

## Analysis of Symposium Articles on Insulin Pen Devices and Alternative Insulin Delivery Methods

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### Abstract

Insulin therapy is a fundamental component of diabetes management, yet there is often resistance to insulin initiation by both prescribers and patients. A barrier to insulin use is the perceived shortcomings with the traditional vial-and-syringe administration method (inconvenience, difficulty of use, association with disease and addiction, etc.). This symposium in the journal discusses the advantages of alternative insulin delivery methods, primarily insulin pen devices. Although these administration methods, especially insulin pens, have some clear advantages over the vial/syringe, there are also limitations to their use and careful patient selection and education are still needed.

*J Diabetes Sci Technol 2010;4(3):558-561*

Since the discovery and purification of insulin by Banting and Best in 1922, the clinical characteristics and delivery methods of insulin have been refined constantly. Despite its proven place in therapy in the management of diabetes mellitus, insulin is underprescribed by health care providers and underused by patients. A number of factors are thought to contribute to this underutilization, including difficulty with insulin administration using the traditional syringe-and-vial method. In the past 40 years, two major advances in the delivery of insulin—pen devices and continuous subcutaneous insulin infusion—have been introduced to address this and other barriers to insulin management. The articles in this symposium of this journal review the development, benefits, limitations, and practicality of these insulin delivery methods.

Limited awareness of the benefits of insulin pen devices among providers and patients is thought to lead in their underutilization in the United States. The article entitled “Evolution of Diabetes Insulin Delivery Devices” discusses the benefits and limitations of insulin pens and insulin pumps over the traditional vial and syringe.<sup>1</sup> Advantages of insulin pen devices described by the author include improved accuracy of measured doses, easier administration, higher patient preference, improved adherence, and better patient satisfaction and quality of life.<sup>1</sup> Although there are indeed clear advantages to using insulin pen devices, caution should be used when interpreting some of the studies cited in this review. For example, support for greater accuracy using insulin pens was based on data from pediatric patients with type 1 diabetes and only

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**Abbreviations:** (MPR) medication possession ratio

**Keywords:** adherence, insulin administration, insulin pen, insulin pump

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at doses less than 5 units. Data regarding improved adherence with insulin pens are based on two studies that utilized claims data and the medication possession ratio (MPR). These studies (from the same group of authors who used what appears to be the same large database for both studies) reported statistically significant improvements in the MPR from 62 to 69% and from 59 to 68% in patients with type 2 diabetes who switched from vial-and-syringe insulin administration to insulin pen administration.<sup>2,3</sup> The author noted that the MPR cannot measure whether patients administer their medications accurately or share or waste their medications. However, other limitations to using the MPR to assess insulin adherence should be considered. The MPR is an imperfect measure of oral medications and is even more inaccurate when it comes to liquid medications. Given the difficulty in calculating the day supply for insulin vials (in-use vials are recommended to be discarded after 28 days even if there is insulin remaining in the vial; 42 days with insulin detemir), it is not clear how the authors of these adherence studies minimized the inaccuracies of assessing the insulin MPR for a very large claim database. The MPR calculation may be biased more favorably toward insulin pens, as it is somewhat easier to determine the day supply for pen devices. In addition, the studies included patients who were switched from using single insulin with vial and syringe to insulin pen devices containing either single insulin or premixed insulin (i.e., insulin aspart mix 70/30). Furthermore, even with the improvement in the MPR to 68–69%, this is still an adherence level below the generally accepted optimal MPR adherence rate of at least 80%. Finally, the author only mentions cost and the inability to mix insulins as barriers to insulin pens, but other potential limitations, such as mechanical failure, possible user error, not all insulin regimens are available as pen devices, and the lower maximum dosage that can be administered per injection compared to syringe administration, should also be noted.

Underutilization of insulin pens in the United States is also likely due to health care professionals' unfamiliarity with differences among the pens and with actual operations of the pens. In her article, Pearson reviews practical concepts to initiating and using insulin pen devices.<sup>4</sup> This article includes a comprehensive table of insulin pens currently available on the U.S. market and provides nuances of several pen devices. The article also includes general instructions on how to operate insulin pens, as well as clinical pearls on pen selection, which will be especially useful in increasing health care professionals' comfort with insulin pens and with

teaching patients how to use these devices. A few limitations to this article should be noted. Although the author includes information regarding insulin pens manufactured by Eli Lilly, Novo Nordisk, and Sanofi-Aventis, the article tends to emphasize comparative studies with results that are more favorable toward Novo Nordisk pens, which may create a positive bias toward these products. Additionally, the review focuses on benefits of insulin pens over the vial/syringe method and somewhat understates the benefits that can still be achieved using the vial and syringe.

In addition to raising awareness of insulin pen devices, knowing factors that are influential in their use can be beneficial to health care providers. Lee and colleagues<sup>5</sup> studied predictors to initiating insulin in patients with type 2 diabetes using a variety of insulin delivery systems. Study investigators examined data extracted from medical insurance claims thoroughly to evaluate variables that could impact study outcomes, such as demographics, insurance plan type, and provider information. In addition, the availability of insulin pens at the insurance level and adherence to antihyperglycemic agents were also assessed. Results of the study showed that, not surprisingly, previous insulin pen use and having an endocrinologist visit were the best predictors of prefilled insulin pen use over vial/syringe.<sup>5</sup> Including patients with type 1 diabetes in a future study may offer more insights to patient preferences regarding these alternative delivery systems, as this population would likely use these types of insulin administration devices more widely. In addition, similar studies may be beneficial in determining predictors of insulin use based on type of insulin (i.e., basal versus bolus or premixes versus individual insulins).

Another advantage of insulin pen devices over the vial and syringe is that they are typically easier to use by those with visual impairments or dexterity problems. Refinements made to insulin pen devices (e.g., audible clicks and large dose displays) have made insulin use more manageable for patients with visual impairments that may or may not be diabetes related. Despite this, major manufacturers warn against using their insulin pens in visually impaired patients.<sup>6</sup> In their study, Williams and Schnarrenber<sup>6</sup> compared dosing accuracy in visually impaired and sighted patients. At the end of the study, no significant correlation in dosing accuracy was found based on the visual status of patients. However, with the exception of sample size, visually impaired and sighted patients were not matched equally at baseline. The visually impaired group was younger,

included more males, had a longer duration of diabetes, and had a larger proportion of patients using insulin at baseline. Although not considered a statistically significant difference, the sighted group made a larger number of clinically significant dosing errors compared to the visually impaired group. Only one insulin pen device was studied, the HumaPen® Luxura™. Although more complex to use compared to other pens, further research regarding feasibility of use and dosing accuracy of other pens may provide more insights on which pens may be more beneficial in the visually impaired population. Along with the numerous refinements made to pen devices over the last two decades, this study provides the needed support for a wider use of insulin pens in visually impaired patients.

Although insulin pens may offer several advantages for patients with diabetes, they are not beneficial if a patient forgets to use it. The HumaPen® Memoir™ device was developed to address this barrier. Although a good review, the authors (all from the two companies that developed and market this device) may have been more effective in providing insights to others interested in creating novel insulin delivery products by detailing their specific trials and tribulations rather than providing a very general guide to product development. In addition, the authors indicate that the primary reason for development of this novel insulin pen was to address the unmet need of nonadherence due to patient forgetfulness, yet this was not mentioned as an outcome in their clinical trial prior to market launch.<sup>7</sup>

In addition to pen devices, even more advanced insulin delivery administration methods that can enhance insulin management are either available or in development. The article by Selam summarizes nicely the features, benefits, and potential complications of insulin pumps.<sup>1</sup> A potential new insulin delivery system and new insulin type are described in the article entitled "Development and Testing of Solid Dose Formulations Containing Polysialic Acid Insulin Conjugate: Next Generation of Long-Acting Insulin."<sup>8</sup> This article reported on the characteristics of a novel insulin analog (recombinant insulin bound to the biopolymer polysialic acid to lengthen the duration of action) that can be injected as a solid dose formulation (small rods) using a needle-free delivery system. This solid dose injector is said to be easy to use, inexpensive, and less painful. Results from *in vitro* and *in vivo* (rats) testing are presented. If this delivery system is ultimately approved and marketed, this could represent a major advancement in the

management of diabetes, as it can address some of the major barriers to insulin administration.

In summary, insulin pen devices can offer several advantages over the traditional vial and syringe, including improved ease of use, patient acceptability, dosing accuracy, and patient satisfaction, which may lead to improved treatment adherence. A variety of insulin pens are now available, including prefilled insulin pens, reusable insulin pens, insulin pens with a memory feature, and (in the future) needle-free insulin pens. Although numerous advancements have been made to insulin pen devices, there are still some limitations. Insulin pens have a higher upfront cost compared to vial/syringe, although the potential for better diabetes control related to improved adherence and decreased hypoglycemia due to dosing accuracy may justify the initial upfront cost. Nevertheless, cost can be a major barrier to the prescribing of alternative insulin administration devices. For example, some Medicare Part D plans do not provide coverage for insulin pens or require a prior authorization request that outlines the clinical need for the device be submitted before approving payment. Additionally, pen devices and pumps are still subject to user error, as well as the possibility of mechanical malfunction, which can lead to worsened glycemic control.<sup>9-11</sup> Finally, more randomized controlled trials in a wider variety of patient populations (such as those with low health literacy, visual impairment, or dexterity problems) should be conducted to compare dosing accuracy, patient satisfaction, adherence, and efficacy of insulin pen devices versus vial/syringe.

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