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The Declining Role of Sulfonylureas as Add-on Therapy in Diabetic Patients

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Sulfonylureas are a class of medications commonly used in the treatment of type 2 diabetes mellitus; the second generation sulfonylureas currently used in practice include glimepiride, glyburide, and glipizide. These medications work by stimulating the pancreatic beta cells to secrete insulin, thereby lowering the body's blood glucose level. Sulfonylureas have a history of effective use and provide a cost-conscious option for the treatment of type 2 diabetes. Traditionally, they are often used as first line adjunct therapy to metformin; however, as new research comes to light and newer agents emerge, sulfonylureas' role as the "go-to" second line agent has been questioned.¹

In every diabetic patient, it is important to select an appropriate drug regimen during the early stages of the disease so as to prevent the need for insulin as long as possible. Unless otherwise contraindicated, metformin is the drug of choice for

initial management.¹ Unfortunately, poor patient adherence or inadequate lifestyle changes decrease likelihood of monotherapy adequately controlling glycemic levels. It is important that clinicians are aware of appropriate adjunct therapy. Sulfonylureas have long filled this role, and understandably so based on their effectiveness in lowering HbA1c and low cost. When adherence is a concern, an affordable medication is a very attractive option. However, there are additional factors to consider, including side effects and other related outcomes.

Pancreatic beta cell apoptosis is a key factor in disease progression and poor long-term prognosis in diabetic patients. As the pancreas loses the ability to secrete insulin due to beta cell exhaustion, patients must rely on more aggressive therapy such as insulin. Sulfonylureas act upon these beta cells, and may accelerate this "burn-out" process. This mechanism is one of the main reasons widespread sulfonylurea use warrants caution. Within 1 to 2 years, sulfonylureas begin to lose their effectiveness, and in the process limit the extent of treatment success.^{2,3}

Additionally, sulfonylureas carry with them undesirable side effects, which can have a distinct influence on adequate control of the underlying diabetes. Most patients will experience weight gain after starting a sulfonylurea. This can have negative effects on a patient outcomes, such as circulatory problems. More importantly, hypoglycemia is a major concern in patients taking a sulfonylurea, especially longer acting options such as glyburide; glyburide has lost favor as an early stage option due to its pronounced risk of hypoglycemia and accompanying cardiovascular complications. Glyburide is included on the Beers List because the elderly are more likely to experience hypoglycemia, as well as show reduced renal function, which further increases the risk of hypoglycemia.^{2,3,4}



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The Declining Role of Sulfonylureas

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Risk of hypoglycemia should always be assessed when selecting any antihyperglycemic medication with insulin effects. The risk of hypoglycemia is one of the primary reasons to delay injectable insulin therapy for as long as possible. In several trials (ACCORD, ADVANCE, and VADT), hypoglycemic events resulted in increased all-cause mortality, particularly with cardiovascular events. This includes possible arrhythmias, QT prolongation, and poor myocardial infarction outcomes. For

these reasons, the role of sulfonylureas in the treatment of diabetes should be reexamined.³

Sulfonylureas are currently a viable second-line agent for clinicians due to their pronounced A1c lowering effects and affordability. As newer agents begin to prove their effectiveness and improve their cost-effectiveness, we must consider these additional options.

[<Click here for references>](#)

The Second FDA Approved Inhaled Insulin

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In the United States, 29.1 million people have diabetes.¹ Patients are prescribed insulin due to insulin deficiency (type 1 diabetes) or insulin resistance (type 2 diabetes). Injectable insulin has been available since the 1920s. Insulin is the single most effective agent at controlling blood glucose levels and lowering hemoglobin A1C, however patient satisfaction and compliance are often barriers to use. Injectable insulin can induce undesirable complications including weight gain, and hypoglycemic risk. An alternative route of administration that bypasses or minimizes these complications while providing similar glycemic benefits is of interest.

Due to the lungs' large surface area, inhaled insulin is a feasible alternative for insulin drug delivery. In June 2006, the FDA approved the first inhaled insulin for diabetes under the trade name Exubera® (insulin human [rDNA origin]). The rapid-acting inhaled powder insulin was administered to the lungs through a bulky hand-held inhalation device. The device delivered powder insulin in blisters that contained 1 and 3 mg doses, approximately 3 and 9 units, respectively.² Safety and efficacy clinical trials were conducted in approximately 2,500 adult patients with type 1 or type 2 diabetes. The studies found that Exubera® reached peak insulin concentration faster than regular insulin at 49

minutes and 105 minutes, respectively. In type 1 diabetes, Exubera® was used with basal insulin, replacing meal time insulin. In type 2 diabetes, it was used as monotherapy or combination therapy with an oral anti-diabetic agent or basal insulin.

Although Exubera® provided optimism for the possibility of a new insulin delivering device, there were challenges with the product. Many clinicians were concerned with the long-term effects of insulin administration through the lungs. Cough was the most common respiratory side effect, and pulmonary function tests showed changes in lung function.³ Prior to therapy, FEV1 assessment was recommended. Exubera® was not recommended in patients with declining lung function, asthma, COPD, or baseline FEV1 <70%.⁴ There were also complications with the delivery method and dosing. Patients who required high doses of insulin required multiple blisters at each administration. Improper inhalation technique led to inadequate drug administration.

The concerning changes in lung function, requirement of pulmonary testing, and complications with the delivery method gave Exubera® an unfavorable safety profile. Exubera® was discontinued by Pfizer not due to safety concerns, but lack of demand.

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Side by side comparison of the 2 FDA approved devices used to deliver inhaled insulin.

Left: Exubera® and its inhaler device were withdrawn from the market by Pfizer in October of 2007.

Right: Afrezza® and the Dreamboat® inhaler device manufactured by MannKind Corporation were approved by the FDA in June 2014



Effective dosing of gabapentin for diabetic peripheral neuropathy

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Diabetic peripheral neuropathy (DPN) is a common long-term complication of type 2 diabetes and occurs in up to 50% of patients with long-standing disease.¹ DPN and its complications cost between \$4.6 and \$13.7 billion dollars in the United States annually.² Gabapentin, an anticonvulsant first approved in the U.S. in 1994 for the treatment of epilepsy, is widely used off-label for the treatment of DPN. Although the exact mechanism of action is unknown, gabapentin is thought to disrupt excitatory neurotransmitter release through blockade of voltage-dependent calcium channels.³



Studies evaluating the maximum effective dose of gabapentin to treat DPN are conflicting and are generally limited by small population sizes and short study durations. In a small randomized, placebo-controlled study, Backonja and colleagues evaluated the efficacy of gabapentin in 165 patients with DPN using doses initiated at 900 mg per day and titrated up to a dose of 3,600 mg per day. Following 8 weeks of therapy, patients receiving gabapentin showed significant reductions in mean pain scores compared with placebo ($p < 0.001$) as measured on an 11-point Likert scale. Gabapentin also improved sleep interference scores ($p < 0.05$), reduced total mean pain ($p < 0.01$), reduced mean visual analog scale ($p < 0.01$) and present pain intensity scores ($p < 0.05$) when compared to placebo. The most frequently reported adverse effects were dizziness and somnolence.⁴ Backonja and colleagues also performed a review of five randomized controlled trials evaluating the efficacy of gabapentin for the treatment of DPN and other neuropathic pain syndromes. Gabapentin was shown to be effective in the treatment of DPN at doses of 900 mg/day, with greater efficacy achieved at doses of 1,800 to 3,600 mg/day. Backonja and colleagues concluded that gabapentin should be initiated at 300 mg on day 1 and then titrated to 600mg on day 2, and then 900 mg on day 3.⁶

In a randomized crossover study evaluating the efficacy of gabapentin 900 mg daily in 40 patients with DPN, there were no significant differences in mean change of visual analog pain scale and present pain intensity scores compared with placebo.

However, statistically significant improvements were seen in the McGill pain questionnaire ($p = 0.03$). The most common side effects were drowsiness, fatigue and ataxia.⁵

At present, the recommended starting dose of gabapentin for diabetic neuropathy is 900 mg per day in 3 divided doses.³ According to 2011 guidelines published by the American Academy of Neurology (AAN) and based on the previously mentioned studies, gabapentin is regarded as “probably effective” at daily doses between 900 and 3,600 mg.⁷

Summary

There is moderate clinical literature supporting modest effectiveness of gabapentin for the treatment of DPN at daily doses up to a maximum 3,600 mg given in 3-4 divided doses.⁵ There is no evidence to support efficacy of doses less than 900 mg/day and doses between 1800 mg/day and 3600 mg/day have demonstrated superior efficacy to doses of 900 mg/day. In a patient with adequate renal function, therapy should be initially titrated to a minimum of 900 mg/day given in 3 divided doses and gradually increased as tolerated to treatment effect. Do not exceed 3,600 mg of gabapentin per day. Consider increased monitoring for adverse effects such as somnolence, dizziness and ataxia in patients undergoing dose escalations. Gabapentin is primarily eliminated through the kidneys and in advanced stages of diabetes, the majority of patients have some degree of renal dysfunction. Dose adjustments are required in patients with reduced creatinine clearance to avoid accumulation of drug and subsequent adverse effects (Table 1).⁸ There is no clinical trial data assessing effectiveness of gabapentin for the treatment of DPN in patients with advanced renal disease.

Table 1: Gabapentin dosing in renal impairment

Creatinine Clearance	Dosing Regimen	Maximum Daily Dose
≥ 60 mL/min	300 – 1200mg TID	3600mg
$> 30 - 59$ mL/min	200 – 700mg BID	1400mg
$> 15 - 29$ mL/min	200 – 700mg daily	700mg
15 mL/min	100 – 300mg daily	300mg
< 15 mL/min	Reduce daily dose in proportion to creatinine clearance [†]	

[<Click for references>](#)

New Inhaled Insulin

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The size of the bulky delivery device (25 cm in length) made the product unpopular with patients.⁵

On June 27, 2014, the FDA approved the second rapid-acting inhaled insulin under the trade name Afrezza® (MannKind Corporation).⁶ Similar to Exubera®, this new insulin is for adult type 1 and type 2 diabetic patients. The primary difference is the size of the drug delivery device. The insulin powder is administered through a drug-device combination product. The device (called Dreamboat®) is the size of a whistle. Afrezza® cartridges are available in two strengths: 4 units and 8 units. Multiple cartridges are needed if a patient requires more than 8 units. It is not a substitute for basal insulin and is recommended to be administered before each meal.⁷ After inhalation, the insulin dissolves rapidly and reaches the bloodstream within 12 to 15 minutes. A decline in circulating levels of insulin is seen approximately 180 minutes after administration.⁸

Safety and effectiveness were assessed in approximately 1,026 type 1 and 1,991 type 2 diabetic patients. Less weight gain and a reduced risk of hypoglycemia versus injectable rapid-acting analogs were observed. In type 1 diabetic patients, mealtime Afrezza® was compared to mealtime insulin aspart; both groups received basal insulin. At 24 weeks, a significant A1C reduction was seen in the Afrezza® group. However, Afrezza® provided a smaller reduction in A1C compared to insulin aspart. In type 2 diabetic patients, Afrezza® was compared to placebo inhalation in combination with oral anti-diabetic drugs. After 24 weeks of treatment, Afrezza® with oral anti-diabetic drugs showed a statistically significant reduction in A1C compared to the placebo group.

There are concerns of possible lung complications with long-term use of Afrezza®. Non-productive cough was the most common respiratory side effect seen in clinical trials. The FDA

approved Afrezza® with a Risk Evaluation and Mitigation Strategy and black box warning stating the risk of acute bronchospasm in patients with chronic lung disease. Patients with asthma and COPD are not advised to use Afrezza®. Prior to therapy initiation, physical examinations and FEV₁ measurements are recommended. The FDA is also requiring post-marketing studies regarding potential risk of pulmonary malignancy and long-term effect of pulmonary function.⁹



Although Afrezza® is less efficacious when compared to injectable insulin and has similar concerns of possible lung complications as Exubera®, it may still find a place in therapy. Afrezza® can be utilized as a potential substitute in the subset of patients who prefer an alternative route of administration and require less insulin. An appeal of Afrezza® is the sizing of the delivery device. It provides patients with a distinct route of administration as well as easy storage. MannKind Corporation and Sanofi officially launched Afrezza® at the beginning of February 2015 and it is now available to pharmacies nationwide.

[<Click here for references>](#)

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