Introduction

Insulin is delivered via devices that include syringes, pens, pumps and other technologies being tested in clinical trials.\(^1\) Traditionally, insulin was administered via syringe once or twice daily, but studies showed that intensive treatment, such as multiple insulin injections (MII) or continuous insulin infusions, provided better glucose control. Better glucose control led to less morbidity and mortality.\(^2\)\(^-\)\(^4\) Patients are reluctant, however, to undergo intensive insulin treatment using syringes, because of the pain associated with needle injections. They are also reluctant to use pumps for this purpose, because of the expense and the bulkiness of the device.\(^1\) Insulin pens are useful in overcoming some of these problems. They are easy to use, safe, accurate, less painful and discreet.\(^5\)

The first insulin pen, the Novolin-Pen by Novo Nordisk, was introduced in October 1986 (Kathleen Savage, Therapeutic Products Directorate, Ottawa: personal communication, 2003 October 15). Today, disposable and reusable pens are available on the Canadian market. An insulin cartridge is inserted into a reusable pen’s chamber and replaced when it is empty. The disposable pen is unit dose and discarded after use.

Research Questions

The following research questions were suggested by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA)’s Scientific Advisory Panel:
1. What are the implications for patients who are using insulin pens, given the current evidence?
2. How does the pen compare to the pump?
3. Are the refills (cartridges) interchangeable?

Assessment Process

Published literature was identified by searching MEDLINE® via PubMed (1966 to 28 August 2003). Retrieval was not limited by language. The CD-ROM version of The Cochrane Library (2003 Issue 3) was also searched.

Grey literature was obtained by searching the web sites of regulatory agencies, health technology assessment agencies, near-technology assessment agencies and clinical trials registries. The Google™ and other Internet search engines were used to search for web-based information.
Summary of Findings

1) Review of Evidence
Pens have been available for over 15 years. The studies that we found are older and mostly European. As a result, the pens used in the trials may not have been marketed or are no longer available in Canada.

We found 91 studies that evaluated the insulin pen in type 1 and type 2 diabetes mellitus. There were randomized cross-over studies, randomized studies, cross-over studies with no randomization, open-label studies, surveys and chart reviews. The comparators used included syringes, pumps and other pens. The duration of studies ranged from one week to 4.5 years, with sample sizes of eight to 20,262 participants. Most studies included a questionnaire to assess patients’ acceptance or preference. This review focused on randomized cross-over studies, with patients acting as their own control.

a) Pen Versus Syringe
A randomized cross-over design was used in 15 studies that compared insulin therapy via a pen to that via a syringe (Table 1). All studies assessed treatment effects on metabolic control and on acceptance by patients. The duration of studies ranged from six to 48 weeks, with sample sizes of 16 to 96 participants. Two studies focused on children and two on patients over the age of 60. All questionnaires used to assess patients’ preferences, except one, were not validated instruments. Results showed no significant difference for any of the surrogate outcomes measured, including the extent of glucose control, the need for insulin, the change in body weight and the number of hypoglycemic episodes. Most patients preferred the pen over the syringe.

<table>
<thead>
<tr>
<th>Author(s)</th>
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<tbody>
<tr>
<td>Arslanoglu et al., 2000</td>
<td>22</td>
<td>NovoPen II® versus conventional syringe twice daily</td>
<td>Children (8.2 to 19.6 years), type 1</td>
<td>6 months: 3 months on each treatment</td>
<td>Efficacy, patients’ acceptance, safety, cost</td>
<td>No significant difference in metabolic parameters. Nighttime hypoglycemia tended to occur later in patients on pen (7 a.m. instead of 3 a.m., p&lt;0.05). All patients found pens more convenient and less painful. Pens more expensive than syringes.</td>
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</table>
## Insulin Pen-fill Formulations

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### PRE-ASSESSMENT

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<tr>
<td>Chen et al., 1999¹³</td>
<td>19</td>
<td>NovoLet® (disposable)</td>
<td>Type 1 and 2</td>
<td>24 weeks: 12 weeks on each treatment</td>
<td>Efficacy, safety, patients’ acceptance</td>
<td>No significant difference in metabolic parameters. No significant difference in hypoglycemic episodes. 84% (16/19) preferred to continue treatment with pens. 68% (13/19) found no difference in pain.</td>
</tr>
<tr>
<td>Corsi et al., 1997¹⁴</td>
<td>21</td>
<td>NovoLet® (disposable)</td>
<td>Insulin-naive, &gt;60 years, type 2</td>
<td>16 weeks: 8 weeks on each treatment</td>
<td>Efficacy, safety, compliance</td>
<td>HbA1c significantly lower with pen (p&lt;0.02). No difference in insulin requirements, body weight and hypoglycemic episodes. All patients preferred pens.</td>
</tr>
<tr>
<td>Coscelli et al., 1995¹⁵</td>
<td>60</td>
<td>NovoLet® (disposable)</td>
<td>&gt;60 years, type 2 (except for one patient with type 1)</td>
<td>12 weeks: 6 weeks on each treatment</td>
<td>Efficacy, safety, patients’ acceptance</td>
<td>3 patients did not complete study because of difficulties understanding pen. Pre-lunch blood glucose lower with pen (p&lt;0.01). No difference in insulin requirements, body weight and hypoglycemic episodes. 90% of patients preferred pens.</td>
</tr>
<tr>
<td>Dunbar et al., 1994¹⁶</td>
<td>32</td>
<td>NovoPen II®</td>
<td>Type 1</td>
<td>4 months: 2 months on each treatment</td>
<td>Efficacy, patients’ acceptance</td>
<td>5 patients did not complete study (2 because of concerns about pen). No significant difference in metabolic parameters. 82.8% of patients preferred pens.</td>
</tr>
<tr>
<td>Engstrom et al., 1990¹⁷</td>
<td>40</td>
<td>NovoPen®</td>
<td>Insulin-dependent diabetes mellitus</td>
<td>24 weeks: 12 weeks on each treatment</td>
<td>Test pen with NPH insulin, efficacy, patients’ acceptance</td>
<td>No significant difference in metabolic parameters. More soluble insulin required in NPH pen group (p=0.04). Patients found NPH easy to re-suspend with pen. 38/40 chose to continue with pens for NPH dose.</td>
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<td>Fisken and Goulbourn, 1989&lt;sup&gt;18&lt;/sup&gt;</td>
<td>26</td>
<td>Basal-prandial schedule using NovoPen® with meals and syringe at bedtime versus conventional syringe twice daily</td>
<td>Insulin-dependent diabetes mellitus</td>
<td>32 weeks: 16 weeks on each treatment</td>
<td>Efficacy, patients’ acceptance</td>
<td>4 patients did not complete study (3 because of dislike of multiple injections). No significant difference in metabolic parameters. 21/23 patients preferred basal prandial treatment regimen.</td>
</tr>
<tr>
<td>Houtzagers et al., 1989&lt;sup&gt;19&lt;/sup&gt;</td>
<td>16</td>
<td>NovoPen® with meals and syringe at bedtime versus conventional syringe twice daily</td>
<td>Insulin-dependent diabetes mellitus</td>
<td>48 weeks: 24 weeks on each treatment</td>
<td>Efficacy, psychological assessment</td>
<td>No significant difference in metabolic parameters. Less anxiety in pen group (p&lt;0.05). 13/16 wanted to continue with pen treatment at end of study.</td>
</tr>
<tr>
<td>Hung and Wang, 1992&lt;sup&gt;21&lt;/sup&gt;</td>
<td>20</td>
<td>NovoPen II® versus conventional syringe</td>
<td>Insulin-dependent diabetes mellitus</td>
<td>24 weeks: 12 weeks on each treatment</td>
<td>Efficacy, patients’ acceptance</td>
<td>No significant difference in metabolic parameters. 9 patients preferred syringes, 8 preferred pens and 1 was undecided.</td>
</tr>
<tr>
<td>Jorgensen et al., 1988&lt;sup&gt;22&lt;/sup&gt;</td>
<td>50</td>
<td>Insuject® versus syringe for NPH (bedtime) insulin, all other doses with NovoPen®</td>
<td>Insulin-dependent diabetes mellitus</td>
<td>6 months: 3 months on each treatment</td>
<td>Test pen with NPH insulin, efficacy, patients’ acceptance</td>
<td>No significant difference in metabolic parameters. 86% found pens less complicated to use.</td>
</tr>
<tr>
<td>Kadiri et al., 1998&lt;sup&gt;23&lt;/sup&gt;</td>
<td>96</td>
<td>NovoPen 3® versus conventional syringe</td>
<td>Non-insulin-dependent diabetes mellitus patients who have failed treatment with oral agents and changes in diet</td>
<td>24 weeks: 12 weeks on each treatment</td>
<td>Safety, patients’ acceptance</td>
<td>18 did not complete study (15 for failure to comply with protocol). No significant difference in metabolic parameters. 68/76 preferred pen treatment.</td>
</tr>
</tbody>
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### Insulin Pen-fill Formulations

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<tr>
<td>Kolendorf <em>et al.</em>, 198824</td>
<td>19</td>
<td>NovoPen II® versus syringe for NPH (bedtime) insulin.</td>
<td>Insulin-dependent diabetes mellitus</td>
<td>24 weeks: 12 weeks on each treatment</td>
<td>Test pen with NPH insulin, safety, patients’ acceptance</td>
<td>No significant difference in metabolic parameters. 17/19 patients preferred pens. 18/19 wanted to continue with pens at end of study.</td>
</tr>
<tr>
<td>O’Hagan <em>et al.</em>, 199325</td>
<td>40</td>
<td>PenMix 30/70® (disposable) versus conventional syringe</td>
<td>Children (7 to 16 years)</td>
<td>6 months: 3 months on each treatment</td>
<td>Efficacy, patients’ acceptance</td>
<td>No significant difference in metabolic parameters. 95% of patients preferred pens.</td>
</tr>
<tr>
<td>Saurbrey <em>et al.</em>, 198526</td>
<td>16</td>
<td>NovoPen® with meals and syringe at bedtime versus conventional syringe</td>
<td>Insulin-dependent diabetes mellitus</td>
<td>6 weeks: 3 weeks on each treatment</td>
<td>Safety, efficiency, patients’ compliance</td>
<td>No significant difference in metabolic parameters. All patients found pens quicker and easier to use.</td>
</tr>
<tr>
<td>Tallroth <em>et al.</em>, 198927</td>
<td>18</td>
<td>NovoPen® with meals and syringe at bedtime versus conventional syringe</td>
<td>Insulin-dependent diabetes mellitus</td>
<td>6 months: 3 months on each treatment</td>
<td>Metabolic control, quality of life (instrument used: “Mood Adjective Checklist”)</td>
<td>No significant difference in metabolic parameters. Increase in freedom and improvement in mood and well-being seen in the pen group. All patients except one preferred pens.</td>
</tr>
</tbody>
</table>

#### b) Pen Versus Pump

Five studies compared insulin delivery via a pen to continuous subcutaneous insulin infusion by pump. Three of these were randomized cross-over studies (Table 2). All three assessed the effects of metabolic control and patients’ acceptance of the pen compared to the pump. One study lasted 20 weeks, while the other two lasted 12 months, with sample sizes of 10, 20 and 21 participants. One study showed no significant difference between the pen and the pump with respect to metabolic control. In another study, hemoglobin A1c (HbA1c) levels were significantly improved when both treatments were compared with baseline (p<0.001) and blood glucose levels were lower when the pump was compared with the pen (p<0.05). In the third study, blood glucose control and HbA1c levels improved when the pump was compared with the pen (p=0.01 and p=0.002 respectively).
More patients preferred the pen over the pump. All three studies, however, did not report the method of randomization. The similarity between groups was unknown. One study included an intent-to-treat analysis.

Table 2: Pen versus pump

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<tr>
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<tr>
<td>Bak <em>et al.</em>, 1987[26]</td>
<td>20</td>
<td>NovoPen® multiple injections with syringe at bedtime versus pump</td>
<td>12 months: 6 months on each treatment</td>
<td>Efficacy, insulin dose, patients’ acceptance</td>
<td>4 patients did not complete study because they disliked pumps. No statistically significant difference in metabolic control. Insulin dosage 11.4% higher with pens (p&lt;0.05). 80% of patients preferred pens.</td>
</tr>
<tr>
<td>Saurbrey <em>et al.</em>, 1988[29]</td>
<td>21</td>
<td>NovoPen® multiple injections with syringe at bedtime versus pump</td>
<td>20 weeks: 10 weeks on each treatment</td>
<td>Efficacy, patients' acceptance</td>
<td>2 patients did not complete study because they disliked pumps. HbA1c significantly improved with both treatments (p&lt;0.001). Blood glucose lower with pump compared with pen (p&lt;0.05). Blood glucose lower in both groups compared with entry (p&lt;0.02). Total daily dose of insulin unchanged. 12 patients preferred pens, 6 preferred pumps and 1 was unsure.</td>
</tr>
<tr>
<td>Schmitz <em>et al.</em>, 1989[30]</td>
<td>10</td>
<td>Insuject® multiple injections with syringe at bedtime versus pump</td>
<td>12 months: 6 months on each treatment</td>
<td>Efficacy, kidney function, patients’ acceptance</td>
<td>Blood glucose control and HbA1c better on pump compared with pen (p=0.01 and p=0.002 respectively). Insulin dose significantly decreased in pump group compared to pen (p=0.02). Kidney function unchanged. 4 patients preferred pumps, 6 preferred pens.</td>
</tr>
</tbody>
</table>
2) **Interchangeability of Cartridges and Availability of Pens**

Eli Lilly and Novo Nordisk make insulin cartridges; and reusable and disposable insulin pens in Canada. Both companies provide free reusable pens.⁶

The cost of disposable pens (prefilled syringes) ranges from $8.83 to $11.95 per 3 mL pen.⁷,⁸

The cost of insulin available in cartridges for use in reusable pens ranges from $2.20 to $3.50 per mL (100 U/mL cartridges). The cost of insulin available in vials for use in plastic syringes ranges from $1.60 to $2.50 per mL (100 U/mL vials).⁹ These costs exclude dispensing fees and the cost of the plastic syringes, needles and alcohol wipes. All provincial government-sponsored drug plans cover cartridges and none cover disposable pens.

Representatives for Eli Lilly and Novo Nordisk state that their respective cartridges cannot be used with each other’s reusable pens (Steve Cox, Eli Lilly, Scarborough, ON: personal communication, 2003 September 30; Sharmila Dhupar, Novo Nordisk, Mississauga, ON: personal communication, 2003 September 30). Furthermore, Novo Nordisk indicates on its US web site that its pen should not be used with Lilly cartridges, because no scientific testing has been conducted to determine compatibility. It states that the warranty would be nullified if its pen is used with a product not made by Novo Nordisk.¹⁰

Owen Mumford produces an insulin pen (Autopen® and Autopen Junior® distributed by Auto Control Medical) that can be used with Eli Lilly cartridges and with the new insulin product Lantus® by Aventis (Casey Vary, Auto Control Medical, Mississauga, ON: personal communication, 2003 October 3).

Health Canada has issued a licence to Aventis Pharma Inc. to market a product called Optipen Pro (licence 31978).¹¹ This Optipen® Pro is designed to be used with insulin cartridges from Aventis (Luc Sauriol, Aventis Pharma Inc, Laval, QC: personal communication, 2003 October 22).

**Conclusion**

The metabolic effect of insulin delivered by pen compared to syringe is unclear. Studies show no significant difference in surrogate outcomes when the pen is compared to the syringe. The studies, however, are of short duration, with small sample sizes. They are not powered to study morbidity and mortality.

The studies comparing pen and pump were conducted in the late 1980s on older pump models. Definitive conclusions cannot be made, although these older studies favour the pump for surrogate outcomes. Studies comparing more recent models of the pump have not been conducted.
The pen is the preferred device among patients, although the questionnaires used to assess their preference are not validated.

Cartridges are not interchangeable among the various pens that are available on the Canadian market.

References


insulin pen-fill formulations


