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A REVIEW ON INSULIN DELIVERY DEVICES USED IN DIABETES MELLITUS

Anilasree B. P.[1*], Shaimol T.[1], Anagha R. G.[1], Prajeesh T.[1], Asla K. K.[1], Jamsheeda P.[1]

[1]Devaki Amma Memorial College of Pharmacy, Malappuram, Kerala.

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***Corresponding Author**
Anilasree. B. P.
Devaki Amma Memorial College of Pharmacy, Malappuram, Kerala.

ABSTRACT

Insulin therapy, using the vial and syringe method, can be complicated and time consuming. Insulin pens were introduced in the United States in 1987 and have simplified insulin administration for many patients. Continuous Subcutaneous Insulin Infusion (insulin pumps or CSII) is being utilized to achieve and maintain tight glycemic control for persons with Diabetes Mellitus (DM). CSII therapy has existed since the 1960s. These insulin delivery devices provide improvements in flexibility, convenience, and freedom for patients-with diabetes. These devices may also help promote dosing accuracy and often improve compliance. It uses only rapid acting insulin, which has more reliable and predictable absorption. Gone are the days of sliding scales and feeding times to match the insulin delivery systems. This article focuses on insulin pen therapy and other alternative methods of delivering insulin including insulin pump therapy.

KEYWORDS:

INTRODUCTION

The number of patients diagnosed with diabetes mellitus (DM) in the United States in 2007 totaled almost 18 million people. An additional 5.7 million people are considered undiagnosed, which brings the total to 8% of the US population considered to have DM.[1] While this disease affects a large percentage of the overall population, it also affects a large number of elderly patients. The prevalence of DM in patients 60 years of age or older was estimated to be greater than 12 million in 2007, which represents almost one-quarter of the elderly population and over one-half of the overall DM population. This number will almost surely continue to rise as a result of several factors, most notably the increase in the size of the elderly population. In 2000, an estimated 12% of the US population was 65 years of age

or older. This number is projected to grow to over 16% by the year 2020.[2] Additionally, an estimated 35% of the elderly population has impaired fasting glucose, which could later progress to DM.

The treatment of Type 2 DM often requires a multi drug regimen that includes insulin in order to maintain glycemic control. The American Diabetes Association (ADA) consensus algorithm lists basal insulin as a possible option in step 2 therapy after lifestyle changes and metformin have inadequately controlled glucose levels, as well as in patients with an HbA1c >8.5%.[3] Statistics in 2007 showed that 14% of those diagnosed with DM are on insulin alone, and 13% are on a combination of insulin and oral medications. Additionally, a 2006 survey found that nearly 32% of the elderly population who were diagnosed in their middle-age were on insulin, and almost 7% of those who were classified as elderly when diagnosed were on insulin. These numbers will continue to rise not only as the proportion of the elderly population increases, but also as the role of insulin in treatment of DM continues to evolve and guidelines continue to place more of an emphasis on insulin therapy.

Insulin is a very effective drug and is vital treatment for people with type 1 diabetes. Type 2 diabetes is an insidious diseasewith progressive destruction of the insulin-producing betacells.1,2 Eventually more than 30% of patients require insulinto attain their blood glucose targets.3 Many people with type2 diabetes are reluctant to start insulin for a number of reasonsincluding fear of needles, fear of hypoglycaemia, weight gainand believing they only have a mild form of diabetes.4Historically, patients injected insulin using glass syringeswith detachable needles. They had to boil the syringes andneedles between injections and store them soaked in alcoholto keep them sterile. These needles were large, and injesctionswere painful.

The advent of the disposable plastic ‘diabeticsyringes’ with a fixed needle represented a considerableadvance and injections were less painful. They did, however, have a number of disadvantages, and doses and administrationpractices were often inaccurate. This was partly because of therange of insulins available and the need to mix each dose ofshort- and longer-acting insulin in the same syringe at the timeof injection. The advent of biphasic insulin made drawing upinsulin doses easier and less confusing for patients.The last five years have seen an increase in the range of insulindelivery devices (Table 1). These devices have revolutionisedinsulin self-care, but have also placed extra burdens of choiceon people with

diabetes, and they do not necessarily improve compliance. One of the most significant advances has beenthe production of short, fine needles as they considerablyreduce injection pain. In practice, patients report that blood glucose testing is more painful than insulin injections. The prevalence of diabetes mellitus (DM) in the elderly population currently represents almost one-half of the overall diabetic population. Treatment of DM often requires a multidrug regimen that includes insulin therapy; however, due to concomitant comorbidities such as dementia, vision loss, neuropathies, poor mobility, and poor manual dexterity, elderly patients may be at increase risk for hypoglycemia and other dosing errors that are associated with insulin administration. Insulin pen devices have been shown to provide more reliable, accurate, and simplified dosing, and therefore may be a safer, easier, and more acceptable method of insulin delivery in the elderly population. This review will describe the various insulin pen devices available today, as well as discuss the potential advantages of these devices in the elderly population.

For over 50 years, vial and syringe was the only method of delivering insulin. While life-saving, it was crude at best, and ever since its discovery much effort has gone into improving the insulin. Initially, insulin was used primarily for people with Type 1 diabetes mellitus (T1DM), but research has shown that most people with Type 2 diabetes mellitus (T2DM) will also require insulin to maintain HbA1c at levels recommended by the American Diabetes Association/European Association for the Study of Diabetes.1,2While insulins have improved, they still require an injection. Additional effort has gone into finding an adequate delivery method; in the 1970s insulin pumps became available, and in 1985, the first insulin pen was introduced. Insulin pens have been shown to have several advantages over the traditional vial and syringe method of insulin delivery, including improved patient satisfaction and adherence, greater ease of use, and superior dosing accuracy.4-10 About two-thirds of insulin prescriptions in Europe and about three-quarters in Japan are for pen devices9 while only 15% of patients are thought to use insulin pens in the US.11 According to the recent report, Access to Quality Medicines and Medical Devices for Diabetes Care in Europe,12 there remains a great disparity in access to insulin pens across Europe. While insulin seems to be a covered benefit in most countries, use of insulin pens varies more widely and may, in some cases, be restricted to people with T1DM and/or to children under the age of 18 years.

In spite of the convenience and greater ease of use, cost may be an issue. The greater cost of insulin cartridges and prefilled insulin pens, compared with insulin vials, can impact the acceptance of insulin pens as a viable option for people with T2DM. For some patients, the cost may be the same depending on coverage, and in fact, if they have one co-payment per box of pens, the cost to the patient may actually be less per unit of insulin. If this seems to be an issue it is important to consider that despite the higher unit cost of insulin in pen devices versus vials, several studies have found that overall diabetes-related treatment costs are lower with pen devices than with vial and syringe.3,4,11 Increased adherence with the use of insulin pens has been demonstrated and further emphasises the need to consider them as an option when initiating insulin.5, 11, 13 Therefore, in theory, costs should not prevent the use of these devices.

While many patients of all ages are treated with insulin for DM, concerns arise over the safety and efficacy of this high-alert medication in the elderly population. The use of insulin in this population is often complicated by multiple comorbidities such as dementia, vision loss, neuropathies, poor mobility, and poor manual dexterity. These factors can affect the patient's ability to self-inject insulin, increase reliability on caregivers, and ultimately may limit the use of insulin in treatment of DM in this population.

Safety, especially hypoglycemia, is always a concern when using insulin, and individual studies have shown that the overall incidence of hypoglycemia in the elderly may be between 21%27%. Additionally, it has been shown that many patients, including the elderly, may make significant errors in drawing up the correct insulin dose for injection, furthering safety and efficacy concerns.

As a result of these complications and concerns, there is a need to simplify insulin regimens and dosing in the elderly population. One option for doing this is through the administration of insulin with a pen device rather than the traditional vial and syringe method of delivery. Insulin pen devices were first marketed in the mid-1980s, and since that time the design of these devices has continued to evolve. The result is a device which may allow for more elderly patients to be treated with insulin as administration of insulin is possibly made safer, easier, and more acceptable.

The purpose of this review is to describe the various insulin pen devices available today, as well as discuss the potential advantages of these devices in the elderly population. The safety,

efficacy, patient preference, and overall patient satisfaction with regards to ease of use will be reviewed in order to determine the role of these devices in the utilization of insulin therapy in the elderly population. This review will focus on insulin pens.

REVIEW OF LITERATURE

INSULIN DELIVRY DEVICES

INSULIN PENS

An insulin pen is used to inject insulin for the treatment of diabetes.

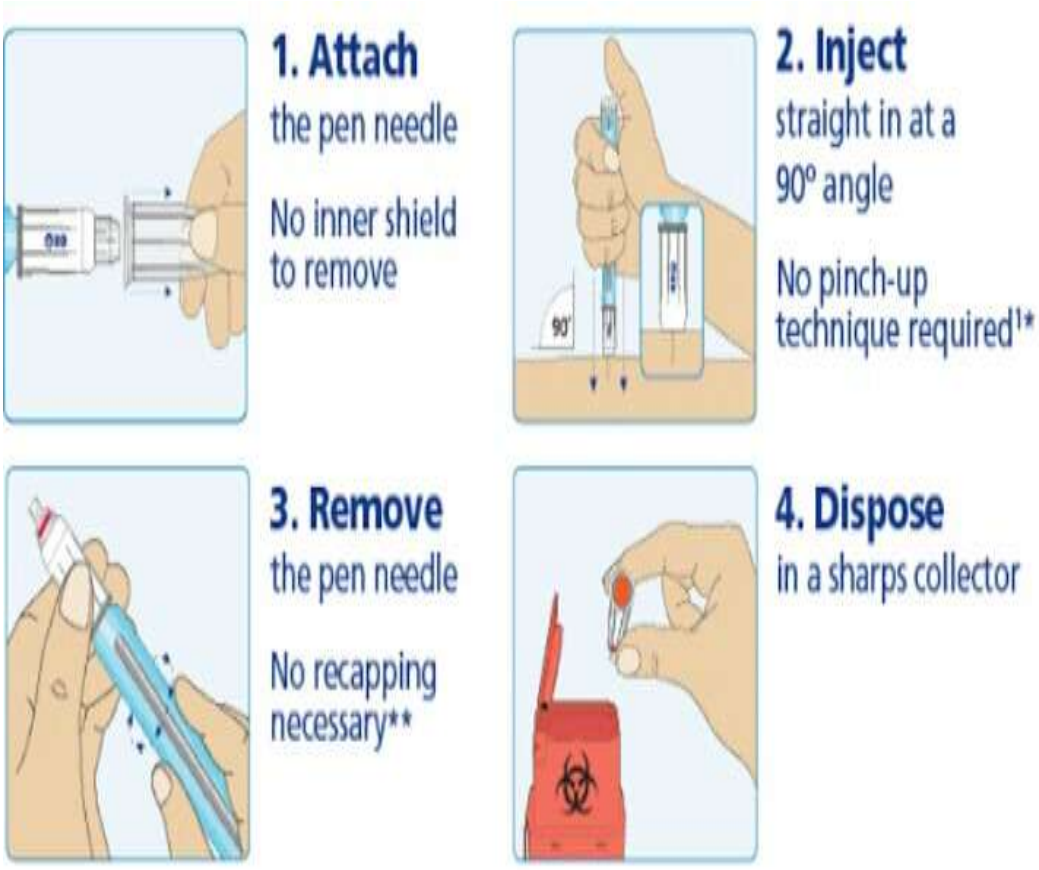
It is composed of an insulin cartridge (integrated or bought separately) and a dial to measure the dose, and is used with disposable pen needles to deliver the dose.

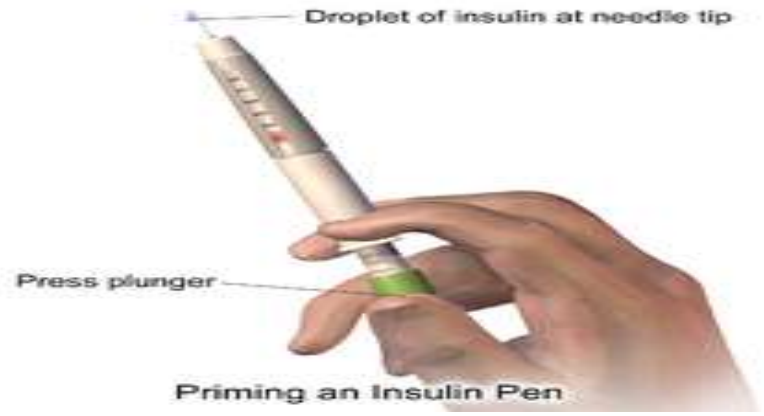
It was introduced and marketed as Novo pen in 1985.

TYPES OF INSULIN PEN

Reusable insulin pen- must load it with insulin

Disposable insulin pen- pre-filled with insulin





1) Remove the cover
2) Attach the pen needle to the insulin pen
3) Expel the air from the pen
4) Dial the dose to the number of units of insulin needed
5) Insert the pen needle into the layer of fat under the skin
6) Press the button at the top of the pen

ADVANTAGES	DISADVANTAGES
Easy to use and carry **No need to draw the dose** **Can use most type of insulin** **Less waste of insulin** **More accurate dosages** **Less injection pain**	**Cannot mix different kinds of insulin (two injection one of each type should be given)** **Takes more time** **More expensive** **Insulin pens should only be used for self-injection**

Insulin pen injectors are a convenient and discreet way of administering insulin. They have a built-in dial that allows you to determine the amount of insulin to be injected, a short needle at one end, and a plunger at the other. Some are disposable, and don't need to be assembled before use, while others have a replaceable insulin cartridge that needs to be inserted (much like a fountain pen cartridge).

Insulin pens are particularly useful if you need to take premixed insulin. They have become popular for use by people with both type 1 and type 2 diabetes.

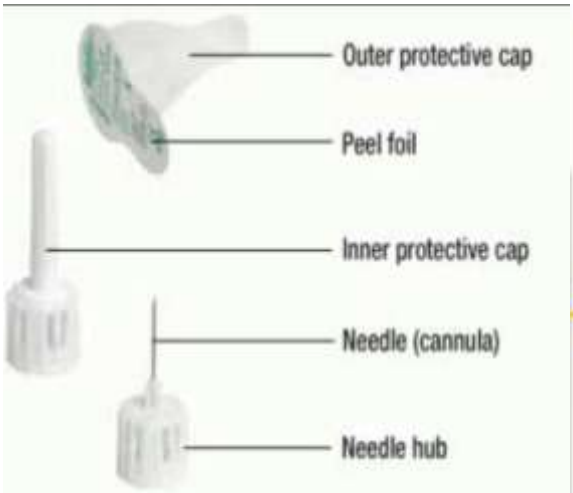
Needle and syringe

A common way of administering insulin is with a needle and syringe. Syringes come in a range of capacities (1 mL, 0.5 mL or 0.3 mL) and with a range of needle types (different gauges — that is thicknesses — and lengths) attached. The needles have very fine points and

special coatings to make injections relatively pain-free. Select a syringe that suits the size of the insulin dose you take and that has your preferred needle type and needle size attached.

One of the main advantages of the syringe system is the variety of products available. Needles and syringes also make it easy to use a mixture of different types of insulin ('mixed insulin').

However, some people find syringes daunting and not very convenient. For this reason a number of other delivery devices have been developed, including insulin pens, jet injectors and pumps



ADVANTAGES	DISADVANTAGES
Easy to use Can use most type of insulin Widely available Disposable Less expensive	Need to draw insulin Low blood glucose levels can occur because of using different types of insulin. Frequent injections may develop resistant areas of the body where insulin will not absorb properly.

Insulin jet injectors

Jet injectors offer an alternative to needles, and work by sending a fine spray of insulin into the skin using a pressurised jet of air instead of a needle. However, jet injection isn't any less painful than administering insulin with a needle, and may cause bruising or altered absorption levels. Jet injectors also require frequent cleaning and maintenance. They are not commonly used.

External insulin pumps

External insulin pumps are small devices the size of a pager that can be attached to your belt or placed in your pocket. They run off batteries. They are made up of an insulin reservoir connected to a tube, ending in a cannula or catheter, which is inserted under the skin of your abdomen. They can be set to deliver insulin at a slow, continuous rate throughout the day, or to release larger quantities at meal times or when blood sugar levels are high.

The main advantage of a pump is that it closely mimics the slow but continual release of insulin by the pancreas. However, you will still need to monitor your blood glucose levels regularly. Pumps have been useful in helping people with diabetes achieve tighter blood glucose control, but the risk of episodes of low blood sugar (hypoglycaemia) is higher. Another drawback of pumps is the risk of ketoacidosis if the catheter becomes blocked. Expense may also be an issue.

There are two types of insulin pumps

A) Pumps that you set based on measurements from a blood glucose meter.

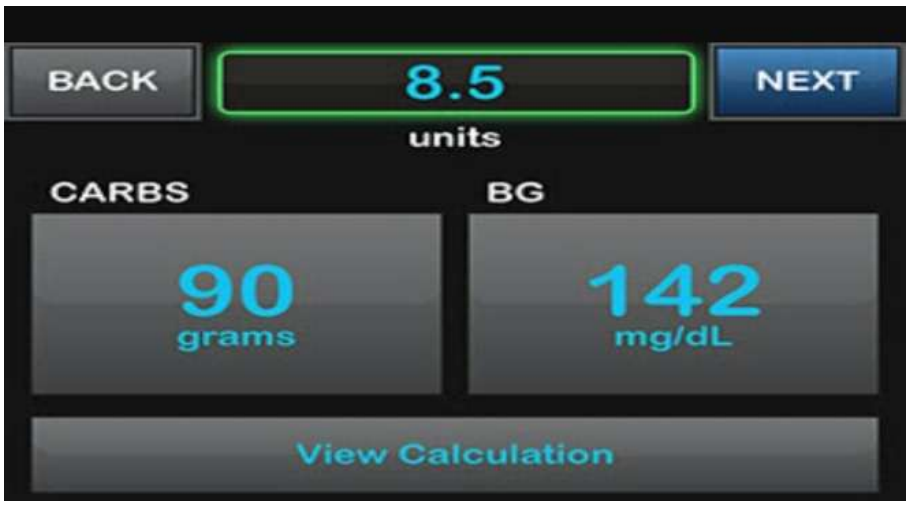
B) Pumps that receive automatic continuous monitor readings. These are called "sensor-augmented pumps." The monitor sends readings to the pump, then you use the readings to set the pump to deliver the insulin you need.

Continuous glucose monitoring systems

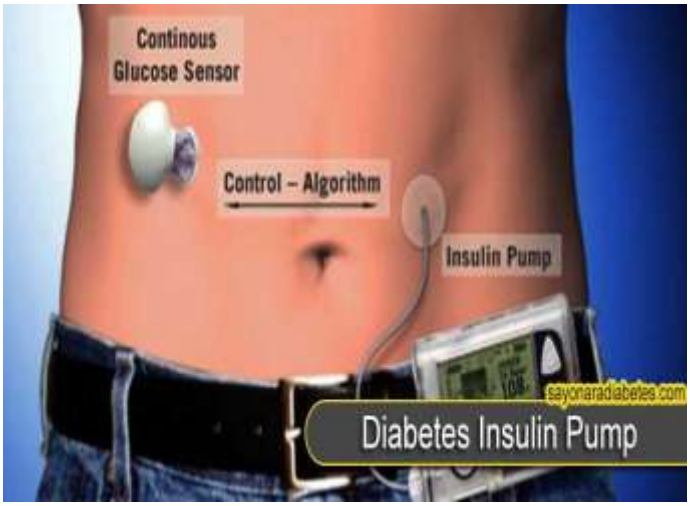
It measures real time glucose level through out day and night (RBS)

It provides early notifications of upcoming glucose level

It provides alerts for low or high glucose level even when the patient is sleeping



A disposable infusion set, including a cannula for subcutaneous insertion (under the skin) and a tubing system to interface the insulin reservoir to the cannula. Cannula can be placed in stomach, hip and leg areas and should be changed every2-3 days.



Your infusion sites should be at least

2 inches (5.0 cm) away from your sensor site

2 inches (5.0 cm) away from your belly button

3 inches (7.5 cm) away from the previous site

ADVANTAGES	DISADVANTAGES
Allow more flexible lifestyle Deliver more precise amounts of insulin Use of insulin pumps in type 2 diabetes shown improvements in HbA1c and neuropathy pain.	Breakdown in equipment More expensive Chance of occuring ketoacidosis and allergic reactions Experience scar tissue build up around the inserted cannula

Implantable pumps

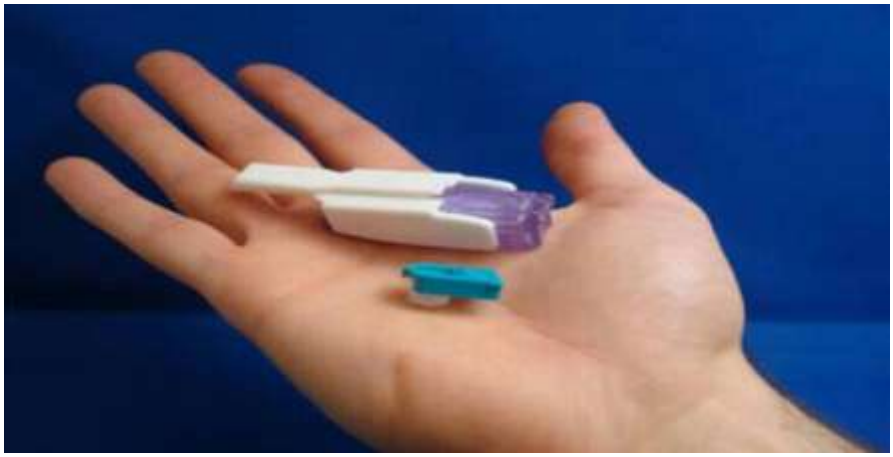
Implantable pumps which deliver insulin either intravenously or directly to the liver are currently being tested in people with diabetes (they are not yet available in Australia). They are usually implanted into the left side of the abdomen, and are designed to work in a similar way to external insulin pumps, that is, by giving a continuous 'basal' dose of insulin with the ability to deliver additional 'bolus' doses at meal times. Also under investigation is a version of the pump that measures blood glucose as well, and so delivers the correct insulin dose automatically. However, these devices are complicated and expensive, and can become blocked. If there are complications or infection at the implantation site the pump may have to be removed.

Insulin patches

Insulin patches are also currently under development, but it is difficult for insulin to be absorbed through the skin. The patch is designed to release insulin slowly and continuously. Additional doses can be administered by pulling off a tab on the patch.

Insulin inhalers

Insulin inhalers have been used to deliver pre-mealtime insulin. Insulin inhalers work like an asthma inhaler, but deliver dry powdered insulin into the bloodstream via the lungs. However, because the system can only be used to deliver fast-acting insulin, long-acting insulin must still be injected. Large doses are needed because only around 10 per cent of the dose actually reaches the bloodstream and that amount may vary, for instance, if you have a cold or asthma. Two types of inhalers were released commercially in the US, but have since been withdrawn from the market. Insulin inhalers are not currently available in Australia.



Insulin dissolved in a dry powder is placed in a single dose catridge. These powders are breath in through a small inhaler which get absorbed to the lungs and passes to the bloodstream.

Exubera was the first FDA approved insulin inhaler, then a new inhaled insulin product called Afreezza was approved in 2014.

ADVANTAGES	DISADVANTAGES
It works quickly and goes in to action for short-term (12-15) min Less risk of low blood sugar and weight gain	Risk of diabetes ketoacidosis Risk of bronchospasm,cough and sore throat

Other delivery devices

Insulin sprays, either for the nose or mouth, and oral insulin (insulin pills) are methods of insulin delivery that continue to be investigated. These options represent long-term possibilities for insulin delivery, as difficulties in obtaining adequate amounts of insulin in the bloodstream are yet to be overcome.

ISLET CELL TRANSPLANTATION

This is a recently developed surgical procedure — called the Edmonton protocol — whereby islet cells from a donated human pancreas are injected into the liver of a recipient with type 1 diabetes. The transplanted cells begin to secrete insulin, while the recipient needs to take immunosuppressive medications for life to prevent rejection of the transplanted tissue. Clinical trials continue to establish the safety and long-term effectiveness of this procedure as a means of supplying insulin, with encouraging early results.

INSULIN PILL

New oral insulin alternative has been developed as insulin pill, with an enteric coating to surround the pill, with special patches contained inside that are loaded with insulin. The enteric coating first protects the medication from highly acidic environment of the stomach, the coating only breaks once it reach the environment of the small intestine. And then the insulin-loaded patches are released, where they attach onto the intestinal wall and safely passes the insulin into the bloodstream

Insulin Pens versus Insulin Vials and Syringes

In order to determine if insulin pen devices have a role in the treatment of elderly DM patients, it is important to understand the advantages these devices offer over traditional vials and syringes. Many patients find that these devices are more convenient as they eliminate the need for drawing up a dose. The ability to dial up the desired dose may lead to greater accuracy and reliability, especially for low doses which are often needed in the elderly. The sensory and auditory feedback associated with the dial mechanism on many pens may also benefit those with visual impairments. Pen devices are also more compact, portable and easier to grip, which may benefit those with impairments in manual dexterity. Finally, less painful injections and overall ease of use may contribute to the increased patient preference seen with the pen devices.

Despite the advantages associated with pen devices there are potential disadvantages. Most importantly the devices are more costly than the insulin vial, and this may be difficult for many elderly patients. It should be noted, however, that most insurance plans, including Medicare part D, charge the patient the same amount for a month supply of insulin in the pen device as insulin in the vial. Patients may also find that pen devices take longer to use, as they

must remain in the subcutaneous tissue for 5–10 seconds after dose release. Lastly, not all forms of insulin are available in the pen device; this is discussed in more detail below.

Dosing and Safety

An important consideration with insulin administration in the elderly population is the possibility of dosing errors. Correct administration and accurate dosing is important in order to prevent serious complications, such as hypoglycemia and hyperglycemia. The traditional vial and syringe method of insulin administration involves several steps, including injecting air into the vial, drawing an amount out of the vial into a syringe with small measuring increments, and verifying the correct dose visually. In addition to the complexity of insulin administration, visual impairment, joint immobility, and peripheral neuropathy in elderly patients with diabetes may contribute to inaccurate dosing, and insulin pen devices may be beneficial in terms of safety for elderly patients due to these visual or physical disabilities. Additionally, insulin pens may provide ease in setting and reading the amount of insulin to be injected and are also preferred for smaller doses of insulin due to improved dose accuracy.

Studies have demonstrated that patients using a traditional vial and syringe method of delivery have a higher risk of inaccurately drawing up the insulin dose, with a relative error of approximately 19% seen in accuracy of dosing. Higher inaccuracies may be seen in the elderly population. Puxty and colleagues found that a 12% variation in drawing up and expelling 20 units was seen with syringe users (average age 66 years).These errors in administration could lead to either an increased risk of hypoglycemia or an increased risk of inadequate glycemic control.

The occurrence of hypoglycemia is one of the most important barriers to achieving tight glycemic control, and rates of hypoglycemia may be more common in the elderly patient. However, use of insulin pen devices may actually improve rates of hypoglycemia often seen with the traditional vial and syringe method of delivery. One observational study demonstrated that patients treated with insulin pens experienced a significant improvement in rates of hypoglycemia ($P < 0.05$), and another analysis of third party claims found that the initiation or addition of a pen device both increased medication adherence while decreasing hypoglycemic events. In Korytkowski et al two serious hypoglycemic events occurred in those patients using the vial/syringe method. There were no cases of hypoglycemic events in those patients who used the pen device. In contrast, Coscelli et al reported no significant

difference in the incidence of hypoglycemic episodes in patients 60 years of age or older using the vial/syringe compared to the pen.

Dose accuracy may be an advantage to insulin pen devices over the traditional vial and syringe method especially with smaller doses (<5 units). Some products also allow for dosage correction, and if too many units are dialed, the dose can be corrected by dialing backwards. According to Korytkowski et al 73% of patients reported more confidence in injecting the correct dose with the insulin pen device compared to 19% of patients using the vial/syringe method. When assessing dose accuracy in the Humalog® KwikPen™ compared to the vial/syringe method, Ignaut et al found that moderate to high doses (30–60 units) prepared with the pen were more accurate than vial and syringe.

Insulin pen devices may also be especially advantageous for those patients with visual impairment or dexterity issues due to the availability of larger digits in a dose window or digital dose display. Some of the pens also provide audible clicking with dosage selection and injection completion which can help with accurate dosing. In a trial assessing safety and efficacy of the prefilled disposable pen compared to vial and syringe administration, 85% of patients reported they found the dose scale on the prefilled pen easier to read. The patient questionnaire reflected that 82% of patients reported greater confidence with setting the required dose when using the insulin pen device. Additional studies note that patients find selection of the correct insulin dose easier compared to the vial and syringe method of insulin administration.

Other considerations for safety in choosing an insulin pen device for an elderly patient may include the type of device. The device types and features will be discussed in further detail later in this review; however, when discussing the dosing accuracy of pen devices, it should be noted that minimum and maximum dosage, as well as the minimum dosage increments, should be considered when individualizing therapy. Many elderly patients may only require small doses of insulin, and therefore pen devices allowing 0.5 unit adjustments may be advantageous. Digital dose displays and memory features are also available with specific products such as the OptiClik® and HumaPen® Memoir™ and may help the patient obtain a more accurate dose. It should also be noted that pen devices need to be primed prior to use. The insulin pen devices require an “air shot”, “safety shot”, or priming in order to prevent the injection of air and ensure accurate dosage for delivery. This is an important area of education for elderly patients in order to ensure dose accuracy.

Efficacy

It is estimated that less than half of patients with diabetes achieve a HbA1c goal of <7% as set forth by the ADA, and this amount is even higher when considering a HbA1c goal of ≤6.5% as set forth by the American Association of Clinical Endocrinologists (AACE); up to two thirds of patients do not reach this level of glucose control. As diabetic complications are often the result of inadequate glucose control, it is important to also consider the efficacy of available insulin pen devices in comparison to the traditional vial and syringe method. Few studies have evaluated an objective direct association between glycemic control and the use of pen devices; often it is the patient's perception of efficacy and dosing accuracy that lead to an assumption of improved glycemic control. However, several studies have evaluated both the perceived and actual clinical efficacy of insulin pen devices in the overall population as well as the elderly.

In one 12 week crossover study in patients with an average age of 57 years, the use of biphasic 70% insulin aspart protamine suspension and 30% insulin aspart in both the prefilled insulin pen device (FlexPen)® and the vial/syringe method was compared.[15] In this study, there was an overall statistically significant improvement in glycemic control, with a mean reduction in HbA1c values of 0.3% ($P < 0.05$), regardless of which method of insulin delivery was used.[15] Another 12 week crossover study conducted in patients who were over the age of 60 compared the NovoLet pen device to the vial/syringe method.[9] Investigators found that pre-lunch glucose levels were significantly lower in the patients who used the pen device ($P < 0.01$); however, no significant differences were found in HbA1c values or other prandial glucose levels.[9]

A study involving 25 elderly patients who were suboptimally controlled on two doses of NPH alone found significant decreases in HbA1c, from 7.8% to 7.6%, preprandial breakfast and lunch glucose levels, and postprandial breakfast and dinner glucose levels ($P < 0.05$ for all values) when subjects were given an alternate pen device. Interestingly, a decrease was seen in the total daily insulin dose when patients received therapy with the pen device. Although no patients were optimally controlled at study entry, 29% of patients were able to reach HbA1c goals at the end of the three month period. Patient perception of clinical efficacy may also impact use of insulin therapy. A comparison of the FlexPen®device and the vial/syringe method found that patient perception of clinical efficacy was found to be higher with the FlexPen®,with the greatest improvement seen in insulin-naïve patients ($P < 0.001$).

While insulin has been shown to decrease complications that may arise from uncontrolled hyperglycemia, the method of injection should be considered. Insulin pen devices have shown comparable efficacy to the traditional vial/syringe method, and some evidence exists to suggest that this efficacy is also similar and potentially better in the elderly population. Additionally, the perception of efficacy has been shown to be higher in patients using pen devices.

Ease of Use

Ease of use is an important aspect to consider when choosing insulin delivery devices for all patients, but particularly in the elderly as older patients may need more time than younger patients to learn the various functions of the different available pen devices. Diabetic patients often experience age-related complications such as poor vision or impaired manual dexterity, which can lead to inaccuracies in dosing. Visual impairment in particular is common in the aging diabetic population; 16 to 27% of diabetic patients ages 65 to 75 have a visual acuity of approximately 20/40 feet or worse, respectively. Pen devices offer several features, such as single-unit dosing increments, an easy-to-push release button, an audible click when dialing doses, large dose selectors, and a dial that clearly shows the selected dose that make pen devices easier to use than the traditional vial/syringe method.

In one 12 week study of elderly diabetic patients age 60 years and older, patients were assessed on their ability to use a pre-filled insulin pen device compared to the vial/syringe method. Patients were randomly assigned to either the vial/syringe or the pen device for 6 weeks and were then switched to the other delivery system for an additional 6 weeks. At weeks 2 and 6 of pen device insulin delivery, patients were asked to complete a questionnaire that assessed the patients' ability to use the pen device versus the vial/syringe method of delivery; 90% of patients rated the pen device either very easy or easy to understand.[9] Likewise, Korytkowski et al found that 85% of patients found it easier to read the insulin dose scale with the pen device in comparison to the 10% of patients using the vial/syringe; overall 74% of patients found that the pen device was easier to use than the vial/syringe method of insulin delivery.

Shelmet et al followed 79 elderly diabetic patients who had visual and/or motor disabilities severe enough that they experienced ongoing difficulties with insulin injection with the vial/syringe method of insulin delivery or required the assistance of a caregiver. Patients were randomized to receive either the vial/syringe method or the InnoLet® pen device for six

weeks and then were switched to the alternate regimen for an additional six weeks. The study also found that while 60% and 36% of patients required assistance in drawing up the appropriate dosage and injecting insulin, respectively, over half of the study population (53%) were able to independently administer insulin with the pen device. Another interesting aspect of this study is that costs associated with daily nursing assistance were significantly reduced as a result of the increase in independence found with the pen device.

Despite the above findings, ease of use cannot necessarily be considered equal with all pen device delivery systems. Haak et al assessed usability and pen features for Solostar®, Humulin/Humalog® (Lilly pen), and the FlexPen® device. Usability involved completing such tasks including removing the cap, attaching the needle, activation of the dose knob, delivering a safety dose, dialing a 40 unit dose, and delivering the dose. A comparison of the SoloStar, FlexPen®, and the Lilly Disposable pen in patients 60 years of age and older found that a higher percentage of patients were able to correctly complete the assessed steps with the SoloStar (90%) and FlexPen® (83%) versus the Lilly Disposable pen (47%). Likewise, patients with visual and manual dexterity impairments were more able to complete the steps when using either SoloStar (94% and 91%) or FlexPen® (84% and 89%); in comparison, only about 50% of patients using the Lilly Disposable pen were found able to complete the assessed steps. Lower injection force associated with the Solostar®pen may contribute to the success of this device in those with dexterity issues and this finding has been seen in other studies as well. Additionally, several studies have found that patients prefer the ease of use associated with the FlexPen® device in comparison with other insulin pen devices. One simulation study comparing the Humalog Pen to the FlexPen® demonstrated that patients scored the FlexPen® significantly higher in overall ease of use, including ease of dose setting ($P < 0.001$), ease in pressing the release button ($P< 0.01$), and simplicity ($P < 0.01$); the higher rating for the FlexPen® was consistent for patients with both visual and manual dexterity impairments as well. Similarly, another study comparing the FlexPen® to the Humalog pen device found that 74% of patients preferred the FlexPen® for overall ease of use, including the following parameters: ease of reading the dose scale, ease of feeling the click for each unit increment, ease of depressing the injection button, ease of turning the dose selector, and ease of determining that push button was completely depressed. Health care professionals have also expressed a preference for the ease of use of the FlexPen® device when compared to both the Humulin Pen and the OptiSet; of 102 health care professionals

supervising patients initiating therapy, 85% thought that it would be easy to teach patients to use the FlexPen®, and 71% thought that less induction time would be required for FlexPen®.

Preference

As patient adherence plays an important role in glycemic control, it is important to consider factors that may impact patient preference and therefore adherence with insulin therapy. Barriers to insulin therapy are both practical and psychological, and patients may worry that insulin injections will be painful, difficult to administer, adversely affect their independence, or cause a social embarrassment or stigma. Several studies have demonstrated that these barriers can be overcome and patient preference and acceptability improved when insulin is delivered through a pen device, with up to 90% of elderly patients expressing a preference for insulin pen devices in certain instances.

When the pre-filled disposable FlexPen® was compared to the conventional vial/syringe method, 74% of patients indicated a preference for the pen device versus 20% of patients who preferred the vial/syringe method, and more patients reported an increase in confidence with the insulin pen method, confidence in dosing accuracy and ability to maintain glycemic control, and felt that the pen device was more discreet for public use.

Patient preference with the FlexPen® device

A study in which 44% of diabetic patients were age 56 or older compared the Novolin Prefilled® pen device to the traditional vial/syringe delivery method and found that a higher percentage of patients reported less pain with the pen device than with the vial/syringe method.[8] More patients were also likely to take their insulin at home or while away, reported a better social life, and stated that they were more active with the pen device. Patients also felt that the Novolin pen had greater convenience and flexibility, and a larger percentage of patients reported that they preferred that method of delivery (79% vs. 7%), felt a positive impact on wellbeing (75% vs. 47%), were willing to continue using the pen device (88% versus 32%), and would recommend that treatment to someone else (91% vs. 39%).

In a comparison trial of the InnoLet® pen device to the vial/syringe method, significantly more patients indicated preference for the InnoLet® pen (82%, $P < 0.001$), and a higher proportion of patients indicated that they felt the InnoLet® pen was more reliable than the vial/syringe method. Seventy-three percent of patients also reported “no pain at all” when judging the pain of injections with the pen device. Finally, in a study of 25 elderly patients

with type 2 diabetes previously treated with the vial/syringe method, a significant increase in patient satisfaction was seen with the pen device ($P < 0.05$).

Availability

When considering insulin pen use in the elderly it is important to understand what products are available and the differences in the various devices. Many of the currently available insulins are available in both insulin vials and insulin pen devices. All available formulations are available in vial formulation, and all insulins other than regular human insulin (Humulin® R and Novolin® R), NPH (Novolin® N and Humulin® N), and the regular mix insulins (Novolin® 70/30 and Humulin® 70/30) are available in pen devices. The latter 2 Novolin products were previously available in a device called the Innolet®, however this device was recently discontinued by Novo Nordisk. The latter Humulin products were available in the Original Prefilled Pen Device, but this device is currently being discontinued by Eli Lilly and Company.

Cost and availabilty.

Insulin pen devices can be divided into 2 categories: durable (or reusable) pens and prefilled pen devices. Durable pen devices combine the reusable syringe and insulin container with a disposable insulin cartridge that houses the actual insulin. These devices are designed to be reused by the patient as only the insulin cartridge and pen needles need to be replaced, which allows a single device to be used for several years. Some of these devices are available with a digital display and require batteries with the average lifespan of the battery being around 3 years. Although overall use of the pen devices may be easier for older patients, loading an insulin cartridge into a durable pen device may be especially difficult for older patients with visual and dexterity impairments. The durable devices hold 3 ml cartridges containing 300 units of insulin per cartridge. These devices can deliver insulin in 0.5, 1, or 2 unit increments up to a maximum of 80 units depending on the actual device being used. Most of the durable pens are designed with special features that may benefit certain patient populations including the elderly. However, it should also be noted that many manufacturers are planning to move away from certain durable pen devices as they are more expensive and difficult to manufacture than the prefilled devices.

Characteristics of pen devices.

Prefilled pen devices are also available, and these tend to be more commonly used than the durable pen devices. These devices are disposable, and unlike the durable devices, these

prefilled pens are designed with a built-in and prefilled insulin reservoir. Once these devices are empty, the patient must discard the device and obtain a new device. Like the durable devices, these pens are designed prefilled with 3 ml (300 units) of insulin, and many patients may find that these devices are easier to use than durable devices as there is no need to install a new cartridge when the device is empty. All of these devices feature audible clicks to help with dosing. Some of these devices may also have special features related to dosing. The prefilled devices include the FlexPen® (Novo Nordisk), the Humalog Kwikpen and Original pre-filled pen device (Eli Lilly and Company), and the SoloSTAR device (Sanofi-Aventis). As mentioned previously the Original prefilled pen device is being phased out by the manufacturer.

Cost

Pen devices generally are associated with a higher cost per unit insulin than traditional vials and syringes; however one box of pen devices (5 pens) contain 1500 units of insulin as compared to 1000 units in one 10 mL vial of insulin. As individual pen devices are smaller and contain only 300 units, one advantage of this delivery method is the possibility of less insulin wastage due to expiration of open vials. This could be advantageous in the elderly population since many elderly patients require only a small amount of insulin and may experience an increase in insulin wastage with the traditional vial and syringe. Analysis of Medicaid data indicates that patients who initiate insulin therapy with a pen device had significantly lower insulin prescription costs than those who initiated insulin therapy with a vial and syringe.

In addition to lower pharmacy costs, pen devices may be associated with lower diabetes-related costs. Hypoglycemia can be a costly adverse effect associated with insulin therapy, and as discussed previously, insulin pen devices may be associated with a lower overall incidence of hypoglycemia. This effect may be most important in older patients who are already susceptible to hypoglycemia. Lee et al reported significant decreases in annual hypoglycemia-attributable costs with pen devices and overall this cost savings represents 57% of the total savings in diabetes-related health care resource use. In addition to hypoglycemia cost savings, initiating therapy with a pen device has shown significant reductions in hospital and outpatient costs when compared to initiation with vials and syringes.

A significant decrease in overall health care costs was also seen with diabetic patients switching to or initiating therapy with an insulin analogue pen. In a study of Medicaid data, total health care costs were comparable in patients switching to a pen device and patients using vials and syringes; however, the costs were significantly lower in patients initiating therapy with a pen device compared with a vial and syringe.

CONCLUSION

Glycemic control is imperative in decreasing the risk of the long-term complications associated with DM. Insulin therapy is an important aspect of glycemic management; however, physical limitations and psychological barriers exist to both initiating and continuing insulin therapy in the elderly. As insulin is considered a high alert medication in the elderly, and as the elderly have a higher risk of hypoglycemia than the general adult population, it is imperative to find a method of delivery that is safe and efficacious while positively impacting patient preference and acceptability. A number of studies have demonstrated that insulin pen devices are a reasonable alternative to the traditional vial and syringe method of insulin delivery in elderly patients. Both the reusable durable pens and the disposable prefilled devices are available with special features that may improve the use of insulin in the elderly. Features such as audible clicks and large dosing windows may help patients with visual impairments, while the convenience, size, and overall ease of use may help patients with impairments of dexterity. Although patient perception of insulin delivery may impact their willingness to begin injections, pen devices offer a greater simplicity, flexibility, and convenience over the traditional vial and syringe method of delivery. While pen devices may be perceived as more expensive than a vial of insulin, an increase in patient acceptability and adherence can positively impact glycemic control, leading to a lower rate of long-term complications and healthcare costs often associated with DM. Additionally, pen devices have been found to be safe, efficacious and potentially more accurate in the elderly population. As a result, these devices offer an appealing alternative method for insulin delivery in the elderly.

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