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ARxCH
Annual Review of Changes in Healthcare

Sodium-Glucose Co-transporter 2 Inhibitors: Safety Considerations and Clinical Implications for Healthcare Providers

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Learning Objectives
•Recall fundamental nephron anatomy and physiology
•Describe clinical implications associated with SGLT inhibitors
•Discuss the key evidence behind clinical implications
•Identify which patient populations would apply to these considerations

Abstract

Sodium-Glucose Co-transporter-2 inhibitors have been adopted into the most recent American Diabetes Association Guidelines as a now integral part of diabetes care. These medications may be involved in effective strategies to lower glycosylated hemoglobin (A1C), blood glucose, long-term neuropathies and other diabetic complications. Specifically, these drugs have recently been accepted as the drugs of choice in diabetes care for those with cardiovascular comorbidities. Additionally, recent updates regarding Black Box Warnings with canagliflozin have stated it may cause long term increases in the overall number of amputations. Knowledge concerning the new guidelines and the clinical implications with this class of drugs is essential to providing patient care and optimizing outcomes for patients suffering from type two diabetes mellitus.

There are approximately 30.3 million Americans with type two diabetes mellitus (T2DM) in the world today. This statistic tells us that nearly one in ten people in the United States has T2DM. Research involving safe and effective drug products that may benefit this population have serious implications to the health of our country. A specific class of medications used to treat T2DM are the Sodium Glucose Cotransporter-2 (SGLT-2) inhibitors. Agents within this class include empagliflozin, canagliflozin, and dapagliflozin. Canagliflozin and dapagliflozin have received an FDA indication for the treatment of T2DM, and empagliflozin has received an FDA indication for the treatment of T2DM and reduction of cardiovascular (CV) mortality.

SGLT2 agents exert their glucose lowering effects through a unique mechanism. To understand this mechanism, recall the anatomy and physiology of the nephron. The nephron is the functional unit of the kidney and is composed of many distinct sections that are involved in the filtration and reabsorption of waste and electrolytes. The glomerulus, the proximal convoluted tubule, the Loop of Henle, the distal convoluted tubule, and the cortical collecting ducts are the major sections that make up a nephron. The proximal convoluted tubule contains the SGLT2 transporter and is responsible for glucose reabsorption. This transporter serves as an attractive pharmacologic target as there is evidence of increased expression and activity of the transporter in the presence of hyperglycemia.[1] Inhibition of these channels inhibits glucose reabsorption and lowers the renal threshold for glucose. This subsequent decrease in glucose reabsorption (30-50%) into the bloodstream and urinary excretion has been shown to positively affect patients' blood glucose who have been diagnosed with T2DM.[1] Current evidence suggests a modest but beneficial A1C reduction in T2DM patients in the range of 0.5-1.0%.

As these agents become more widely used in practice, it is important to be aware of clinical implications and nonglycemic outcomes when using these agents in patients with T2DM. Major clinical implications to take into consideration include CV benefits, changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP), weight loss, dehydration, diabetic ketoacidosis, bone fractures, renal effects, and potentially severe urinary tract infections.[1-4]

Studies in the past decade have analyzed these clinical endpoints, with The Rationale, Design, and Baseline Characteristics of a Randomized, Placebo-controlled Cardiovascular Outcome Trial of Empagliflozin (EMPA-REG OUTCOME). This study included important cardiovascular outcomes relevant to T2DM patients. The EMPA-REG OUTCOME trial evaluated CV outcomes associated with SGLT2 inhibitors used in T2DM patients with cardiovascular disease (CVD) with the primary outcome of a composite of CV death, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke.[1,2] Collectively, the trial consisted of 7020 patients enrolled and treated with a median treatment time of 2.6 years with a total of 772 outcome events.[2] Noninferiority for the primary outcome was determined if the upper boundary of the confidence interval was less than 1.3.[2] The trial demonstrated that CV related deaths occurred in a significantly

lower proportion of patients receiving empagliflozin versus those receiving placebo (10.5% vs 12.1%; hazard ratio [HR] 0.86, 95.02%, CI 0.74–0.99, p<0.001 for noninferiority; p=0.04 for superiority).[2] The rate of myocardial infarctions and strokes were not significantly reduced with empagliflozin versus placebo (4.8% vs 5.4%; HR 0.87, 95% CI 0.70–1.09, p=0.23, and 3.5% vs 3.0%; HR 1.18, 95% CI 0.89–1.56, p=0.26 respectively). However, when compared with placebo, there was a 38% relative risk reduction in CV mortality in the empagliflozin group (3.7% for empagliflozin vs 5.9% for placebo; HR 0.62, 95% CI 0.49–0.77, p<0.001), a 35% relative risk reduction in hospital admission for heart failure (2.7% for empagliflozin vs 4.1% for placebo; HR 0.65, 95% CI 0.50–0.85, p=0.002), and a 32 percent relative risk reduction in death from any cause (5.7% for empagliflozin vs 8.3% for placebo; HR 0.68, 95% CI 0.57–0.82, p<0.001).[2] The mechanism of said benefits is unclear.[5]

Additionally, the Canagliflozin Cardiovascular Assessment Study (CANVAS) program (consisting of both the CANVAS and renal outcome specific CANVAS-R trials) was designed to compare canagliflozin vs placebo and subsequent CV and renal outcomes.[6] The primary outcome measured was a composite of death from CV disease, nonfatal myocardial infraction, and nonfatal stroke. The study concluded that the primary outcome was lower when comparing canagliflozin vs placebo. The primary outcome occurred in 26.9 vs 31.5 participants per 1000 patient years (HR, 0.86; 95% CI, 0.75 to 0.97; p<0.001 for noninferiority, p=0.02 for superiority). CV safety was to be shown if the upper boundary of the 95% confidence interval of the hazard ratio with canagliflozin as compared with placebo was less than 1.3, and superiority was to be shown if the upper boundary was less than 1.0.[6] Due to the hazard ratio of 0.86, this study concludes that there was cardiovascular superiority demonstrated by the administration of canagliflozin to T2DM patients.

In terms of blood pressure changes, studies have demonstrated a reduction of SBP and DBP without a compensating increase in heart rate.[1] The mechanism of both systolic and diastolic blood pressure reduction is not well understood, but it is thought to be due to modest osmotic diuresis and mild natriuresis.[1] These effects are important to take into consideration in patient populations who are already susceptible to volume depletion. These patients include those with renal impairment, concomitant diuretic use, elderly patients, and patients taking Renin-Angiotensin-Aldosterone-System (RAAS) modulators.

Previously described volume depletion is likely not a contributing factor to weight loss, as changes in blood pressure are typically seen long before quantifiable weight loss occurs. These agents have demonstrated weight loss properties in patients taking them.[1] In clinical trials, weight loss was sustained for up to 104 weeks in patients taking SGLT2 inhibitors.[1] Weight loss is thought to be due to medication induced urinary glucose excretion, resulting in a loss of approximately 200kcal/day in caloric load.[1]

In the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 inhibitors (CVD-REAL) study, over 300,000 participants across 6 different

countries were enrolled to evaluate whether long term clinical outcomes were better when a diabetic patient was started on an SGLT2 inhibitor versus another diabetic medication.[5] It was found that SGLT2 inhibitors reduced the risk of hospitalization caused from heart failure by about 39% and reduced all-cause mortality by 51%.[5] These numbers reflect a sample that was tested with primarily canagliflozin (53%) and dapagliflozin (42%), with empagliflozin reflecting only about 5% of the sample.

A secondary analysis of the EMPAREG OUTCOME trial also found substantial benefit on progression of kidney outcomes.[7] There appeared to be a protective effect on estimated glomerular filtration rate (eGFR), with a lower rate of decline in the empagliflozin group compared to placebo group.[7] Of the treated patients 59% had normoalbuminuria at baseline, 29% had microalbuminuria, and 11% had macroalbuminuria. Reductions in urinary albumin-to-creatinine ratios of 7%, 25%, and 32% were seen after 12 weeks of treatment in the normo-, micro- and macroalbuminuria groups, respectively.[7] These reductions were maintained after a median follow-up of 3.1 years.[7] The general hypothesis is that a reduction of albuminuria following an intervention is primarily reflecting a reduction in intraglomerular pressure, thereby decreasing filtration of large proteins such as albumin.[7] This in turn leads to a reduction in inflammation, endothelial dysfunction, oxidative stress and fibrosis, leading to less long-term damage to the kidney.[7] This data is supported by the CANVAS-R study. The purpose of this study was to assess the effect of canagliflozin compared to placebo on the progression of albuminuria in T2DM patients who have inadequate glucose control and are at an elevated risk of cardiovascular disease but have had standard diabetes care. Results for the primary endpoint of the progression to micro or macoalbuminuria with an albumin/creatinine ratio of greater than 30% from baseline showed no statistically significant change, but did show modest benefit in renal outcomes (HR 0.73; 95% CI 0.67-0.79).

Since these agents require adequate renal function to be effective in hyperglycemia management, their use is contraindicated in patients with severe renal impairment (those patients with an eGFR of <30mL/min/1.73m2) and those requiring dialysis.[1,8] It is recommended to avoid starting canagliflozin or empagliflozin in patients with moderate impairment (those patients with an eGFR of <45 mL/min/1.73m^2).[1,8] No dosage adjustment is needed for empagliflozin if eGFR is ≥ 45 ml/minute/1.73 m^2, whereas the dose of canagliflozin is limited to 100 mg once/day in patients with moderate renal impairment or CKD with an eGFR of 45 to < 60 ml/minute/1.73 m^2. Dapagliflozin should not be initiated if the eGFR is <60 ml/minute/1.73 m^2 and is not recommended if eGFR is persistently between 30 and < 60 ml/minute/1.73 m^2.[1] Renal function should be assessed before the initiation of SGLT2 inhibitor therapy and subsequently monitored on a regular basis.[1]

In a study from the University of Birmingham Diabetes Centre, the effect of empagliflozin in treatment of patients with CKD stage 2 and stage 3 achieved reductions in HbA1c, but no change in HbA1c was observed in patients with stage

4 CKD.[1,9] Canagliflozin use in patients with T2DM and stage 3 CKD was also analyzed in two studies and was associated with reductions in HbA1c, BP, and body weight and was generally well tolerated in this vulnerable population.[1] In both analyses (one 26-week study and one analysis of four studies of 18–26 weeks' duration), eGFR declined roughly 10–15% during the initial weeks of therapy but then returned toward baseline levels by the end of each study.[1,10,11]

Knowledge Check: True or False? SGLT-2 inhibitors have demonstrated a beneficial A1C reduction in T2DM patients up to 2 percent.

Answer: False

Black box warnings for canagliflozin and dapagliflozin include an increased risk for acute kidney injury (AKI) (and an increased risk of mineral loss resulting in bone fractures). An AKI is defined by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines as an increase in serum creatinine (SCr) of >0.3mg/dL in 48 hours, an increase in SCr more than 1.5 times baseline known to have occurred within the past seven days or a urine output of less than 0.5ml/kg/hr for 6 hours. If a patient is found to have an AKI and has been on either aforementioned SGLT2 inhibitors, it is important be aware that the SGLT2 inhibitors may have had some influence on the development of the AKI. The FDA recommends that if an AKI has occurred, then the SGLT2 inhibitor should be discontinued and if there is an infection it should be treated. Furthermore, the FDA recommends that patients should exhibit caution if taking SGLT2 inhibitors with congestive heart failure or if taking with ACE inhibitors, NSAIDs, or angiotensin receptor blockers.

Evidence has shown that some patients may be at risk for bone fractures when taking specific SGLT inhibitors. Studies show that canagliflozin may increase the risk for bone fractures in all patient populations, whereas dapagliflozin was only found to increase the risk of bone fractures in patients with some form of renal impairment.[12] According to the product label for canagliflozin, reported data does indicate an increased risk of bone fractures in patients taking 100mg doses and 300mg doses (incidence rates of 1.4 and 1.5 per 100 patient years respectively).[1,13] Currently, there is no evidence that empagliflozin causes any bone mineral density disorders. According to the CANVAS study, canagliflozin was shown to increase the concentration of a bone resorptive marker, 1 beta-carboxy telopeptide, while having very little change in parathyroid hormone and serum calcium.[13] The Invokana product label sites a study discussing changes in bone mineral density (BMD) in patients taking Invokana. The CANVAS program showed that canagliflozin increased fracture risk by 4% vs placebo at 2.6%.[13] Conversely, one meta-analysis indicated that there was no increased risk of bone fracture among T2DM patients being treated with SGLT2 inhibitors when compared with placebo.[2] The authors did indicate that results were potentially limited

by the short duration of treatment/follow up and low incidence of the event of interest. Overall, it is important to consider the clinical consequences of this information such as hospitalization, death, and/or disability, especially for patients that are at a high risk for fractures, who have a comorbidity of osteoporosis or related mineral bone disorders. These treatment studies may imply that those with a strong family history, or those with a high risk of fractures may benefit from a different therapy rather than an SGLT-2 inhibitor. In select patients, it may be more advisable to step up therapy to injectables rather than try an SGLT-2 inhibitor if the risk for amputation is high enough and clinical judgement validates the decision.

Information concerning the increase in risk for amputations was derived from the CANVAS and CANVAS R trials over longer than a five year period.[13] There were approximately 5.9 amputations per 1000 people on canagliflozin enrolled in the study compared to about 2.8 amputations per 1000 people in the placebo group. Toe and foot amputations were the most common in the study, however there were amputations involving the leg. Leg amputations were performed both above and below the knee. Some patients had more than one amputation done in the study. A new black box warning was introduced in May 2017 for canagliflozin that showed that there was an increased risk of leg and foot amputations in Type 2 Diabetic patients. This evidence has not yet surfaced for empagliflozin or dapagliflozin, however it may be important to consider clinically for patients at high risk for leg and foot amputation. Considerations before initiating canagliflozin, per the FDA, include whether or not the patient has a history of peripheral vascular disease, prior amputation, neuropathy, and diabetic foot ulcers. A possible implication of these recent results include special considerations prior to prescribing an SGLT2 inhibitor for patients at a high risk of developing a diabetic foot infection.

Overall clinical impression of the SGLT2 inhibitors as a class shows that in specific populations they can potentially be beneficial to improving patient outcomes for T2DM patient, especially in patients with a high ASCVD risk. In terms of CV health, there seems to be a small benefit to using SGLT2 inhibitors versus other medications. The EMPA-REG OUTCOME trial did demonstrate that CV related deaths occurred in a significantly lower proportion of patients receiving empagliflozin versus those receiving placebo, and the CVD-REAL study demonstrated that SGLT2 inhibitors reduced the risk of hospitalization caused from heart failure by about 39% and reduced all-cause mortality by 51%. Beneficial changes in urinary albumin-to-creatinine ratios may also be seen and maintained in patients taking empagliflozin, and could allow empagliflozin to be a possible therapeutic consideration given renal function is adequate. Conversely, SGLT2 inhibitors have varying effects in CKD patients and some evidence does suggest risk for acute kidney injury. Therefore, special consideration should be given in this patient population and these agents should be used with caution.

The CANVAS program did conclude that the composite primary outcome of death from CV disease, nonfatal myocardial infraction, and nonfatal stroke was lower with canagliflozin vs placebo, with the

primary outcome occurring in 26.9 vs 31.5 participants per 1000 patient years. With that being said, it is difficult to determine if this difference is significant enough to suggest canagliflozin over other second line agents, especially when taking into consideration the risk of amputations and fractures. Recent findings highlight the importance of taking special consideration before initiating an SGLT2 inhibitor in patients with a high risk of diabetic foot infections and those that have a history of mineral bone disorders or kidney dysfunction.

In conclusion, SGLT2 inhibitors may have more safety precautions for certain patients, however they are drugs that successfully lower A1C, blood glucose, and may lead to positive patient health outcomes. While SGLT2 inhibitors are often very well tolerated, dehydration, hypoglycemia, bone fractures, UTIs and DKA can occur and become life threatening. It is important to educate patients on signs and symptoms of these complications, what to do if any of these complications do occur, and how to prevent their occurrences. The SGLT2 inhibitors are effective drugs for lowering blood glucose and serum A1C for T2DM patients. These drugs also do not cause weight gain and may be beneficial in patients where this is a particular concern. While there seem to be various minor clinical benefits that may sway prescribers to use these agents over others especially patients with an elevated ASCVD risk, it is difficult to definitively say that these agents do cause a reduction in certain outcomes.

References

1. Trujillo J, Nuffer W. Impact of Sodium-Glucose Cotransporter 2 Inhibitors on Nonglycemic Outcomes in Patients with Type 2 Diabetes. American College of Clinical Pharmacy. 2017. 37(4):481–91.
2. Ruanpeng D, Ungprasert P, Sangtian J, et al. Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors and Fracture Risk in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis. Diabetes Metab Res Rev. 2017. 33: e2903.
3. Zinman B, Wanner C, Lachin J, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. NEJM. 2015. 373: 2117-28.
4. Kohler S, Zeller C, Iliev H, et al. Safety and Tolerability of Empagliflozin in Patients with Type 2 Diabetes: Pooled Analysis of Phase I–III Clinical Trials. Adv Ther. 2017. 34:1707-26.
5. Kosiborod M, Cavender A, Fu, J et al. Lower Risk of Heart Failure and Death in Patients Initiated on SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study. 2017. Retrieved June 14, 2017, from http://circ.ahajournals.org/content/early/2017/05/16/CIRCULATIONAHA.117.029190.long
6. Kosiborod M, Cavender M, Fu A, et al. Lower Risk of Heart Failure and Death in Patients Initiated on SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study. Retrieved June 14, 2017, from http://circ.ahajournals.org/content/early/2017/05/16/CIRCULATIONAHA.117.029190.long
7. Borg R, Persson F. Empagliflozin Reduces Albuminuria—a Promise for Better Cardiorenal Protection from the EMPA-REG OUTCOME Trial. Ann Transl Med. 2017. 5(23): 478. Web.
8. LexiComp Online [Internet]. Hudson (OH): Wolters Kluwer, Inc. c1978-2016 [cited 2018 Mar 19]. Jan Available from http://online.lexi.com/action/homeBarnett A, Mithal A, Manassie J, et al. Efficacy and Safety of Empagliflozin Added to Existing Antidiabetes Treatment in Patients with Type 2 Diabetes and Chronic Kidney Disease: a Randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2014. 2:369–84.
9. Yale J, Bakris G, Cariou B, et al. Efficacy and Safety of Canagliflozin in Subjects with Type 2 Diabetes and Chronic Kidney Disease. Diabetes Obes Metab. 2013. 15:463–73.
10. Yamout H, Perkovic V, Davies M, et al. Efficacy and Safety of Canagliflozin in Patients with Type 2 Diabetes and Stage 3 Nephropathy. Am J Nephrol. 2014. 40:64–74.
11. Summary Safety Review - SGLT2 Inhibitors (canagliflozin, dapagliflozin, empagliflozin) - Assessing the Potential Risk of Bone-Related Side Effects. 2016. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-sglt2-inhibitors-canagliflozin-dapagliflozin-empagliflozin-risk-bone.html
12. Neal B, Perkovic V, Mahaffey, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. NEJM. 2017. 7; 377:644-57.
13. Invokana [package insert]. Online: Janssen Pharmaceuticals; 2016 updated August 2017.

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Annual Review of Changes in Healthcare

New Insulin/GLP-1RA Agents: Overview for the Pharmacist

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Learning Objectives
•Describe two novel diabetic agents that combine insulin and a GLP-1 Receptor Agonist
•Recognize clinical trials which define safety and efficacy of these agents
•Describe common side effects, drug interactions and precautions of each agent
•Identify how these agents may fit into existing guidelines and pharmacy practice

Abstract

Diabetes is a rapidly growing disease that is progressive in nature. Many medications are approved for the treatment of diabetes however, several novel agents show improved efficacy and safety over current therapies. In late 2016, two novel diabetic agents became available, insulin glargine and lixisenatide and insulin degludec and liraglutide. These medications combine basal insulin and a glucagon-like peptide-1 receptor agonist and were approved by the FDA to improve glycemic control in patients with Type 2 Diabetes Mellitus. Both products have shown benefits to patients during clinical trials. This review will discuss characteristics of each agent and where the use of these drugs may be implemented into current treatment guidelines.

Diabetes Mellitus (DM) is a common illness that affects more than 30 million Americans.[1] DM is rapidly increasing in prevalence in the United States and is expected to double by the year 2030. DM is currently the 7th leading cause of death.[1,2] Diabetes Mellitus Type 2 (DMT2) accounts for 90-95% of all diagnosed cases in the United States.[1]

It is no surprise that with the increasing prevalence and progressive nature of DMT2, that nearly 300 drug companies are involved with the development of new DMT2 drugs, and others are developing new delivery systems.[3] Advances are continuously being made to treatment approaches.[4] Diabetes treatment is ever evolving and it appears as though every year there are several new bottles on the shelf or new pens in the refrigerator. Pharmacists must not only be aware of these new drugs, but should feel confident in recommending or determining if these new drugs are appropriate in patient care.[4]

The combination of a basal insulin and glucagon-like peptide-1 receptor agonist (GLP-1RA) is becoming more popular in practice because these pharmacologic actions complement each other.[5] In late 2016, two new combination drugs were approved by the FDA for control of DMT2. Soliqua, a combination of insulin glargine and lixisenatide, and Xultophy, a combination of insulin degludec and liraglutide, contain both a basal insulin and GLP-1 receptor agonist. This article will review these two new insulin/GLP-1RA agents.

These products contain long-acting insulin analogs. Both insulin glargine and insulin degludec form multi-hexamers in the subcutaneous tissue which slowly dissolves into monomers and are absorbed.[6] This contributes to their long-acting activity.[6] The purpose of these insulins is to mimic the natural basal insulin in the body and this can result in decreased fasting and postprandial blood glucose.[6] GLP-1 receptor agonists, on the other hand, bind to several GLP-1 receptors in the body and enhance insulin secretion in a glucose dependent manner.[6] This mechanism ultimately controls postprandial glucose secretion and increases satiety and promotes weight loss.[6] According to the American Diabetes Association (ADA) guidelines, both insulin and GLP-1 agonists are currently considered second line in patients with DMT2 and are reserved for patients who did not respond to metformin monotherapy, or for those who present upon diagnosis with an A1c >9% along with metformin.[7] These agents are also recommended for those who present upon diagnosis with an A1c >10% as part of combination insulin therapy.[7] The combination of these drugs are only appropriate for use in patients with DMT2 due to its GLP-1 receptor agonist component.

Soliqua (insulin glargine and lixisenatide)

Soliqua was developed by Sanofi and approved in November 2016 to improve glycemic control in adults with DMT2 inadequately controlled on basal insulin or lixisenitide.[8] Soliqua's efficacy was studied through the LixiLan-L and LixiLan-O clinical trials.[9,10]

In the LixiLan-O trial, DMT2 patients who were inadequately controlled on metformin therapy were given either Lantus (insulin glargine) alone, Adlyxin

(lixisenatide) alone or Soliqua (in the trial referred to as iGlarLixi) as add-on to metformin.[9] The objective was to evaluate the efficacy and safety of iGlarLixi compared to Lantus or Adlyxin in DMT2 patients inadequately controlled on metformin.[9] The primary outcome was A1c change at 30 weeks. The results of the study showed that there were significant reductions in A1c when patients were given iGlarLixi versus Lantus or Adlyxin monocomponents ($P < 0.0001$).[9] In addition, more patients on iGlarLixi reached goal A1c ($P<0.0001$), had a decrease in mean body weight ($P<0.0001$), and had improved postprandial glycemic control compared to the other groups (95% CI iGlarLixi versus iGlar -2.8 to -2.0, 95% CI iGlarLixi versus Lixi -1.6 to -0.6), while having similar rates of symptomatic hypoglycemia (iGlarLixi 26%, iGlar 24%, Lixi 6%).[9]

In the LixiLan-L trial, DMT2 patients who were inadequately controlled on Lantus (insulin glargine) were randomized and given either Lantus (insulin glargine) alone or Soliqua (in the trial referred to as iGlarLixi).[10] The objective was to evaluate the efficacy and safety of iGlarLixi compared with Lantus in DMT2 patients who were inadequately controlled on Lantus.[10] The primary outcome was A1c change at 30 weeks.[10] The results of the study showed that there were significant reductions in A1c from baseline when patients were given iGlarLixi versus Lantus ($P < 0.0001$).[10] In addition, patients on iGlarLixi had a decrease in mean body weight, while those on Lantus had an increase in mean body weight (both $P<0.0001$).[10] Symptoms of hypoglycemia were comparable between groups (iGlarLixi 40%, iGlar 42.5%).[10]

From these two studies, it was concluded that the expected reduction in A1c for patients was 1.09-2.41% in 30 weeks.[9-11]

Soliqua 100/33 unit-mcg/mL (100 units of insulin glargine and 33 mcg of lixisenitide per mL) is available in a pen and delivers doses from 15-60 units of insulin in a single injection.[8] The injections can be delivered subcutaneously into the thigh, upper arm, or abdomen. Before initiating Soliqua, lixisenitide or basal insulin therapies should be discontinued.[8] Dosing should be based on prior glucose lowering therapy.[8,12] In patients who have previously been inadequately controlled on lixisenatide, or those patients currently on less than 30 units of basal insulin, Soliqua 15 units should be initiated.[9,12] However, in patients who have previously been inadequately controlled on 30-60 units of basal insulin, Soliqua 30 units should be initiated.[8,12] Maximum daily dosage is 60 units per day.[8,12] Manufacturer labeling recommends titrating the dose of Soliqua by 2-4 units per week dependent on the patient's metabolic needs.[8,12] This medication should be taken in the morning.[12]

There are no dosage adjustments specified in the manufacturer labeling for mild to moderate renal impairment, however patients should be monitored carefully as studies have shown lixisenatide concentrations are increased in patients with renal impairment.[8,12] The half-life of Soliqua was found to be 3 hours, and the clearance of Soliqua is 35L/h.[8] Soliqua is not recommended in patients with end stage renal disease.[12] Dosage adjustments are not

specified in the package insert for hepatic impairment, however due to the pharmacokinetic principles of both insulin glargine and lixisenitide, it is unlikely Soliqua will be affected by hepatic impairment.[8,12]

After administration of Soliqua, insulin glargine showed no pronounced peak.[8] Lixisenatide reached a peak concentration at 2.5-3 hours after administration.[8] While there was a small decrease observed in concentration of lixisenitide between combination Soliqua and lixisenitide alone, this difference was not considered clinically relevant.[8]

Like many injectable glucose-lowering agents (i.e. Lantus, Victoza), Soliqua pens should be stored in the refrigerator prior to initial use and stored at room temperature after first use.[12] The pen may be used for up to 14 days following first use.[12]

The most common side effects of Soliqua include hypoglycemia, headache, nausea, diarrhea and hypersensitivity reactions.[8,12] The chances of hypoglycemia are increased when a patient is taking Soliqua in combination with other glucose-lowering agents. In addition, drugs that mask or enhance the signs and symptoms of hypoglycemia, like beta blockers and some antibiotics (e.g. quinolones and sulfmethoxazole) should be avoided.[12] If a patient has pancreatitis, or expected pancreatitis, Soliqua should be discontinued immediately.[8] Lixisenatide slows gastric emptying and therefore this product should not be used in patients with gastroparesis.[8,12] The delayed gastric emptying may affect absorption of oral medications. As a result, oral contraceptives and antibiotics should be taken at least 1 hour before or 11 hours after administration of Soliqua.[8] This can be problematic as patients must take this medication in the morning, so it is important to counsel patients on why this is necessary.[8] In addition, patients on oral medications with narrow therapeutic indexes, such as warfarin or digoxin, should receive careful clinical monitoring.[8] Soliqua has not been extensively studied in pregnancy; however, based on animal studies there may be risks to the fetus from exposure to lixisenatide.[8,12] Therefore, this medication is not recommended in pregnancy.

Since Soliqua contains an insulin analog, patients should be counseled about usual insulin precautions, in particular hypoglycemia.[12-13] Patients should also be counselled on how to administer Soliqua and be encouraged to never reuse needles.[8,12-13]

Summary:

Use: To improve glycemic control in DMT2 patients who are inadequately controlled on basal insulin or lixisenitide.
Dose: 15-60 units subcutaneously once each morning at least 1 hour prior to first meal of the day. Maximum daily dose is 60 units. No dosing adjustments specified for renal or hepatic impairment.
% A1c Reduction: 1.09% to 2.41% after 30 weeks.
Important Considerations: Soliqua should be administered one hour prior to food. Keep Soliqua pens in the fridge prior to initial use. Soliqua should not be used in ESRD or in patients with pancreatitis or gastroparesis. Special precautions must be taken when a patient is receiving oral antibiotics, contraceptives or drugs with a

narrow therapeutic index due to delayed gastric emptying. There is insufficient data to determine if Soliqua is safe in pregnancy. Hypoglycemia is the most common adverse reaction and patients should be counselled on these signs and symptoms.

Xultophy (insulin degludec and liraglutide)

Xultophy was developed by Novo Nordisk and approved for use in November 2016 to improve glycemic control in DMT2 for patients who are inadequately controlled on basal insulin or liraglutide alone. Xultophy's efficacy was studied in a total of 1,393 patients in three different randomized, open-label trials over twenty-six weeks in the DUAL program (including DUAL-II, DUAL-III, and DUAL-V trials). The combination of basal insulin and GLP-1RA provides convenient administration of both products in a single, once-daily injection.[14]

In the DUAL-II trial, DMT2 patients who were inadequately controlled on metformin therapy were given either Tresiba (insulin degludec) alone or Xultophy (in the trial referred to as iDegLira).[15] The objective of this study was to evaluate the efficacy and safety of iDegLira compared to Tresiba.[9] The primary outcome was A1c change at 26 weeks. The results of the study showed that there were significant reductions in A1c when patients were given iDegLira versus Tresiba alone ($P < 0.001$).[15] In addition, more patients on iDegLira had a decrease in mean body weight ($P<0.001$) while having similar rates of symptomatic hypoglycemia (iDegLira 24% iDeg 25%).[15]

In the DUAL-III trial, DMT2 patients who were inadequately controlled on metformin and liraglutide, or metformin and exenatide therapy were randomized and given either their previous GLP-1RA treatment and dose or Xultophy (called iDegLira).[16] The objective of this study was to evaluate the efficacy and safety of iDegLira compared with GLP1-RAs in DMT2 patients who were inadequately controlled on liraglutide or exenatide.[10] The primary outcome was A1c change at 26 weeks.[10] The results of the study showed that there were significant reductions in A1c from baseline when patients were given iDegLira versus GLP-1RA therapy alone ($P < 0.001$).[16] In addition, patients on iDegLira were more likely to reach their goal A1c than those with GLP-1RA alone ($P<0.001$).[16] Symptoms of hypoglycemia were higher in the iDegLira group ($P<0.001$).[16]

In the DUAL-V trial, DMT2 patients who were inadequately controlled on metformin and Lantus (insulin glargine) therapy were randomized and given either Lantus (insulin glargine) or Xultophy (iDegLira).[17] The primary outcome was A1c change at 26 weeks.[17] The results of the study showed that there were significant reductions in A1c from baseline when patients were given iDegLira versus Lantus ($P<0.001$).[17] In addition, patients on iDegLira had a decrease in mean body weight, while those on Lantus had an increase in mean body weight ($P<0.001$).[17] Significantly fewer hypoglycemic events were reported in the iDegLira group ($P<0.001$).[17] From these studies, it was concluded that the expected reduction in A1c for patients is 1.3-1.9% over 26 weeks.[15-17]

Xultophy 100/3.6 units-mg/mL (100 units of insulin glargine and 3.6 mg of liraglutide per mL) is available in a pen and

can deliver doses from 10 to 50 units of insulin per injection. The injections can be delivered subcutaneously into the thigh, upper arm, or abdomen. Xultophy should be injected the same time daily and can be given with or without food. The maximum daily dose is 50 units of Xultophy (50 units insulin degludec and 1.8 mg of liraglutide). The initial starting dose is recommended at 16 units. Xultophy can be titrated up 2 units every 3-4 days as needed based upon blood glucose, metabolic needs, and glycemic control. If patients require doses that are frequently under 16 units, alternative therapy should be considered. At this time, there is no known information on renal or hepatic impairment dosage adjustments.[14]

Like many injectable glucose-lowering agents, Xultophy pens should be stored in the refrigerator prior to initial use and stored at room temperature after first use.[12]

Xultophy reaches steady state in approximately 48-72 hours after consistent daily administration. Protein binding is approximately 99% bound to plasma proteins.

Side effects that were most commonly reported were hypoglycemia, nasopharyngitis, headache, nausea, diarrhea, increased lipase enzymes, and upper respiratory tract infections. Hypoglycemia remains the most common adverse reaction in patients using insulin products. There were no significant differences found in the occurrence of hypoglycemia in patients using Xultophy and comparator medications.[15-16] Major precautions include pancreatitis, hypoglycemia, acute kidney injury, hypersensitivity and allergic reactions, and hypokalemia. A black box warning for Xultophy is the risk of thyroid C-cell tumors. Xultophy can only be used in pregnancy when the benefit outweighs the risk to the fetus.[14]

Since Xultophy contains an insulin analog, patients should be counselled about usual insulin precautions, in particular, hypoglycemia. Patients should also be counseled on how to administer Xultophy and encouraged to never reuse needles.[14]

Knowledge Check: True or False?
Both Soliqua and Xultophy have a black box warning for thyroid C-cell tumors.

Answer: False, only Xultophy

Summary:

Use: To improve glycemic control in DMT2 patients who are inadequately controlled on basal insulin or liraglutide
Dose: Starting dose is 16 units subcutaneously once daily. Maximum daily dose is 50 units.
% A1c Reduction: 1.3-1.9% after 26 weeks
Important Considerations: Xultophy can be administered with or without food, as long as it is given the same time daily to help control blood glucose effectively. The pens should be stored in the refrigerator until they are ready for use, and can be stored at room temperature for 21 days once out of the fridge. Hypoglycemia is the main adverse reaction to this medication. There is a black box warning for thyroid C cell tumors.

Discussion

While Soliqua and Xultophy have different active ingredients, both agents appeared to be effective and may decrease a patient's A1c by roughly 1-2%.[9,10,15-17] Many of the agents adverse events overlap due to the inclusion of similar drug classes.[12,18] Upon literature search, no head-to-head trials of these agents have been found. Therefore, clinical judgment should be used when choosing one agent over the other based upon what is known for each drug individually. This decision should look closely at patient specific factors. For example, a patient who would like to take their insulin/GLP1-RA at night and/or without regard to meals may benefit from choosing Xultophy over Soliqua. However, a patient with family history of thyroid tumors may benefit from Soliqua instead of Xultophy.

Both classes of drugs are considered second line agents in the treatment of DMT2 (metformin is first-line).[7] Particularly, these combination products fit well into the guidelines as options in patients who have been inadequately controlled on metformin in addition to, either a basal insulin or a GLP-1RA alone.[7]

Combinations of basal insulin and GLP-1RAs have shown promising results while limiting episodes of hypoglycemia.[5,9,10,15-17] Patients may enjoy limiting their injections to once daily and potentially losing weight. These agents are convenient due to the fact that patients only have to carry one pen with them instead of two. There is potential for less confusion about "which-pen-is-which" or what drug they have already administered. In theory, this added convenience might improve patient adherence and ultimately help forgetful patients better control their diabetes.

A shortcoming with these agents is in patients who require very high doses of basal insulin to control their blood sugars. Furthermore, while some patients appreciate only needing one injection per day, this may make little difference to patients who are on bolus (mealtime) insulin. Cost is also a considerable factor in choosing these agents, and it is possible not all insurances may cover the combination of these products.

Conclusion

Diabetes is a rapidly growing disease in the United States. Many new drugs are coming to market, and pharmacists must stay up to date on the newest products in order to properly make recommendations for optimal patient care. Soliqua and Xultophy were approved in late 2016 for the use in DMT2 patients for improved glycemic control. Both of these drugs are combinations of basal insulin and different GLP-1 receptor agonists. The medications have fixed ratios of basal insulin to the GLP-1 receptor agonist. Both agents show promising results in the reduction of A1c. The combination of two of these agents may potentially help improve compliance. Patient specific factors should be considered in determining whether these agents are appropriate in the treatment of DMT2. Overall, these drugs may be effective in certain patients to help achieve better glycemic control.

References

1. CDC. Diabetes quick facts. 2017 July [cited 2017 Dec 27]. Available from: https://www.cdc.gov/diabetes/basics/quick-facts.html
2. Olokoba A, Obateru O, Olokob L. Type 2 diabetes mellitus: A review of current trends. Oman Med J [Internet]. 2012 July [cited 2017 Dec 25]; 27(4): 269-73. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3464757/Agnelli G
3. Buse J. New diabetes drugs in development. Medscape [Internet]. 2017 March 10. [cited 2017 Dec 25]. Available from: https://www.medscape.com/viewarticle/876853
4. Stern G, Salvo M, Palazzo C. New and emerging therapies for the treatment of diabetes. Drug Topics [Internet]. 2015. [cited 2017 Dec 25]. Available from: https://ufonline.findlay.edu/bbcswebdav/pid-1530715-dt-content-rid-4448233_2/courses/PHAR473_01_SP2017/PHAR473_01_SP2017_ImportedContent_20161214020856/drtp0215_040-049%20CE-Final.pdf
5. Patel DK, Goldman J. Fixed-ratio combination of basal insulin and GLP-1 receptor agonist. Pharmacy Times [Internet]. 2017 December 29. [cited 2017 Dec 27]. Available from: http://www.pharmacytimes.com/publications/health-system-edition/2017/september2017/fixedratio-combination-of-basal-insulin-and-GLP1-receptor-agonist
6. DiPiro JT, Schwinghammer TL, Wells B. Pharmacotherapy: A pathophysiologic approach, 5th ed., Appleton & Lange, Stamford, CT, 2002.
7. American Diabetes Association. Standards of medical care in diabetes—2018. Diabetes Care. 2018; 41(1):S73-85.
8. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Soliqua application package labelling. 2016 November. [cited 2017 Dec 27]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208673Orig1s000lbl.pdf
9. Rosenstock J, Aronson R, Grunberger G, et al. Benefits of lixilan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: The lixilan-o randomized trial. ADA [Internet]. 2016 November. [cited 2017 Dec 28]; 39(11): 2026-35. Available from: http://care.diabetesjournals.org/content/39/11/2026
10. Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and Safety of lixilan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: The lixilan-L randomized trial. ADA [Internet]. 2016 September. [cited 2017 Dec 27]. Available from: http://care.diabetesjournals.org/content/early/2016/09/09/dc16-1495
11. Neuman L. Soliqua shows promise lowering hemoglobin a1c levels in type 2 diabetes. The American Journal of Pharmacy Benefits [Internet]. 2017 June 12. [cited 2017 Dec 28]. Available from: http://www.ajpb.com/conferences/ada-2017/soliqua-shows-promise-lowering-hemoglobin-a1c-levels-in-type-2-diabetes
12. Lexicomp [Internet]. Hudson (OH): Wolters Kluwer. C2016. Soliqua; [updated 2017 August 8; cited 2017 December 28]; [about 30 screens]. Available from: https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/63417
13. Barrett J. 5 new drugs in primary care pharmacists should know. Pharmacy Times [Internet]. 2017 June 04. [cited 2017 Dec 28]. Available from: http://www.pharmacytimes.com/conferences/ashp-summer-2017/5-new-drugs-in-primary-care-pharmacists-should-know80
14. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Xultophy application package labelling. 2016. November. [cited 2017 Dec 27]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208583Orig1s000LBL.pdf
15. Buse J, Vilsbøll T, Thurman J, et al. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (ideglira). ADA [Internet]. 2016 September. [cited 2017 Dec 27]. Available from: http://care.diabetesjournals.org/content/37/11/2926
16. Linjawi S, Bode BW, Chaykin LB, et al. The efficacy of IDegLira (Insulin degludec/liraglutide combination) in adults with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist and oral therapy: DUAL III randomized clinical trial. NCBI [Internet]. 2017 February; 8(1): 101–14. [cited 2017 Dec 29]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5306117/

17. Lingvay I, Pérez Manghi F, García-Hernández P, et al. Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: The DUAL V randomized clinical trial. NCBI [Internet]. 2016 March 1;315(9):898-907.[cited 2017 Dec 29]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26934259

18. Lexicomp [Internet]. Hudson (OH): Wolters Kluwer. c2016. Xultophy [updated 2017; cited 2017 December 28]; [about 30 screens]. Available from: https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6341566

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Overview of the Gestational Diabetes Educational Gap

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Continuing Education Information

CE Hours: 1.00
CEU: 0.100
CE Expiration Date: 5/1/2020
Activity Type: Knowledge
CE Activity # 0864-0000-18-021-H01-P
Please login at https://cpeconsultants.learningexpressce.com/index.cfm and complete the post-test and evaluation to claim your CE credit.

A short recap video is available at:
https://drive.google.com/file/d/12mFnGt544tTRRdh2sqLQ9Kd3bEb4QWXZ/view?usp=sharing

Learning Objectives
•To express the importance of education in the prevention of gestational diabetes mellitus
•To recognize common barriers with pregnant and postpartum women in receiving appropriate care and education regarding gestational diabetes mellitus and type 2 diabetes mellitus

Abstract

A holistic approach to preventing gestational diabetes mellitus (GDM) in pregnant women may decrease the incidence of recurring GDM and type two diabetes mellitus (T2DM) postpartum. The American College of Obstetricians and Gynecologists state that a glucose screening test is generally given to women between 24 and 28 weeks, unless the woman has a history of GDM. Education on preventing GDM for women early in their pregnancy is not standardized, and GDM may not be discussed unless diagnosed. There are few published studies on education for prevention of GDM and its impact on the incidence of T2DM. In addition, postpartum follow-up for blood glucose screening is not well-documented. Further research on these topics may have global impacts.

Gestational diabetes mellitus (GDM) refers to pregnant women who did not have diabetes prior to pregnancy, but develop high blood sugar levels prior or during the 24th-28th week of pregnancy.[1,2] The prevalence of GDM is up to 14% of all pregnancies and the rate is increasing.[2] This makes GDM the most frequent medical complication of pregnancy, presenting risks for both the mother and newborn.[2] Maternal risks include difficult labor, vaginal trauma, cesarean delivery, or uterine rupture.[2] Newborn risks include fetal macrosomia, hypoglycemia, polycythemia, or metabolic syndrome.[2] Although monitoring of GDM is undertaken during prenatal visits to prevent short-term complications, there is a lack of education given to convey the importance of prevention and post-partum follow-up. This gives room to long-term complications, such as developing T2DM.

The presented literature investigates prevention of GDM and T2DM. The literature reveals that the incidence rate of diagnosed T2DM is growing, and women diagnosed with GDM have a higher risk of T2DM diagnosis when compared to women without GDM.[3] The condition may remit after delivery, however, 40 to 80% eventually progress to T2DM.[2] With that known, it is all the more important to educate on prevention of GDM and the risks of T2DM. Some literature also addresses the lack of proper follow-up care for women with GDM during the postpartum period. The 2018 ADA guidelines for GDM recommend that reclassification of maternal glycemic status should be performed 4 to 12 weeks postpartum using oral glucose tolerance test (OGTT) and then monitored every three years after that.[2] However, there are several barriers preventing women from returning for follow-up and women with GDM often do not receive postpartum blood glucose screening.[4] Through review of the following articles, it is clear that GDM is a major factor that places women at a higher risk of developing T2DM. This suggests that education on GDM and T2DM should be emphasized and there needs to be improvement in postpartum follow-up procedures. Implementing both may help patients to receive better care in prevention and treatment.

To decrease the incidence of GDM and T2DM, education to women who are trying to become pregnant or who are pregnant is an important factor. Most individuals have heard or known of someone with diabetes mellitus. However, many lay-people do not comprehend the seriousness of developing the disease. The lack of awareness in T2DM complications may be an additive factor in the increasing incidence of GDM. Forty-two studies from various countries were systematically reviewed and included 7,949 women.[5] It was noted that there was a broad range of experiences of antenatal GDM care and management. The women in these studies had experienced GDM and reported on knowledge and attitudes toward GDM, attitudes toward postpartum follow-up, and potential barriers in healthcare to reach this population of patients. Some patients felt that GDM care was segmented, and many noted that the information and education available for GDM care was deficient.[5] There was a barrier commonly due to poor knowledge of risk for developing T2DM and putting the

infant's needs first. Therefore, there may be a need for a proactive approach to postpartum GDM care, which would include diabetes screening test, self-blood glucose monitoring, and making follow-up appointments.[5] A greater emphasis of education on GDM and prevention of GDM and T2DM may be beneficial. Knowledge of GDM and T2DM may decrease the incidence of GDM, which should in return decrease the incidence of T2DM.

Minooee et al. conducted a study aimed to confirm that there is a higher risk of developing type II diabetes mellitus (T2DM) when a woman is diagnosed with gestational diabetes compared to pregnant women without GDM.[6] There were 15,005 individuals that were invited to join the study from the Tehran Lipid and Glucose Study that started in 1998.[6] There were follow-up visits every three years.[6] Of this study population, 4,076 women of reproductive age, that had at least one term pregnancy, were eligible to be in the analysis of diabetes incidence between women with a history of GDM and without a history of GDM.[6] Women that had experienced GDM had a higher rate of developing diabetes and a shorter survival time.[6] Family history of T2DM and an elevated BMI were additional risk factors for women.[6] It was estimated that GDM affects about 16.9% of all pregnancies, and the diagnosis greatly increases the risk of developing T2DM within the following ten years by 13-fold.[6] Aiming to prevent new cases of GDM and managing the postpartum health of the mother that was diagnosed with GDM should decrease the new cases of T2DM. This would create more effort upfront from healthcare workers, which would increase costs. However, preventing a case of T2DM and managing the disease for a lifetime should overall decrease time needed from healthcare workers and healthcare costs.

Knowledge Check: True or False?
True or False: A diagnosis of GDM does not have a significant impact on developing T2DM.

Answer: False

Since the incidence of T2DM is much higher in patients with GDM, it is vital to get proper follow-up care. Ying et al. claims in their study, that 50% of women with GDM will develop T2DM within 5 years of delivery if there is no intervention.[4] However, in the study there were several barriers that prevented women from returning for follow-up care and blood glucose screening. In this study, postpartum women who delivered at Tianjin Obstetrics and Gynecology Hospital from 2008 to 2010 were phone interviewed by 30 obstetricians to evaluate awareness and importance of follow-up.[4] The study included 2152 women who had GDM. Of the 2152 women, only 282 (13.1%) were screened for blood glucose levels postpartum and 8 of the 282 (2.8%) were diagnosed with diabetes.[4] The study then investigated reasons for failed blood glucose screening and the top three reasons included not being informed by their physicians, believing that GDM would disappear after delivery, and being occupied

with the baby.[4] Since the top reason was due to no notification from doctors, the 30 obstetricians were interviewed and 25 were aware of the need for postpartum blood glucose screening for women with GDM, but only 15% had informed their patients.[4] This again ties into the importance of education on GDM and T2DM risks. Education may help with adherence to obtain follow-up care and blood glucose screening for the prevention and reduction of GM and T2DM.

Overall, the incidence of gestational diabetes mellitus has been increasing worldwide and is a multifactorial problem. However, education about the disease state and follow-up appointments are two ways of impacting the incidence positively. Since many of the aspects of GDM are controllable, it is reasonable for healthcare professionals to take action in educating women planning to become pregnant or women who are pregnant on ways to prevent and manage gestational diabetes mellitus.

References

1. American Diabetes Association [Internet]. Arlington, VA: Simon & Schuster. 26 Jan 2003 [updated 21 Nov 2016; cited 10 Jan 2018]. Available from: http://accesspharmacy.mhmedical.com/content.aspx?bookid=981&sectionid=60526946
2. American Diabetes Association [Internet]. Arlington, VA: Simon & Schuster. 7 Jun 2013 [cited 10 Jan 2018]. Available from: http://www.diabetes.org/diabetes-basics/gestational/what-is-gestational-diabetes.html
3. Management of diabetes in pregnancy: Standards of Medical Care in Diabetes- 2018. American Diabetes Association [Internet]. Diabetes Care 2018 [cited 10 Jan 2018];41(Suppl. 1):S137–S143. Available from: http://care.diabetesjournals.org/content/41/Supplement_1/S137
4. Chang Y, Chen X, Zhang Z, et al. Follow-up of postpartum women with gestational diabetes mellitus (GDM) [Internet]. 6 Sept 2014 [cited 10 Jan 2018]; 106 (2): 236-40. Available from: http://www.diabetesresearchclinicalpractice.com/article/S0168-8227(14)00383-0/fulltext
5. Middleton P, Shute E, Hague W, et al. Women's views and knowledge regarding healthcare seeking for gestational diabetes in the postpartum period: a systematic review of qualitative/survey studies [Internet]. 25 Sept 2015 [cited 10 Jan 2018]; 110 (2): 109-22. Available from: http://www.diabetesresearchclinicalpractice.com/article/S0168-8227(15)00383-6/fulltext
6. Minooee S, Rahmati M, Azizi F, et al. Diabetes incidence and influencing factors in women with and without gestational diabetes: a 15 year population-based follow-up cohort study [Internet]. 8 Apr 2017 [cited 10 Jan 2018]; 128:24-31. Available from: http://www.diabetesresearchclinicalpractice.com/article/S0168-8227(16)30714-8/fulltext

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Review of Alzheimer's Disease Treatment and Potential Future Therapies

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that leads to decline in cognitive functioning and ultimately loss of social independence. The complete pathology of this disease is not yet understood. However, the mechanisms currently proposed include formation of neurofibrillary tangles, deposition of β-amyloid plaques, and decreased cholinergic neurotransmission. There are no definitive causes of this condition, but age appears to be a risk factor. This article will review current treatments that are used in practice, highlighting the medication class, mechanism of action, and common or serious side effects. Areas of future drug development will also be reviewed. As new information regarding the pathophysiology of AD is uncovered, researchers will continue to develop new potential therapies.

Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder resulting in memory impairment, ultimately leading to changes in thinking and behavior. This neurologic disorder is a form of dementia that causes a long-term decline in cognitive function, leading to decreased ability to perform activities of daily living and loss of social independence.[1] According to the Alzheimer's Association, AD is the most common form of dementia and affects approximately 5.5 million individuals within the United States. It is most commonly seen in those over the age of 65, with approximately 5.3 million Americans with AD being 65 years or older. Since the year 2000, mortality due to AD has increased by 89%.[2] As the population in the United States continues to age, the number of AD cases is expected to rise, with an expected prevalence of 13.2 million Americans by 2050.[3] Currently, there is no single laboratory test that is able to definitively diagnose AD; the diagnosis of AD requires a comprehensive medical assessment. This may include the patient's medical history, mental status testing, physical or neurological examination, and serum tests as well as brain imaging to rule out other causes of dementia.[4] As a result, this disorder may be difficult to diagnose accurately.

There are no definitive causes of this condition, but there are certain factors that contribute to increased risk. The most significant risk factors for AD are age and family history. Individuals age 65 or older are at an increased risk of developing AD, as well as those with a first-degree relative that has the disease.[2] Variations in certain genes may also play a role in development of the disease. The one gene that has currently been found to have the strongest impact is APOE-e4, the e4 isoform of apolipoprotein E. Those inheriting the e4 allele of this gene are at an increased risk of AD and may develop symptoms at a younger age.[5] Mutations in the genes coding for amyloid precursor protein, presenilin-1 and presenilin-2, have also been implicated in development of autosomal dominant early-onset AD.[6] Other risk factors include female gender, serious head injury, and lack of stimulating mental activity.[2] Unfortunately, there is currently no cure for AD and the presently available therapies are unable to reverse the condition. However, there are medications that have some usefulness in delaying the progression of AD and future therapies are currently being investigated to develop agents with greater effectiveness.

There are several key pathologic features of AD. One of these is accumulation of neurofibrillary tangles of the tau protein within neurons in the brain. This protein forms part of the microtubule structure, which is integral to maintaining the shape of the neuron and transporting nutrients from one part of the cell to another. In AD, the tau proteins are hyperphosphorylated and as a result, the microtubules disassemble.[7] The tau proteins then precipitate and form tangles with each other. Another distinguishing feature of AD is the accumulation of β-amyloid plaques between neurons in the brain. These plaques form from the abnormal processing of amyloid precursor protein, resulting in overproduction of β-amyloid protein.[7] The accumulation of these neurofibrillary tangles and amyloid plaques leads to the neuronal degeneration that is

characteristic of AD. Decreased levels of the neurotransmitter acetylcholine are also thought to play a role in the progression of Alzheimer's. Acetylcholine is thought to have some effect on learning and formation of new memories, and it has been hypothesized that destruction of cholinergic neurons in the basal forebrain contributes to the manifestation of AD.[8] Medications that increase the brain levels of acetylcholine have been the primary means of treatment, though their limited effectiveness calls for the need to investigate other pathways.

Symptoms

Symptoms of AD typically start to manifest in the mid-60s, with recent memory being affected first. As the disease progresses, the cognitive impairment becomes more severe and patients will require greater assistance with daily living. AD progresses in several stages. Those with mild AD begin to have some memory impairment but are still largely able to maintain independence. Symptoms in this stage may include misplacing items, taking longer to complete daily tasks, a worsening sense of direction, and repeating questions. In moderate AD, the patient begins to require more frequent supervision and care. In this stage, patients may exhibit increased memory loss, confusion, trouble understanding and/or forming words, difficulty performing routine multi-step tasks, and behavioral changes such as agitation, anxiety, or depression. In severe AD, the patient becomes completely dependent on others for their care. Those in this stage commonly exhibit mutism, long-term memory loss, difficulty swallowing, double incontinence, and are bed-ridden.[9] Early detection of symptoms is important so that treatment may begin as soon as possible, with a greater chance of slowing the progression of AD to preserve the patient's overall health and quality of life.

Current Pharmacologic Treatments

Since none of the currently available therapies for AD are curative or reverse the disease process. The present goal of treatment is to treat the symptoms and preserve cognitive functioning for as long as possible. The first-line agents for treatment of AD are acetylcholinesterase inhibitors. These drugs inhibit the enzyme acetylcholinesterase, which is responsible for metabolizing acetylcholine. As a result, use of these medications causes an increase in the acetylcholine concentrations and this has been associated with mild improvements in cognitive function, behavior, and activities of daily living in those treated for a period of at least 6 months.[10] The currently available acetylcholinesterase inhibitors include donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne).

Donepezil is a reversible and noncompetitive inhibitor of centrally acting acetylcholinesterase, and is approved for use in mild, moderate, and severe AD. It is available as a tablet and an oral disintegrating tablet (ODT). Rivastigmine is a reversible and noncompetitive inhibitor of both acetylcholinesterase and butyrylcholinesterase, and is approved for mild to moderate AD, as well as dementia related to Parkinson's disease. It is available as a capsule and transdermal patch. Only the patch formulation is indicated for severe AD and may be a preferable option for patients

with difficulty swallowing or those experiencing adverse GI effects from the oral formulation. Galantamine is a reversible and competitive central acetylcholinesterase inhibitor that also has a sensitizing effect on nicotinic cholinergic receptors. It is approved for mild to moderate AD and available as a tablet, extended release capsule, and oral solution. All the agents in this class show similar efficacy, and choice is generally based on patient preference and tolerability. The most common side effects of the acetylcholinesterase inhibitors are GI related. These include nausea, vomiting, diarrhea, and decreased appetite. However, these adverse effects are typically mild and the medications are generally well tolerated.[11]

Another agent that is approved for AD is memantine (Namenda). Memantine is an NMDA receptor antagonist indicated for moderate to severe Alzheimer's. In AD, there is thought to be an overexposure of NMDA receptors to the excitatory neurotransmitter glutamate. Overstimulation of these receptors leads to excitotoxicity and contributes to neuronal cell death.[12] By blocking NMDA receptors, memantine reduces the amount of glutamate that can bind to these receptors. A Cochrane review found that treatment with memantine for a 6 month period showed a slight improvement in cognition and ability to perform activities of daily living for those with moderate to severe AD.[10] It is available as a tablet, extended release capsule, and oral solution. Memantine may be administered as monotherapy or combined with an acetylcholinesterase inhibitor for a potentially synergistic effect. Side effects of this drug may include headache, dizziness, confusion, hypertension, constipation, and diarrhea.[12]

There is also a combination of extended release memantine with donepezil (Namzaric) that was approved in 2014 for moderate to severe AD. In an observational study involving 382 AD patients with mean follow-up of 30 months and mean treatment duration of 22.5 months, those receiving this combination showed significantly lower rates of deterioration on measures of cognition and function compared with those on acetylcholinesterase inhibitor monotherapy.[13] Another observational study involving 943 patients with a mean follow-up time of 62.3 months showed that those patients on the combination of memantine and donepezil were significantly less likely to be admitted to a nursing home compared with those on acetylcholinesterase inhibitor monotherapy.[13]

Future Pharmacologic Therapies

Due to the significant prevalence of AD and the minimal effectiveness of current therapies, many clinical trials are assessing new treatment options for the disease. One class of medications that is currently being developed are inhibitors of the beta-site amyloid precursor protein cleaving enzyme (BACE inhibitors). These compounds inhibit the enzyme β-secretase, which is responsible for producing the β-amyloid protein that is responsible for the plaque formation in AD. Results of phase I trials showed these drugs were able to demonstrate 45-95% reductions in β-amyloid protein within the cerebrospinal fluid. However, it is still unclear what degree of reduction is necessary to see clinical benefit, and at what point in the AD process these drugs should be initiated.[14] There are currently 10 phase II or III clinical trials

being conducted involving these molecules.[14] One phase III trial compares lanabecestat 20mg and 50mg versus placebo in patients with early AD. The primary outcome is change from baseline score on the 13-item AD Assessment Scale-Cognitive Subscale (ADAS-Cog13) at week 104. The trial is expected to be completed in September 2019.[15] Another similar phase III clinical trial is being conducted with elenbecestat, which is another BACE inhibitor with the same mechanism as lanabecestat. This trial is expected to be completed in December 2020.[16]

Another class of agents being evaluated are monoclonal antibodies (mAbs). There are currently 16 such antibodies being investigated in 31 clinical trials. These agents target either the tau protein or various forms of β-amyloid, leading to increased clearance of these proteins.[14] Solanezumab is an antibody that targets soluble β-amyloid. In a previous phase III efficacy trial involving 2100 patients with mild AD, this drug failed to separate from placebo. Aducanumab targets multiple forms of β-amyloid aggregates and has shown promising results in phase I/II trials.[14] A previous study in patients with prodromal and mild AD found that one year of monthly IV infusions of aducanumab reduced brain levels of β-amyloid in a dose and time-dependent manner. This was also reflected in a slowing of clinical decline as measured by Clinical Dementia Rating-Sum of Boxes (CDR-SB) and Mini Mental State Examination (MMSE) scores.[17]

Solanezumab is now being assessed in a phase III trial for the prevention of AD in older subjects with confirmed brain amyloid deposits. The planned treatment duration is 240 weeks and the primary outcome is change from baseline of the ADCS Preclinical Alzheimer Cognitive Composite (ADCS-PACC). The study is expected to be completed by July 2022.[18]

Aducanumab is now continuing in several phase III trials, both expected to conclude in 2022. Both trials have an expected treatment duration of 78 weeks, with primary outcome of change from baseline in CDR-SB score.[19,20]

Crenezumab is an IgG_4 antibody that targets both soluble oligomeric and fibrillary β-amyloid. The phase III CREAD study has begun enrolling patients with prodromal to mild AD. The study is expected to conclude in July 2021, and the primary outcome is change from baseline to week 105 in CDR-SB score.[21]

Gantenerumab, an antibody targeting β-amyloid aggregates, is currently being studied in several phase III clinical trials in patients with mild AD. One such trial has a planned treatment duration of 104 weeks, with several primary outcomes. These outcomes include mean change from baseline in ADAS-Cog13 and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scores. The study is expected to conclude in July 2020.[18]

BAN2401 is an antibody that binds to the amino terminus of large soluble β-amyloid aggregates.[14] It is currently in a phase II trial involving subjects with early AD, and is expected to be completed in November 2018. The primary outcome measure is change from baseline in the Alzheimer's Disease Composite Score (ADCOMS) at 12 months.[22]

ABBV-8E12 is a tau targeting antibody. It is currently in a phase II trial of

patients with early AD, with anticipated completion in June 2021. The primary outcome is change from baseline to week 96 in CDR-SB score.[23]

RO7105705 is another antibody targeting the tau protein. It has completed a phase I trial in mild to moderate AD and is now undergoing a phase II trial in prodromal to mild disease. This phase II trial is expected to be completed in September 2020 and the primary outcome is change from baseline to week 72 in CDR-SB score.[24,25]

There are also clinical trials in AD focusing on insulin therapy and drugs that affect insulin release.[26] Proteins involved in insulin signaling have been found in neurons of many brain regions that are affected in AD, such as the temporal lobes and hippocampus. In addition, autopsy examination of brain tissue from AD patients showed impaired neuronal insulin signaling.[26] Insulin-related therapies that are currently being studied include intranasal insulin, liraglutide, and pioglitazone.[14]

Intranasal humulin insulin is being evaluated in a phase II/III trial involving 240 patients with mild cognitive impairment or mild AD. There is a 12 month treatment period, and the study is expected to conclude at the end of 2018.[27] Intranasal insulin glulisine is being investigated in a phase II trial also involving patients with mild cognitive impairment or AD. The treatment duration is 6 months, and completion is targeted for September 2018.[28] Intranasal insulin aspart is undergoing a phase I trial in patients with mild cognitive impairment or AD. This trial has a 3 month treatment duration and expected study conclusion in July 2018.[29]

Liraglutide is a glucagon-like peptide-1 (GLP-1) analog that binds to GLP-1 receptors on pancreatic β cells to stimulate insulin secretion. It is being studied in a phase II trial in patients with mild AD for a 12 month treatment period, with expected study conclusion in March 2019.[30]

Pioglitazone is a peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist, which contributes to increased insulin sensitivity via modulating transcription and translation of various genes. Pioglitazone is also thought to decrease the expression of β-secretase, thus reducing synthesis of β-amyloid. A phase III trial of pioglitazone is currently being conducted in patients with mild cognitive impairment due to AD. The treatment duration is 24 months, and the expected completion date is April 2021.[31]

In addition to the agents discussed above, there are compounds with other mechanisms that are being assessed as well. Some of these include histamine-3 (H3) receptor antagonists, which target histamine heteroreceptors on cholinergic neurons to increase acetylcholine release.[18] Serotonin-6 (5-HT_6) receptor antagonists, which are thought to enhance cholinergic neurotransmission, are also being studied. Active vaccines are being investigated to allow formation of an antibody that can help clear the β-amyloid and tau protein from the body. Anti-inflammatory agents, such as the microglial activation inhibitors, are being investigated to reduce the neuronal inflammation thought to contribute to AD progression.[18]

Conclusion

Alzheimer's is a multi-faceted disease that continues to increase in prevalence, mortality, and healthcare costs. Unfortunately, the current therapeutic options have shown only modest benefit and there is currently no method to reverse the progression of this disease. With the urgent need for more effective therapies, there are a variety of new compounds being investigated. As the results of more clinical trials become available, it should become clear as to whether any of these new agents are able to make a significant impact and what role they might play in the management of AD. With the number of targets being evaluated in the treatment of AD, the hope is that continued research will identify a treatment that will provide clinically meaningful advances in the management of Alzheimer's Disease.

References

1. National Institute on Aging [Internet]. Bethesda (MD): National Institutes of Health. Basics of Alzheimer's Disease and Dementia; [cited 2017 Dec 3]. Available from: https://www.nia.nih.gov/health/alzheimers/basics
2. Alzheimer's Association [Internet]. Chicago (IL); c2017. 2017 Alzheimer's Disease Facts and Figures; [cited 2017 Dec 3]. Available from: https://www.alz.org/facts/
3. Brookmeyer R, Evans DA, Hebert L, et al. National estimates of the prevalence of Alzheimer's disease in the United States. *Alzheimers Dement* [Internet]. 2011 Jan [cited 2017 Dec 3]; 7(1):61-73. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3052294/
4. NIH MedlinePlus [Internet]. Bethesda (MD): National Institutes of Health. Symptoms, Diagnosis, and Treatment; [cited 2017 Dec 3]. Available from: https://medlineplus.gov/magazine/issues/fall10/articles/fall10pg19.html
5. Liu C, Kanekiyo T, Xu H, et al. Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. *Nat Rev Neurol* [Internet]. 2013 Jan 8 [updated 2013 Mar 26; cited 2017 Dec 3]; 9(2):106-18. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3726719/
6. Suh YH, Checler F. Amyloid precursor protein, presenilins, and alpha-synuclein: molecular pathogenesis and pharmacological applications in Alzheimer's disease. *Pharmacol Rev* [Internet]. 2002 Sep [cited 2017 Dec 3]; 54(3):469-525. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12223532
7. Swerdlow RH. Pathogenesis of Alzheimer's disease. *Clin Interv Aging* [Internet]. 2007 Sep [cited 2017 Dec 3];2(3):347-59. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2685260/
8. Ferreira-Vieira TH, Guimaraes IM, Silva FR, et al. Alzheimer's Disease: Targeting the Cholinergic System. *Curr Neuropharmacol* [Internet]. 2016 Jan [cited 2017 Dec 3]; 14(1):101-15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4787279/
9. National Institute on Aging [Internet]. Bethesda (MD): National Institutes of Health. Symptoms and Diagnosis of Alzheimer's Disease; [cited 2017 Dec 3]. Available from: https://www.nia.nih.gov/health/what-are-signs-alzheimers-disease
10. Winslow BT, Onysko MK, Stob CM, et al. Treatment of Alzheimer Disease. *Am Fam Physician* [Internet]. 2011 Jun 15 [cited 2017 Dec 3]; 83(12):1403-12. Available from: http://www.aafp.org/afp/2011/0615/p1403.html
11. Lexicomp [Internet]. Hudson (OH): Wolters Kluwer. c1978-2017 [cited 2017 Dec 3]. Available from: http://online.lexi.com.ezproxy.findlay.edu:2048/lco/action/home
12. Parsons CG, Danysz W, Dekundy A, et al. Memantine and Cholinesterase Inhibitors: Complementary Mechanisms in the Treatment of Alzheimer's Disease. *Neurotox Res* [Internet]. 2013 May 9 [cited 2017 Dec 3]; 24(3):358-69. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3753463/
13. Deardorff WJ, Grossberg GT. A fixed-dose combination of memantine extended-release and donepezil in the treatment of moderate-to-severe Alzheimer's disease. *Drug Des Devel Ther* [Internet]. 2016 Oct 3 [cited 2017 Dec 3]; 10: 3267-79. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5055113/

14. Cummings J, Lee G, Mortsdorf T, et al. Alzheimer's disease drug development pipeline: 2017. *Alzheimers Dement* [Internet]. 2017 Sep [cited 2017 Dec 3]; 3(3): 367-84. Available from: http://www.sciencedirect.com/science/article/pii/S2352873717300379#bib33
15. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2014 Sep 22. unique ID: NCT02245737, An Efficacy and Safety Study of Lanabecestat (LY3314814) in Early Alzheimer's Disease (AMARANTH); [updated 2017 Nov 28; cited 2017 Dec 3]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02245737
16. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2016 Nov 7. unique ID: NCT02956486, A 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects With Early Alzheimer's Disease (MissionAD1); [updated 2017 Nov 24; cited 2017 Dec 15]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02956486
17. Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature* [Internet]. 2016 Sep 1 [cited 2017 Dec 3]; 537:50-56. Available from: https://www.nature.com/articles/nature19323
18. Hung S, Fu W. Drug candidates in clinical trials for Alzheimer's disease. *J Biomed Sci* [Internet]. 2017 July 19 [cited 2017 Dec 3]; 24(47). Available from: https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-017-0355-7
19. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2015 Jun 23. unique ID: NCT02477800, 221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (ENGAGE); [updated 2017 Dec 13; cited 2017 Dec 15]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02477800
20. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2015 Jun 29. unique ID: NCT02484547, 221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (EMERGE); [updated 2017 Oct 3; cited 2017 Dec 15]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02484547
21. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2016 Feb 1. unique ID: NCT02670083, CREAD Study: A Study of Crenezumab Versus Placebo to Evaluate the Efficacy and Safety in Participants With Prodromal to Mild Alzheimer's Disease (AD); [updated 2017 Nov 28; cited 2017 Dec 15]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT02670083
22. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2013 Jan 14. unique ID: NCT01767311, A Study to Evaluate Safety, Tolerability, and Efficacy of BAN2401 in Subjects With Early Alzheimer's Disease; [updated 2017 Nov 14; cited 2017 Dec 15]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT01767311
23. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2016 Aug 26. unique ID: NCT02880956, A Study to Evaluate the Efficacy and Safety of ABBV-8E12 in Subjects With Early Alzheimer's Disease; [updated 2017 Nov 14; cited 2017 Dec 15]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02880956
24. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2016 Jul 1. unique ID: NCT02820896, A Study of RO7105705 in Healthy Participants and Participants With Mild-to-Moderate Alzheimer's Disease; [updated 2017 Jul 21; cited 2017 Dec 15]. Available from: https://clinicaltrials.gov/show/NCT02820896

25. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2017 Sep 20. unique ID: NCT03289143, A Study to Evaluate the Efficacy and Safety of RO7105705 in Patients With Prodromal to Mild Alzheimer's Disease; [updated 2017 Dec 1; cited 2017 Dec 15]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT03289143?term=RO7105705&rank=
26. Morris JK, Burns JM. Insulin: An Emerging Treatment for Alzheimer's Disease Dementia? *Curr Neurol Neurosci Rep* [Internet]. 2012 Oct [cited 2017 Dec 3]; 12(5): 520-27. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3540744/
27. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2013 Jan 15. unique ID: NCT01767909, The Study of Nasal Insulin in the Fight Against Forgetfulness (SNIFF); [updated 2017 Oct 13; cited 2017 Dec 16]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT01767909
28. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2015 Jul 21. unique ID: NCT02503501, Intranasal Glulisine in Amnestic Mild Cognitive Impairment and Probable Mild Alzheimer's Disease; [updated 2017 Dec 14; cited 2017 Dec 16]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02503501
29. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2015 Jun 3. unique ID: NCT02462161, Study of Nasal Insulin to Fight Forgetfulness- Short-Acting Insulin Aspart (SNIFF-Quick); [updated 2017 Nov 6; cited 2017 Dec 16]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02462161
30. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2013 Apr 30. unique ID: NCT01843075, Evaluating Liraglutide in Alzheimer's Disease (ELAD); [updated 2017 Mar 27; cited 2017 Dec 16]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT01843075
31. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine. 2014 Nov 6. unique ID: NCT02284906, AD-4833/TOMM40_303 Extension Study of the Safety and Efficacy of Pioglitazone to Slow Cognitive Decline in Participants With Mild Cognitive Impairment Due to Alzheimer Disease; [updated 2017 Nov 6; cited 2017 Dec 16]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02284906

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Calcitonin Gene-Related Peptide Receptors and the Prevention of Migraines

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Abstract

Migraines are the third most prevalent disease in the world affecting approximately 15% of the population, or over one billion people. Each year, employers lose greater than $13 billion due to 113 million missed work days due to migraine. A great cost-burden and high incidence rate show a continued need for migraine treatment options. In choosing a treatment for a migraine attack, quick onset of action is one of the most important qualities. Common choices include the triptan class, NSAIDs, and a combination of aspirin, caffeine, and acetaminophen. In addition, there has been increased research into calcitonin gene-related peptides (CGRP). Due to side effect profiles, the monoclonal antibodies have been more successful than the antagonists studied. Monoclonal antibodies alone, though, have not completely eradicated migraine days per month and more research is needed.

Although drug developers have attempted to find a cure in numerous drug classes, migraines continue to afflict humans worldwide. Behind dental cavities and tension headaches it is the most prevalent disease in the world affecting approximately 15% of the world population.[1] This is broken down to more than 39 million men, women and children in the United States and over 1 billion worldwide.[1] This alone has a greater prevalence than asthma, diabetes and epilepsy combined.[2] Although not commonly associated with a high mortality rate, studies have shown that patients with migraines have a 50% greater risk for cardiovascular disease and death.[3] It is estimated that United States employers lose more than $13 billion due to 113 million workdays lost each year due to migraines.[1] These issues show that there is a continued need for research in migraine medication development.

Although its prevalence is great, the pathophysiology of migraines is still unclear. Over the past several centuries, two hypotheses have dominated the pathophysiology debate. The vascular hypothesis, which is now beginning to fall out of favor, theorized that migraines were due to an increased vasodilation of cerebrovascular arteries. Further studies using a vasodilator, nitroglycerin, and a vasoconstrictor, ergotamine, showed that vasodilation of these arteries did not trigger migraines.[4] This led to a hypothesis involving neuronal transmission and research into calcitonin gene-related peptide and selective serotonin agonists. What does remain relatively clear in migraine pathophysiology is that genetics play a role. Children with at least one parent with a history of migraines have a 50% chance of developing this disease. This continues into extended family as 80 to 90% of patients with migraines report having family members who also have a history of migraines.[1]

The word migraine originates from the Greek word, hemicrania, meaning half of the skull.[2] This coincides with one of the common characteristics of a migraine being a unilateral headache. According to the International Classification of Headache Disorders (ICHD) criteria, diagnosis of migraine can be confirmed if the patient has the following five qualities: 1. Headache attacks lasting anywhere from 4-72 hours, 2. Headache meets two of the following four symptoms: pulsating headache, unilateral in location, causing moderate to severe pain, exacerbated by or causing avoidance of routine exercise, 3. Headache causes photophobia and phonobia or causes nausea and/or vomiting, 4. History of at least five attacks meeting the above criteria, and 5. Symptoms are not more accurately accounted for by another ICHD-3 diagnosis.[5]

In the clinical presentation of a migraine, patients may endure numerous phases including prodromes, auras and postdromes. These migraines can often be triggered by an external or internal stimulus. Some examples are bright lights, loud

noises, lack of sleep, certain foods or smells and changes in hormones. A prodrome is the first sign a patient could experience before a migraine occurs and gives warning to the patient to begin treatment. This prodrome can appear in many forms from fatigue and excessive yawning, to euphoria and excitement, or photophobia or phonophobia.[6] Fortunately a majority of patients experience prodromes, which allows them to begin treatment before the headache attack phase begins. While a prodrome can last anywhere from one hour to 48 hours, an aura is much shorter and usually less than an hour. An aura begins the next phase of a migraine and precedes the headache attack phase. Auras are not nearly as common as prodromes as only 15 to 20% of patients experience this phase.[6] Visual disturbances such as blurry vision, colored spots and zigzags of light make up one of the most common auras experienced before migraine. Other symptoms may include feeling pins and needles in extremities or difficulty speaking. The next phase is the actual migraine in which the patient experiences a debilitating pulsing unilateral headache. Varying from patient to patient, the frequency and duration of these migraines are unpredictable. Following the attack phase, the patient enters the postdrome phase of exhaustion, confusion and hangover-like symptoms.[6]

Migraine Prophylaxis

Because of a migraine's quick onset and ability to incapacitate a patient for days, prevention becomes the priority. According to the 2012 American Academy of Neurology and American Headache Society guidelines multiple classes of medications are considered to have established efficacy in prevention of migraines. These classes include beta-blockers (metoprolol, propranolol, and timolol), antiepileptic drugs (divalproex sodium, sodium valproate, and topiramate) and frovatriptan for short-term prophylaxis for menstrual related migraines. These guidelines also stated that antidepressants (amitriptyline and venlafaxine), beta-blockers (atenolol and nadolol) and triptans (naratriptan and zolmitriptan for short term prophylaxis for menstrual related migraines) are probably effective at preventing migraines.[7] With uncertainty regarding the pathophysiology of migraines, it is not surprising that there are a number of classes potentially involved in the treatment of migraines that all involve different mechanisms. Beta-blockers are believed to inhibit arterial dilation seen in migraines. The antidepressants amitriptyline and venlafaxine are believed to be effective in migraine prophylaxis due to their down-regulation of serotonin receptors. Antiepileptics are believed to provide prophylaxis of migraines through the suppression of neuronal hyperexcitability by increasing gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter.[8]

Migraine Treatment

For the treatment of an acute migraine headache, therapies mimic regular

pain recommendations. According to the 2011 American Association of Family Physicians, NSAIDs are considered a first line therapy for acute migraine attack. Serotonin receptor agonists, commonly referred to as triptans, are also a first line therapy for these attacks. Unlike NSAIDs, which have many indications, triptans were developed for the treatment of migraine.[9] Sumatriptan was the first serotonin receptor agonist to be released to market. In 1993, Imitrex (sumatriptan) was FDA approved for the treatment of migraines with or without aura. Sumatriptan agonizes the 5-$HT_{1B/1D}$ receptors in the intracranial blood vessels.[10] This results in cranial vessel vasoconstriction and believed inhibition of pro-inflammatory neuropeptides. There are now seven different FDA approved triptans with numerous formulations and salts.[11] Due to the strong efficacy of triptans and NSAIDs as monotherapy, a combination of naproxen and sumatriptan (Trexima) has also been studied.[9] Studies in 2007 and 2013 found that this combination provided more favorable clinical benefits than monotherapy of sumatriptan, naproxen or placebo with a tolerable side effect profile.[12, 13] One of the concerns with the triptan class is the increased risk of cardiovascular and cerebrovascular events. Myocardial infarction, coronary artery vasospasm, subarachnoid hemorrhages, ventricular tachycardia and ventricular fibrillation are rare but have been seen in patients several hours after taking a 5-HT_1. Therefore the use of triptans is contraindicated in patients with a past medical history of the previous stated cardiovascular and cerebrovascular diseases.[10] The combination analgesic of acetaminophen (250mg), aspirin (250mg) and caffeine (65mg) is an inexpensive choice that is available without a prescription.[9]

Even with numerous drug classes explored for prophylaxis and treatment, and many FDA approved medications for migraine therapy, it remains one of the most debilitating chronic diseases in the United States. Therefore research has continued into finding a solution for the prevention of migraines. With the transition from vascular theory to neuropeptide theory, researchers have honed in on calcitonin gene-related peptides (CGRP). CGRP is a neuropeptide made up of 37 amino acids that is found in sensory neurons as well as the cardiovascular and cerebrovascular systems.[14] One of the leading cases for CGRP's involvement in migraine pathophysiology is the evidence of increased CGRP levels in a patient currently experiencing a migraine attack. When patients are given triptans to resolve the migraine attack, CGRP levels have been shown to decrease. Even further evidence of association comes from patients that received intravenous calcitonin gene-related peptide and quickly began experiencing an acute migraine attack.[14]

In targeting calcitonin gene-related peptide, researchers could focus on the peptide itself or its receptor. The first medications developed were small molecule

antagonists of the CGRP receptor.[14] Rimegepant and olcegepant are two of the small molecule antagonists that continue to move towards market, while telcagepant was pursued and then discontinued. Although pain relief rate and pain free rate show significant support for telcagepant and olcegepant compared to placebo, there are concerns of chronic use resulting in hepatotoxicity; one of the causes of telcagepant's discontinuation.[14] Calcitonin gene-related peptide has been shown to be a potent vasodilator.[15] It would make sense that antagonizing this peptide would result in vasoconstriction and relieve migraine headaches similar to the triptan class. One theory that has been supported through these trials is that although the calcitonin gene-related peptide antagonists do cause vasoconstriction and more importantly a decrease in neurogenic inflammation, they do not have an effect on the coronary arteries and do not increase blood pressure like the triptan class.[15] This selective antagonism introduces a new therapy option for patients with migraines, especially those with cardiovascular and cerebrovascular diseases that preclude them from taking triptans. With concerns of hepatoxicity and other side effects, research continued in the search of a safe and effective antagonist of CGRP.

Monoclonal antibodies have continued to be developed in more disease states as targeted and effective therapies. There are currently several different monoclonal antibodies that have recently completed phase III trials and are now applying for biologic licensing applications with the FDA.[16] Fremanezumab, galcanezumab, and eptinezumab, developed by Teva Pharmaceuticals, Eli-Lilly and Alder Biopharmaceuticals, respectively, target the molecule calcitonin gene-related peptide.[16] For Alder's eptinezumab, phase III results were positive and showed a 50% or greater reduction in migraine days in 61% of patients compared to 39% in the placebo group ($p<0.0001$), a 75% or greater reduction in migraine days in 33% of patients compared to 15 % in the placebo group ($p<0.0001$), and three-month migraine free period in 15% of patients compared to 5% in the placebo group ($p<0.0001$).[17] In Teva's fremanezumab, patients were divided in a 1:1:1 ratio to receive monthly dosing of fremanezumab, a quarterly dose followed by placebo, and placebo dosing.[18] The study found at least a 50% reduction in migraine days for 41% of the monthly dosing group, 38% of the quarterly dose group and 18% of the placebo group ($p<0.001$).[18] For Eli-Lilly's galcanezumab, studies showed a reduction of 4.7 migraine days per month for 120 mg, 4.6 days for 240 mg and 2.8 days for placebo ($p<0.001$).[19] A fourth monoclonal antibody being studied is erenumab, co-developed by Amgen and Novartis. Erenumab differs from the previous three monoclonal antibodies in that it targets the calcitonin gene-related peptide receptor instead of the peptide itself.[16] Recently published phase III trials showed a reduction of 3.2 migraine days per month for

the 70mg monthly group and 3.7 days for the 140mg monthly group compared to 1.8 days for the placebo group ($p<0.001$).[20] Amgen and Novartis also found at least a 50% reduction in migraine days per month in 43.3% of the 70 mg monthly dose and 50.0% of the 140 mg monthly dose compared with 26.6% of patients in the placebo group ($p<0.001$).[20] While this reduction of migraine days per month is a positive in developing an efficacious drug, one of the most significant findings in each of these trials was the low rate of adverse effects. Only fremanezumab showed a slight increase in hepatoxicity compared to placebo, a side effect that derailed several of the small molecule inhibitors from FDA approval. Other side effects of eptinezumab, galcanezumab and erenumab were considered either mild and minimal or not statistically significant when compared to placebo.[17-20]

Continued advances in migraine therapy signify a positive future outlook for patients hindered by this disease every day. Monoclonal antibodies appear to have a more favorable side effect profile over the small molecule antagonists, while still maintaining a strong reduction in migraine days per month. However a complete solution has not been found as patients still experience multiple migraine days per month while being prophylactically treated. Further research is needed into the calcitonin gene-related peptide, as this appears to be a significant contributor to a migraine. Through this target as well as other pathways, a combination may be found to effectively prevent a disease that impacts over one billion people.

References

1. About Migraine. *Migraine Research Foundation*. 2018. Available from: http://migraineresearchfoundation.org/about-migraine/migraine-facts/
2. Facts and Figures. *The Migraine Trust.* Available from: https://www.migrainetrust.org/about-migraine/migraine-what-is-it/facts-figures/
3. Kurth T, Winter AC, Eliassen AH, et al. Migraine and risk of cardiovascular disease in women: prospective cohort study. *British Medical Journal.* 2016 Apr 25; 353:1-6.
4. Charles A, Brennan KC. An update on the blood vessel in migraine. *Current Opinion in Neurology.* 2010 June; 23(3): 266–74.
5. Cephalalgia: The International Classification of Headache Disorders, 3rd edition. *International Headache Society*. 2018; 38(1): 1-211.
6. Rothrock JF. Acute Migraine: Treating Early. *American Headache Society.* 2009; 635-6.
7. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults. *Neurology.* 2012 Apr; 78(17): 1337-45.
8. Miles O. Migraine Treatment. *Health Union.* 2010 Nov. Available from: https://migraine.com/migraine-treatment/
9. Gilmore B, Michael M. Treatment of Acute Migraine Headache. *American Family Physician.* 2011 Feb 1; 83(3): 271-80.
10. Lexi-Comp Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc. 2018 [cited 2018 March 11]. Available from: http://online.lexi.com/
11. FDA Approved Drug Products. *United States Food and Drug Administration.* Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
12. Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA*. 2007; 297(13): 1443–54.
13. Landy S, Hoagland R, Hoagland D, et al. Sumatriptan-naproxen sodium combination versus its components administered concomitantly for the acute treatment of migraine: a pragmatic, crossover, open-label outcomes study. *Therapeutic Advances in Neurologic Disorders.* 2013 Sep; 6(5): 279–86.
14. Yao G, Yu T, Han X, et al. Therapeutic effects and safety of olcegepant and telcagepant for migraine: A meta-analysis. *Neural Regeneration Research.* 2013 Apr 5; 8(10): 938–47.
15. Durham PL. Calcitonin Gene-Related Peptide (CGRP) and Migraine. *Headache.* 2006 June; 46(Suppl 1): S3–S8.
16. Tso AR, Goadsby PJ. Anti-CGRP Monoclonal Antibodies: the Next Era of Migraine Prevention? *Current Treatment Options in Neurology.* 2017 Jun 27. 19(8): 27.
17. Cadle A. Alder Announces Eptinezumab Significantly Reduces Migraine Risk Meets Primary and All Key Secondary Endpoints in Pivotal PROMISE 2 Phase 3 Trial for Chronic Migraine Prevention. *Alder Biopharmaceuticals.* 2018 Jan 8. Available from: http://investor.alderbio.com/news-releases/news-release-details/alder-announces-eptinezumab-significantly-reduces-migraine-risk
18. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. *NEJM.* 2017 Nov 30; 377: 2113-22.
19. Dial J, Johnson P. Lilly Announces Positive Results for Three Phase 3 Studies of Galcanezumab for the Prevention of Episodic and Chronic Migraine. *Lilly*. 2017 May 12; Available from: https://investor.lilly.com/releasedetail.cfm?releaseid=1026201
20. Goadsby PJ, Reuter U, Hallstrom Y, et al. A Controlled Trial of Erenumab for Episodic Migraine. *NEJM.* 2017 Nov 30; 377:2123-32.

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