package (SAS, version 9.3, 2008, SAS Institute Inc., Cary, NC) was used for all analyses.

Results

Of all TODAY participants prescribed oral diabetes medications over a two-year period (N = 611, 583, and 525 at 6, 12, and 24 months), 423 [69.2%], 422 [72.4%], and 414 [78.9 %] of the sample, respectively, reported missing one or more doses in the two- or three-month interval since their last visit. The demographic features of the participant sample with missed doses (61.5% female, 13.9 ± 2.0 years, >80% racial/ethnic minorities) was not significantly different from the total medication-taking sample. Baseline characteristics of the participants who reported missed doses, and by the number of oral medication barriers reported at the 6-month visit (n =423), are shown in Table 2. No significant baseline differences were shown to be associated with the number of barriers reported at month 6, and few were identified

consistently at subsequent visits (data not shown). In addition, no baseline characteristics were found to be significantly related to the strategies used except for participant age. At month 6, youth who reported use of at least one strategy were 0.7 years younger than those reporting no strategy (p=0.0048) and this age difference was consistent at month 12, and month 24 (data not shown).

Types and Frequencies of Barriers Reported

Table 1 displays the overall frequency/percentage of TODAY participants reporting missed doses of study medications at 6, 12, and 24 months, the number of barriers (1,2, or 3+), and the proportion of the sample reporting specific types of barriers. About 70% of youth were reported to have missed one or more doses of medication at the 6-month visit and this percentage increased significantly by the 24-month visit (78.9%; $P = 0.0011$). Across each assessment time point, the most commonly cited reason for missed doses, regardless of whether one or multiple barriers were coded, was “forgets or misses in general” (roughly 40% of the total sample) followed by “forgets or misses a particular dose” (about 20% of the sample). Morning doses (56.3%) were missed somewhat more often than afternoon doses (43.7%). Common reasons noted were “late for school or work”, or “wakes up late”. Other medication adherence barriers such as, “sometimes spends a few days away from home” or “routine disrupted by new personal or family issues” were evident only in about 6–10% of the cohort across all visit points. Lack of family support, pill size, taste or swallowing problems, lost or misplaced pills, illness, gastrointestinal reactions, negative perceptions of medication and diabetes, and depressed mood/psychiatric issues were rarely reported as a reason for non-adherence. No youth indicated that they believed oral diabetes medications would cause weight gain or edema.

Types and Frequencies of Strategies Reported

Table 3 shows that 56.2%, 57.3%, and 51.6% of the study participants at 6, 12, and 24 months, respectively, used family members to help them remember to take medications. Approximately 45% of youth also indicated that they used specific times of day or the routine activities of daily living (meals, brushing teeth, etc.) to remember to take medicines. Few youth (< 10%) reported using personal reminder devices (watches, alarms, smart phones) or increasing their number of contacts with study staff to improve their adherence to oral medications.

Number of Barriers and Medication Adherence

Within the group (N = 423) for whom this assessment was conducted, there was a significant relationship ($p < .0001$) between the total number of barriers reported (1, 2, 3+) and the degree of medication adherence. Thus, 76.6% of the group that reported three or more barriers, 51.8% with two barriers, and only 28.7% with only one barrier were shown to have < than 80% adherence to medications.

Impact of Reminder Strategies on Medication Adherence

Results from the six-month visit show that youth who anchored their medication use to time of day or paired it with specific activities of daily living, had significantly higher adherence

rates (p=0.009) compared to those using any other strategy or no strategy at all. Findings were similar at the 12 and 24 month visits. For example, when using schedule and routines, 76.8% (n = 138) and 70.0% (n = 129) of the sample demonstrated ≥ 80% adherence to oral medications. In addition, participants who reported the "family help only" strategy for oral medication adherence were, on average, one year younger compared to those who used the routine strategy only (13.4 [SD 1.9] vs 14.4 [SD 2.0]; $P < .0001$]. The very small group of individuals at 6 months that reported using a "reminder device" (n = 23), demonstrated 91.3% adherence to oral medications.

Discussion

Prior TODAY research [9] has demonstrated that most youth in this racially and ethnically diverse cohort with Type 2 diabetes had good oral medication adherence during the first few months of intervention, but desirable adherence diminished over the subsequent four years, on average. The present study aimed to learn more about medication barriers and strategies and associations with participant baseline characteristics for possible impact on adherence. Although overall adherence rates bore little relationship to ultimate metabolic outcomes, likely owing to chronic beta cell failure [9], our study aimed to better understand any factors related to medication-taking behaviors in youth with Type 2 diabetes. This group is at especially at-risk given rapidly emerging comorbidities and complications that will only increase the complexity of medical regimens prescribed for a lifetime [10].

We examined TODAY participants who remained on glucose-lowering oral medications at three different time points over a 24-month period and found that no significant baseline group differences were associated with either the types or frequency of medication barriers reported. This null finding is consistent with a great deal of previous research indicating that poor medication adherence is a widespread problem among adolescents with a variety of chronic conditions such as asthma [18], transplant recipients requiring immunosuppressant therapy [19], inflammatory bowel disease [20], and Type 1 diabetes [21] independent of age, gender, race/ethnicity, education, or socioeconomic status [1]. Moreover, a large meta-analytic review that evaluated self-reported barriers to medication adherence among chronically ill teenagers also demonstrated that adherence problems in this developmental period were not unique to a specific disease [22]. Specifically, forgetfulness and disorganization were commonly cited themes for poor adherence in this age group. Our results also showed that "forgetting" without naming a particular reason, or forgetting due to typical daily disruptions in schedule and routine, were by far the most frequent explanations given for missed doses of medication in contrast to more idiosyncratic barriers. We also found that among the group of youth showing less than 80% medication adherence at 6 months, there was an increased number of barriers reported. Thus, continued examination of how this mid-adolescent group perceives and approaches the day to day demands of their chronic condition is critical, and comparative effectiveness studies of interventions to improve self-care management behaviors are needed.

In addition, treatment regimens that take into account the social context of adolescents and their families are more likely to promote successful medication adherence. We found in this sample with Type 2 diabetes that the morning dose posed more of a challenge than the

afternoon/evening dose and that there was a primary reliance on family support to manage the overall care regimen. Not surprisingly, youth who reported using “family help only” were, on average, about 1 year younger than those who reported using “routines only”. Here, the large and long-standing body of research pertaining to the self-management of Type 1 diabetes in adolescents would suggest that multi-component treatment regimens (i.e. those that attend to both family communication processes and individual behavioral strategies) are optimal at this stage [23, 24]. Small, focus group analyses conducted by Auslander et al [25] and Mulvaney et al [26] provide some support for this premise that self-management routines are a maturational task and adolescents with Type 2 diabetes, similar to youth with Type 1 diabetes, must be helped to achieve greater self-efficacy and skill. Thus, family support, education, and communication strategies that guide and reinforce youth autonomy are also recommended.

This study also examined how the reminder strategies utilized by this sample of youth corresponded to medication adherence rates over time. Given that the most general barriers (forgetting, disrupted routines) were also the most prevalent in this sample, it was encouraging to observe that adolescents who paired their diabetes medications with daily routines were indeed found to have better overall adherence to medications. Behavioral problem-solving interventions that train individuals to develop personalized strategies in response to environmental cues are also worthwhile and have been integral to work in adults with Type 2 diabetes[27]. Prior pediatric research has shown that youth with complex chronic illnesses do show modest improvements in regimen adherence and health outcomes when such interventions are implemented [4]. In this regard, it is worth noting that when the TODAY study commenced in 2004 very few youth in the cohort were utilizing technology (i.e., smart phones, social media) to support adherence. Capitalizing on these innovations and promoting access specifically for youth with Type 2 diabetes to improve routine self-management warrants further study.

There are limitations to the current study. Diabetes medication barriers were assessed only for youth identified as having missed one or more doses of medication since the previous visit. Participants who were presumably medication adherent in the previous 3–4 months were not queried further so we were not able to determine whether this group with “no missed doses” experienced no problems or were simply more effective in launching strategies to overcome them. Additionally, as reported by Katz et al [9], there are inherent limitations to the pill count method used to quantify the degree to which TODAY youth were taking their medications as prescribed, namely pills can be removed easily from blister packs and discarded. Lastly, the assessment of oral medication barriers and strategies was based on a simple checklist approach. Although there were numerous opportunities to interact and discuss regimen behaviors with trained and supportive clinical specialists, it is possible that “I just forgot” masked more nuanced barriers or perceptions that participants either could not, or would not, articulate. Better adherence assessments[28] or qualitative methods may be better suited to address some of these limitations.

In conclusion, the current study systematically quantified barriers and strategies related to medication adherence in a large diverse sample of youth with Type 2 diabetes and examined whether any of the strategies attempted resulted in improved adherence. We found that

global and specific forgetting was highly prevalent and that youth looked to family and their own behavioral skills to improve their adherence. An important implication of the current study is that although Type 2 diabetes in youth is complex, chronic and associated with unremitting beta cell failure, the developmental and behavioral characteristics associated with medication adherence strategies for youth with this condition appears to be more similar than different than youth with other chronic and complex pediatric conditions. A more uniform approach to family communication, self-management and regimen adherence behaviors for serious pediatric conditions, including Type 2 diabetes, may prove to be the most fruitful.

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Materials developed and used for the TODAY standard diabetes education program and the intensive lifestyle intervention program are available to the public at https://today.bsc.gwu.edu/.

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Table 1

Frequency/percentage of TODAY participants at 6, 12, & 24 months reporting different categories of oral medication barriers

Study visit	Month 6	Month 12	Month 24
N of participants prescribed oral diabetes medications	611	583	525
N (%) of participants who missed doses of study medications	423 (69.2%)	422 (72.4%)	414 (78.9%)
			P-value = 0.0011[1]
Number of barriers reported[2]:			
1	56.0%	63.0%	63.0%
2	32.6%	24.6%	25.9%
3+	11.4%	12.3%	11.1%
Specific barriers reported[2]:			
Forgets/misses in general	39.3%	43.2%	42.7%
Forgets/misses a particular dose	21.9%	20.9%	23.0%
Spends a few days away from home	9.5%	8.1%	6.5%
Disruption of routine due to new personal/family issues	9.3%	9.3%	7.2%
Lack of/change in family support	5.7%	6.2%	8.4%
Size of pill, swallowing is a problem	5.1%	6.7%	9.0%
Lost or misplaced pills/no follow-up	4.1%	3.1%	4.2%
Inter-current illness, temporary protocol break	3.3%	0.9%	1.7%
Negative perception of medication and diabetes	2.9%	4.8%	7.6%
Gastrointestinal reaction	2.8%	2.7%	3.6%
Depressed mood or other psychiatric issue	2.3%	2.1%	2.7%
Permanently discontinued study medication	0.0%	0.0%	0.4%
Believes pill cause weight gain/edema	0.0%	0.0%	0.0%

[1] P-value for differences in proportion of participants who missed doses of study medications across the three time points.

[2] Barriers were only assessed among participants who missed doses of study medications since the last visit; Visit form instructions were to check all barriers that applied (i.e. frequencies of specific barriers reported are not mutually exclusive).

Table 2

Overall baseline characteristics of TODAY participants reporting missed doses of oral diabetes medications (at the six-month visit) and by the number of barriers reported

	# of Oral Diabetes Medication Barriers at 6-Months				
Baseline Characteristics	**Overall (n=423)**	**1 barrier (n=232)**	**2 barriers (n=135)**	**3+ barriers (n=47)**	**P-value[1]**
Age (years; mean ± SD)	13.9±2.0	13.8±2.1	13.9±2.0	14.1±1.9	ns
% Female	61.5%	62.5%	61.5%	63.8%	ns
Race-Ethnicity (%)					
Non-Hispanic Black	33.6%	31.5%	40.7%	25.5%	ns
Hispanic	40.4%	43.5%	37.8%	40.4%	
Non-Hispanic White	19.4%	19.0%	16.3%	23.4%	
Other	6.6%	6.0%	5.2%	10.6%	
Highest Household Education (%)					
Less than high school	24.8%	25.8%	26.1%	17.0%	ns
High school or equivalent	26.0%	25.8%	28.4%	21.3%	
Some college	33.4%	31.9%	32.1%	42.5%	
Graduate degree	15.6%	16.6%	13.4%	19.2%	
Annual Household Income (%)					
<$25,000	44.2%	43.3%	44.3%	45.0%	ns
$25,000–49,999	31.2%	29.3%	34.4%	35.0%	
≥$50,000	24.6%	27.4%	21.3%	20.0%	
Household Composition (%)					
Both biological parents	39.5%	42.5%	38.3%	29.8%	ns
One biological parent	50.1%	47.8%	51.9%	55.3%	
Neither biological parent	10.4%	9.6%	9.8%	14.9%	
Depressive Symptoms (%)[2]	13.9%	12.6%	15.0%	15.2%	ns
Randomized Treatment Arm (%)					
Metformin	33.3%	33.6%	28.9%	40.4%	ns
Metformin + Rosiglitazone	31.9%	32.3%	32.6%	31.9%	
Metformin + Lifestyle	34.8%	34.1%	38.5%	27.7%	

[1] P-value is for differences in baseline characteristics across the number of barriers reported among participants who missed doses of study medications at month 6 in the study. 'ns' indicates not significant ($P > 0.05$).

[2] The presence of clinically significant mood impairment or depressive symptoms within the last 2 weeks was indicated by a score on the Children's Depression Inventory (CDI) ≥ 13 (for participants <16 years old) or a score on the Beck Depression Inventory (BDI) ≥ 14 (for participants ≥ 16).

Table 3

Frequency/percentage of TODAY participants at 6, 12, & 24 months reporting different oral medication adherence strategies[1]

Study visit	Month 6 (n=584)	Month 12 (n=554)	Month 24 (n=500)
Number of strategies reported[1]			
0	11.6%	10.8%	16.2%
1	63.0%	61.7%	62.2%
2+	25.3%	27.4%	21.6%
			P-value = 0.0304
Strategies reported[2]:			
Uses family help	58.7%	61.2%	52.5%
Uses schedule or routine	47.4%	48.9%	45.6%
Uses reminder device	8.7%	7.0%	7.8%
Increases contact with staff/change in staff	1.2%	1.3%	1.4%

[1] P-values shown are based on a test examining differences in # of strategies reported across the three time points.

[2] Visit form instructions were to check all strategies that applied (i.e., frequencies of specific strategies reported are not mutually exclusive).