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REVIEW

Addressing the Burden of Multiple Daily Insulin Injections in Type 2 Diabetes with Insulin Pump Technology: A Narrative Review

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ABSTRACT

The growing prevalence of type 2 diabetes (T2D) remains a leading health concern in the US. Despite new medications and technologies, glycemic control in this population remains suboptimal, which increases the risk of poor outcomes, increased healthcare resource utilization, and associated costs. This article reviews the clinical and economic impacts of suboptimal glycemic control in patients on basal-bolus insulin or multiple daily injections (MDI) and discusses how new technologies, such as tubeless insulin delivery devices, referred to as "patch pumps", have the potential to improve outcomes in patients with T2D.

Keywords: Insulin pump; MDI; Patch pump; Type 2 diabetes

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Key Summary Points
Many individuals with type 2 diabetes (T2D) have suboptimal glycemic control and may require basal-bolus insulin therapy.
The transition from oral or basal insulin therapy to multiple daily insulin injections (MDI) may result in suboptimal adherence, persistence and glycemic outcomes, and increased health care resource utilization and costs.
Insulin pumps can reduce the burden and complexity of MDI therapy, improve glycemic outcomes, reduce insulin utilization, and costs in T2D previously on MDI.
Use of tubeless patch pumps can further reduce the burden of MDI therapy and eliminate complexity of conventional insulin pumps.

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INTRODUCTION

An estimated 38.4 million Americans are living with diabetes; more than 32 million have type 2 diabetes (T2D) [1]. The increasing prevalence of T2D is driven mainly by the increasing prevalence of obesity, which now affects an estimated 123 million adults and children/adolescents in the US [2].

Despite the availability of newer classes of medications, innovative glucose-monitoring technologies, and advanced insulin delivery systems, people with T2D are often not achieving their glycemic goals [3]. This is particularly relevant for racial/ethnic minority and lower socioeconomic populations who are disproportionately impacted by T2D, poor glycemic control, and its associated complications [4]. Moreover, the percentage of Americans with T2D who achieved a glycated hemoglobin (HbA1c) < 7.0% declined from 57.4 to 50.5% from 2010 through 2018 [3]. Persistent elevated glucose levels result in several micro- and macrovascular complications, including coronary artery disease (CAD), peripheral artery disease (PAD), cerebrovascular disease, nephropathy, neuropathy, and retinopathy [5].

Transitioning from oral medications to injectables is often needed to achieve glycemic control. The addition of glucagon-like peptide-1 receptor agonist (GLP-1 RA) formulations is recommended for most individuals, particularly those with underlying cardiovascular disease [6]. However, adding basal insulin and, eventually, bolus insulin is often required due to the progressive nature of T2D [7]. The need for basal-bolus insulin therapy may also arise earlier in individuals who cannot tolerate the side effects (e.g., gastrointestinal) of GLP-1 RA [8] or afford these medications due to inadequate insurance coverage or socioeconomic status. Results from real-world studies have shown that discontinuation rates for GLP-1 RA medications are higher than reported in randomized trials [9]. One retrospective cohort study showed that in individuals with T2D who were started on GLP-1 RA therapy, 35.5 and 40.8% were nonadherent and 45.2 and 64.7% had discontinued therapy at 12 and 24 months, respectively [10]. Weiss et al. found that 47.7 and 70.1% of adults started on a GLP-1 RA had discontinued therapy at 12 and 24 months [11]. However, adherence and persistence to basal-bolus insulin therapy in adults with T2D also remains suboptimal.

In this narrative review, we describe the clinical and economic impacts of suboptimal glycemic control with multiple daily insulin injections (MDI) and discuss how new technologies, such as tubeless insulin delivery devices, referred to as "patch pumps", have the potential to improve insulin adherence, therapy persistence, and glycemic control, in addition to increasing treatment satisfaction, reducing the barriers to insulin pump therapy, and lowering costs of their overall diabetes management compared with MDI therapy in individuals with T2D [12]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Rationale for Insulin Therapy

T2D is a progressive, complex metabolic disorder characterized by progressive deterioration of pancreatic beta cell function, increasing insulin resistance in muscle and adipose tissue, unrestrained hepatic glucose production, and other hormonal deficiencies. With progressive worsening of insulin resistance over time, the body attempts to compensate by secreting more insulin [7]. As the beta cells become unable to produce enough insulin to normalize glucose, individuals will require treatment with exogenous insulin, starting with basal insulin and, eventually, multiple daily insulin injections (MDI) using basal plus bolus insulin [13].

Although initiation of insulin therapy often occurs late in disease progression [14], early insulin initiation can result in long-lasting restoration of beta-cell function [15]. Investigators have reported durable remission of hyperglycemia in up to 50% of cases [16–19]. The lack of progress in building on such promising therapeutic interventions remains one of the persistent treatment enigmas in diabetes management.

Root Causes of Poor Glycemic Control

Therapeutic Inertia

A major driver of poor glycemic control in T2D is therapeutic inertia, defined as failure to intensify or deintensify therapy as needed [20]. This is particularly relevant to delays in initiating and intensifying insulin therapy. As reported in a 2018 systematic review by Khunti et al. the time to treatment intensification from noninsulin medications to basal insulin therapy is often delayed by up to 7 years in patients with HbA1c levels of ≥ 8.0%, and the average time required to transition patients from basal-only insulin to basal plus mealtime insulin is 3.2 years [14].

Currently, less than 50% of patients with T2D with persistent hyperglycemia are treated with insulin [21], potentially limiting their ability to achieve recommended glycemic targets [22]. In a large retrospective database analysis, investigators reported that insulin was used by 54.7% of those achieving an HbA1c level ≤ 7.0% but only 26.3% of those with an HbA1c > 7.0% [21]. As reported in a cohort covered primarily by commercial insurance, only 5.8% of patients with T2D who are receiving medication therapy to manage their diabetes are treated with basal-bolus insulin therapy [23]. Although basal-bolus therapy has been proven effective in achieving and sustaining optimal diabetes control, > 80% of patients on basal-bolus regimens have an HbA1c of > 7.0%, and 40% have an HbA1c of > 9.0 [23].

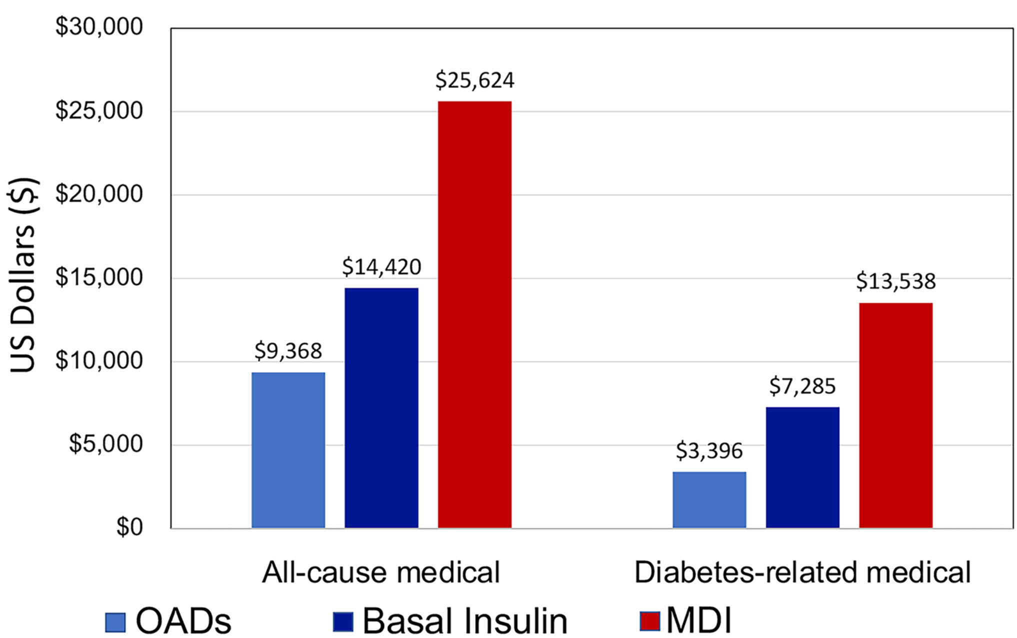

Fig. 1 Patients with type 2 diabetes (T2D) who progress to basal-bolus therapy account for higher all-cause and diabetes-related medical costs [23]. *OADs* oral antidiabetic drugs, *MDI* multiple daily insulin injections

Poor glycemic control in adults with T2D receiving basal-bolus (MDI) insulin is associated with higher medical costs and health care resource utilization compared to other treatment regimens. In a retrospective claims analysis of 225,135 patients with T2D, Brixner et al. observed higher 1-year costs per-patient driven by increased hospitalizations and emergency room visits (all-cause and diabetes related) among those treated with MDI therapy ($n = 13{,}181$) compared with those treated with oral antidiabetic drugs (OAD) ($n = 188{,}230$) or basal-insulin only ($n = 23{,}724$) [23] (Fig. 1).

Nonadherence and Nonpersistence with Prescribed Insulin Regimens

Although clinician reluctance to add bolus insulin to patients' basal insulin regimen plays a role in therapeutic inertia, patients' nonadherence to their prescribed diabetes regimens also plays a role. Peyrot et al. found that 73% of physicians reported their patients (88% T2D) do not take insulin as prescribed despite advances in insulin and insulin delivery, with omission of bolus insulin injections averaging 5.7 days per month [24]. Yavuz et al. reported that among 433 individuals with T2D, nonadherence to insulin therapy was observed in 44.3% of patients, including all-cause treatment discontinuation (24.0%) and nonadherence to daily insulin (20.3%) [25]. Among participants, 52% of those receiving basal-bolus therapy reported skipping doses compared to 19% on premixed insulin and 29% on basal insulin.

In a recent study by Edelman et al., investigators assessed persistence among adults with T2D using basal-bolus insulin in a retrospective matched cohort study over a 12-month period [26]. Among the patients who met the inclusion criteria, only 21.1% were persistent with their prescribed therapy. Non-persistence was associated with significantly higher HbA1c than those who were persistent (8.84 vs. 8.38%, $p < 0.005$, respectively) and lower treatment success (39 vs. 55%, $p < 0.009$, respectively). Treatment success was defined as a ≥ 1.0% HbA1c decrease from baseline of and/or baseline HbA1c ≥ 7.0% with post-index HbA1c < 7.0%.

Barriers to Adherence and Persistence

The barriers to optimal utilization of MDI insulin therapy are multifactorial, which contributes to therapeutic inertia. Major patient barriers include fear of injections, complexity of the dosing regimen, difficulty of injecting, fear of hypoglycemia, weight gain, disruption of daily activities, and social embarrassment [27]. For clinicians, barriers often include a lack of knowledge, training, and experience with insulin therapy, concerns about the risk of hypoglycemia, weight gain, and patient adherence due to perceived lack of patient motivation or socioeconomic status [28]. Fear of needles and self-injection have also been reported among individuals treated with GLP-1 RA medications [29].

Another barrier to optimizing insulin therapy is underutilization of diabetes technologies. In a recent cross-sectional survey of 76 primary care providers, the majority of respondents reported they were uncomfortable initiating (88%) or adjusting (89%) conventional insulin pump therapy for their patients with T2D [30]. In another cross-sectional pilot survey that included 41 rural clinic healthcare providers, less than half (47.4%) reported prescribing any diabetes devices due to lack of experienced personnel to provide initial training and ongoing insulin management [31].

Advances in insulin pens have led to the development of insulin "smart pens" that offer connectivity with "connected" insulin pens featuring built-in memory, download capability, and connectivity with continuous glucose monitoring (CGM) devices and some blood glucose monitoring (BGM) meters. In a recent proof-of-concept study using smart pens in individuals with T1D using MDI in conjunction with CGM, Adolfsson et al. noted improved adherence to insulin therapy as evidenced by fewer missed bolus doses compared with use of conventional insulin pens [32]. However, despite improvements with traditional insulin pen technology, many of the patient obstacles associated with MDI such as injection burden, inconvenience and interference with daily living, time commitment, and social embarrassment are not addressed.

Economic Impact of Nonadherence/Nonpersistence and Clinical Outcomes

The total estimated cost of diagnosed diabetes in 2017 was $327 billion; most of these costs were due to suboptimal diabetes management [33]. Approximately $149 billion was directly related to treating diabetes complications (e.g., hospitalizations, emergency room [ER] visits, non-diabetic prescription medications), with another $90 billion in indirect costs resulting from work-related absenteeism, reduced productivity, unemployment from chronic disability, and premature mortality. Notably, approximately 61% of diabetes costs are for adults with T2D age ≥ 65 years [33]. Among Medicare beneficiaries aged ≥ 65 with T2D, the annual estimated median costs associated with diabetic complications per person are $58,763 [34]. As reported by Eby et al. the outpatient, acute, and total costs for nonadherence to basal-bolus regimens are significantly higher than for an adherent cohort [35] (Fig. 2A).

Although higher drug costs were observed in the insulin adherent cohort, overall total yearly costs were significantly greater for the cohort that was non-adherent to their basal-bolus therapy. Similar costs differences trends were observed in the Edelman et al. analysis of therapy persistence discussed earlier [26] (Fig. 2B). In addition to reduction in costs, patients who are adherent on basal-bolus insulin therapy have demonstrated significantly better quality-of-life (QoL) scores, less impairment of work and daily living activities, and greater work productivity compared with nonadherent patients [36].

Rationale for Patch Pumps

Use of insulin pump therapy in individuals with T2D improves glycemic control [37], increases treatment satisfaction [37], reduces bodyweight [36], and improves quality of life in adults previously treated with MDI [38]. However, therapy with conventional insulin pumps, which are small computerized devices that are worn outside the body and deliver insulin into the subcutaneous tissue through an infusion set, remains under-utilized [39] due to a variety of factors, including negative perceptions by patients (cost, complexity, pain, complexity) [40], clinician perception of patient acceptance [41], clinician time/resource constraints, and clinician inexperience with initiating insulin pump therapy [30]. Kinking of the tubing with conventional pumps can also be a serious issue, which can result in reduced, delayed, interrupted, or failed infusion of insulin and subsequent hyperglycemia [40]. Another

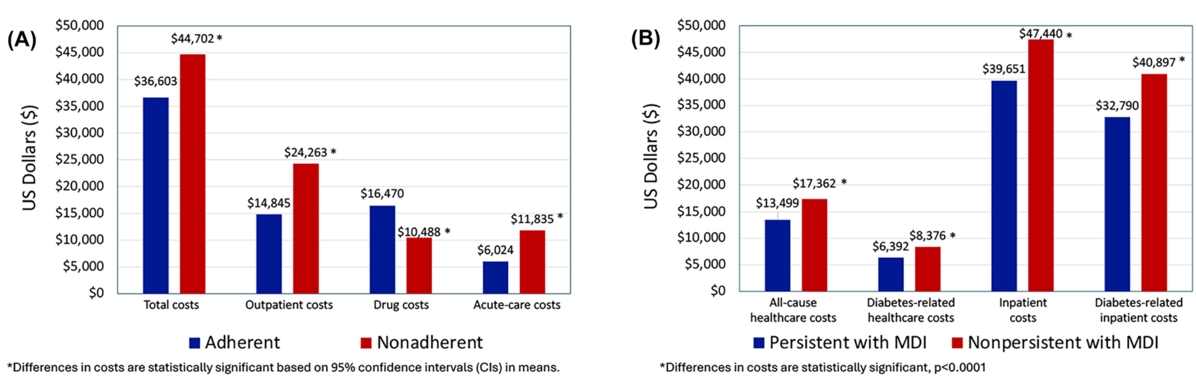

Fig. 2 **A** Patients with type 2 diabetes (T2D) who are nonadherent to basal-bolus therapy account for higher all-cause medical costs [34]. **B** Mean annual all-cause and diabetes-related healthcare costs associated with persistence vs. nonpersistence with MDI therapy [26]. *MDI* multiple daily insulin injections

disadvantage of conventional insulin pump use is the "siphon effect", which can occur in the tubing when the insulin pump's height relative to the cannula changes during various daily activities [42]. This can affect the accuracy of insulin delivery [42].

Unlike conventional insulin pumps, patch pumps are worn directly on the skin without external tubing and deliver insulin through a small needle that is connected to the device. Patch pumps are currently available in several variations, including non-programable basal/bolus, non-programable bolus only, programable basal/bolus with a wireless controller, and automated insulin delivery (AID) systems. AID systems utilize an algorithm that continuously adjusts insulin delivery in response to real-time sensor glucose levels, residual insulin action and other inputs (e.g., meal intake and exercise announcement) [43].

Both conventional pumps and patch pump devices effectively address the barriers to adherence by eliminating the need for MDI. However, because patch pumps are smaller than conventional insulin pumps and lack external tubing [44], insulin administration is rendered more convenient and discreet [40]. These patch pumps eliminate the potential risk of tubing kinks or dislocation, which may interrupt insulin delivery [45].

Additional advantages of patch pump devices include convenience and flexibility. Unlike conventional insulin pumps, most patch pumps can be worn during daily activities such as showering, swimming, and exercise. However, patch pumps must be replaced with a new device if they are removed and any remaining insulin is discarded [46]. Moreover, the small reservoir size requires patients to frequently refill the reservoir or replace the device, depending on the type of device used [40]. Whereas current patch pumps feature reservoirs that accommodate up to 200 units of insulin, the average insulin requirement of patients with T2D receiving MDI therapy (≥ 3 injections/day) has been shown to be approximately 109 units/day [47], suggesting that patients may need to change or refill their device at least once every 2 days.

Economic Benefits

Patch pumps are also less costly up front than conventional pumps and often less costly overall compared with other basal-bolus insulin delivery methods (conventional insulin pump or MDI) [48–50]. This is particularly important if an individual chooses to discontinue therapy. With disposable patch pumps, individuals "pay as they go," typically on a monthly basis, versus incurring the high up-front cost of a conventional pump.

Patch pumps have demonstrated significant clinical and economic benefits for patients with T2D on daily MDI therapy, such as improved glycemic control [51–53], reduced frequency and severity of hypoglycemia [53], improved treatment satisfaction [36], reduced diabetes burden [53, 55], and cost savings through reductions in total daily insulin dosages (TDD) [54, 56]. In a recent retrospective observational study of 3592 adults with T2D who transitioned from either conventional insulin pump therapy or MDI to a programable, multi-day wear patch pump device, investigators reported significant improvements in both study groups, with reductions in HbA1c (– 1.5% and – 0.9%, respectively, both $p < 0.0001$) and TDD (– 35 U and – 20 U, respectively) [52].

Layne et al. reported findings from a multicenter, retrospective study that assessed glycemic control in adults with T2D using a programable, multi-day wear patch pump vs. previous MDI therapy. At 3 months, investigators observed significant reductions in both HbA1c (– 1.2%) and TDD (– 27.6 U), both $p < 0.001$) [51].

A retrospective analysis of a large electronic medical record (EMR) database showed similar results in a cohort of 103 patients with T1D ($n = 4$) and T2D ($n = 99$) who were naïve to insulin therapy or who transitioned from other traditional modes of insulin delivery to a daily non-programable patch pump device [50]. At 14 months, the mean HbA1c decreased 1.7% and TDD decreased from 84 to 67 U ($p < 0.05$). Among those treated with basal-bolus therapy, the total direct pharmacy cost decreased from $1122 to $1097 over the 14-month study period. In an earlier retrospective study of 116 adults with T2D, investigators reported that total per-patient per-month (PPPM) costs of insulin therapy were significantly lower with insulin delivery with a daily patch pump device vs. MDI ($118.84 vs. $217.16, $p = 0.013$).[57]

In a pragmatic clinical trial that compared the real-world effectiveness of a daily, non-programable patch pump device vs. standard delivery of insulin in adults with advanced T2D, Cziraky et al. reported reductions in cost per day among patch pump users compared to an MDI cohort ($30.59 vs. $32.20, respectively, $p = 0.006$) with greater cost effectiveness per 1.0% reduction in HbA1c ($24.02 vs. $58.86, respectively) [48].

CONCLUSIONS

Retrospective observational studies have demonstrated that many individuals with T2D who progress to basal-bolus/MDI insulin therapy are at risk for poor glycemic control, demonstrate poor insulin adherence and persistence, and incur increased health care resource utilization and costs relative to other treatment cohorts. New technologies such as insulin patch pumps have demonstrated improved glycemic control, reduced costs, and improved patient outcomes. However, considerable education is needed to raise awareness about newer delivery devices such as patch pumps among clinicians and patients. Importantly, these technologies should be accessible and affordable to patients who may potentially benefit from their use. The diabetes community, including providers, payers, and patients, need to be more aware about the availability of patch pumps, and how they may address the limitations of traditional MDI and conventional insulin pump therapy. Manufacturers need to develop patch pump devices that address the needs of patients with T2D who require higher insulin dosages. Moreover, they need to inform providers and patients about the availability of patch pumps and how they may address the limitations of traditional MDI and conventional insulin pump therapy. These same target audiences urgently need to be informed about how they may improve clinical and economic outcomes, reduce the burden of diabetes, and improve patients' quality of life.

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Declarations

Conflict of interest. Diana Brixner has received consulting fees from Embecta, Tandem, and Sanofi. Steven V Edelman has received consulting fees from Embecta. Ray Sieradzan is an employee of Embecta. James R. Gavin III has received from Embecta and served on advisory boards and/or speaker bureaus for Abbott Diabetes Care, Novo Nordisk, Medtronic, and Boehringer Ingelheim.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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