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Semaglutide: Hope for Alzheimer's Prevention

Alzheimer's Disease (AD) is the leading cause of dementia in older adults, affecting over 6 million Americans. While there is currently no cure, the onset of AD may be delayed through optimization of modifiable risk factors, such as type 2 diabetes (T2DM), obesity, hypertension, depression, and smoking. Initially approved as treatment for type 2 diabetes in 2017, semaglutide (Ozempic) now has proven benefits in other disease states, such as obesity and cardiovascular risk reduction. Given its effects on multiple AD risk factors, new research suggests that semaglutide may also lower the risk of developing AD in high-risk individuals.

Using a nationwide database of electronic health records, approximately 1 million eligible US patients (with T2DM and no prior AD diagnosis) were identified from a study period of December 2017 to May 2021. Among the eligible patients, six patient populations were assessed: all patients, patients over 60 y/o, women, men, patients with obesity, and patients without obesity. Each population was split into seven target trials that separately compared the new use of semaglutide with the new use of other antidiabetic medications (insulins, metformin, DPP-4i, SGLT-2i, SUs, TZDs, and other GLP-1RAs). Over a 3-year follow-up period, first-time diagnosis of AD (primary outcome) was evaluated using Cox proportional hazards and Kaplan-Meier survival analyses.

Results showed that semaglutide had a 40-70% reduced risk of first-time AD diagnosis in T2DM patients compared to other antidiabetic medications. Effect of semaglutide in reducing the primary outcome was strongest when compared to insulin (HR, 0.33 [95% CI: 0.21 to 0.51]), and weakest when compared to other GLP-1RAs (HR, 0.59 [95% CI: 0.37 to 0.95]), such as albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide. The semaglutide group also had less AD-related prescription medications (secondary outcome). Older patients, both genders, and those with and without obesity showed similar results.

The results suggest that semaglutide may be beneficial in reducing the incidence of AD in high-risk patients. Although the exact mechanism of semaglutide's effect in the brain is unknown, this study sets the stage for more research to fully understanding the role of semaglutide in AD's, as well as the potential for semaglutide and other antidiabetic medications in other dementias and neurodegenerative diseases.

Written by: Christy Xiong
Alzheimer's Dement. 2024; doi: 10.1002/alz.14313

A New Potential Indication for Tirzepatide

Obstructive sleep apnea (OSA) is characterized by disordered breathing during sleep. This condition may result in daytime sleepiness, worsening an individual's quality of life. Research has demonstrated a connection between OSA and cardiovascular complications, including hypertension, type 2 diabetes mellitus, coronary artery disease, cardiac arrhythmias, heart failure, stroke, and death. This is proposed to be due to episodes of hypoxia, disturbances in sleep, and increased sympathetic tone. With this in mind, obesity can contribute as a risk factor to OSA and its cardiovascular complications. OSA is primarily treated with continuous positive airway pressure (CPAP) therapy. Tirzepatide, a long-acting GLP-1 agonist indicated for type 2 diabetes mellitus and weight management, has been considered as a potential treatment option for OSA with its weight loss mechanism

Two double-blind, randomized, controlled Phase 3 clinical trials were conducted with 469 patients diagnosed with moderate to severe OSA and obesity. The participants were primary male and White for both trials. Trial 1 participants did not receive positive airway pressure (PAP) therapy while Trial 2 participants did. Participants with type 1 or type 2 diabetes mellitus were excluded. The primary endpoint was the change in the apnea-hypopnea index (AHI) from baseline. The secondary endpoint included measurement of percent change in AHI and body weight, hypoxic burden, patient-reported sleep impairment or disturbance, high-sensitivity C-reactive protein (hsCRP) concentration, and systolic blood pressure. AHI was measured at screening, 20 weeks, and 52 weeks using polysomnography. Tirzepatide was administered at a starting dose of 2.5 mg once weekly subcutaneously and was titrated every 4 weeks up to the max tolerated dose of 10 or 15 mg by week 20.

At 52 weeks, there was a treatment difference of 20.0 less events per hour (95% CI) (P<0.001) between the tirzepatide and placebo groups for Trial 1. There was a treatment difference of 23.8 less events per hour (95% CI) (P<0.001) for Trial 2. For both trials, reductions in AHI, hypoxic burden, body weight, systolic blood pressure, and hsCRP concentrations were observed. Therefore, tirzepatide demonstrates efficacy in reducing events related to OSA compared to placebo with or without PAP therapy. Since the trials assessed short term outcomes, they are not indicative of long-term cardiovascular outcomes. Additional testing for efficacy may be needed before FDA approval for this indication.

Written by: Harnoor Gill
N Engl J Med 2024;391:1193-205; doi: 10.1056/NEJMoa2404881

New Drug Target for Treating Schizophrenia

Schizophrenia is one of the leading causes of disability, with around 1% of Americans suffering from the illness. As severe and chronic as it is, only one mechanism of action characterizes the current drugs for its treatment until now.

Schizophrenia, a psychotic disorder, can cause a range of symptoms, including but not limited to hallucinations, disorganized thoughts, and delusional thinking. In addition, schizophrenia may influence a person's ability to process social cues and impair cognition. A possible theory as to the cause may be due to an excess of dopamine, a monoamine neurotransmitter involved in a variety of psychological and physiological processes. This has led to the development of drugs targeting the dopamine receptor, which has been the standard therapy for some time now.

Cobenfy, a combination of xanomeline and trospium chloride, has been approved by the U.S. Food and Drug Administration to treat schizophrenia. With the approval of Cobenfy, a new drug target has come into play. Cobenfy targets cholinergic receptors, rather than dopamine receptors, and is the first antipsychotic drug to do so.

The approval was based on two studies, both of the same design consisting of a five week multi-centered, double-blind, placebo-controlled, randomized study in adults diagnosed with schizophrenia using the DSM-5 criteria. The primary measure of efficacy was a change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at the fifth week. The PANSS is a scale consisting of thirty items measuring the symptoms of schizophrenia where each item is rated by a clinician on a seven point scale. The results of both studies showed a meaningful reduction in symptoms over the five week study period in patients taking Cobenfy in comparison to the placebo group based on the change in the PANSS total score.

Cobenfy comes in a capsule form, and should not be opened upon administration. The list price is set to be $1,850 per month before insurance. Cobenfy should not be prescribed to patients with mild to moderate kidney and liver disease, urinary retention, gastric retention, and untreated narrow-angle glaucoma. In addition, Cobenfy is approved for monotherapy, and is not indicated to be used with other antipsychotics at this time. Some side effects include nausea, angioedema, constipation, hypertension, and tachycardia.

Overall, Cobenfy provides patients with a unique alternative to the typical antipsychotic drugs, helping to treat such a complex disorder as schizophrenia.

Written By: Zeenat Entezar
U.S. Food and Drug Administration 2024

The Prevent Calculator: Does America Have A Statin Problem?

In early 2024, the American Heart Association (AHA) piloted the PREVENT (Predicting Risk of cardiovascular disease EVENTs) calculator, intended for adults ages 30-79 to calculate CVD, ASCVD, and HF risk. An upgrade from its predecessor, the ASCVD calculator created in 2013: PREVENT provides both 10 and 30 year risk estimates by extending the age range to include younger adults and newly considers urine albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and glycated hemoglobin (HbA1c).

Controversial in today's medical dialogue is the use of race in diagnosis and treatment algorithms, especially since the ASCVD calculator was developed from only White and Black adults. Eliminating race, the PREVENT calculator introduces the "social deprivation index" which uses a patient's zip code which involves social determinants such as income, education, employment, and housing.

To estimate the number of individuals that would be affected by applying the PREVENT calculator, a study was conducted of 7,765 U.S adults from survey data dated from 2011-2020, a sample assumed to be representative of the entire U.S population by the investigators. It was found that those recommended for statin therapy would decrease by 14.3 million and 5.78 million fewer patients will actually receive a statin. Along with 2.62 million fewer antihypertensive therapy recommendations, 1.74 million fewer adults would receive an antihypertensive. As cardiovascular medications are the most prescribed in the U.S., a risk overestimation compared to the ASCVD calculator reveals that Americans could be wrongfully overprescribed on heart medications.

However, discontinuing statins could be costly, as over 10 years, reductions in treatment eligibility could result in an estimated 107,000 additional occurrences of MI and stroke and 57,000 fewer cases of onset diabetes. Historically, the ASCVD calculator considered co-morbidities and race, but eligibility changes would affect more men and Black adults in their CV risk. Although current guidelines still endorse the ASCVD calculator, PREVENT could be in guidelines by the end of 2024 or early 2025 and has potential to be the new practice standard. With huge implications for the future of cardiovascular health, providers will have a lot on their hands deciding whether the risk of tapering off medication is worth the benefit.

Written by: Kristie Chau
JAMA. 2024 Sep 24;332(12):989-1000. doi: 10.1001/jama.2024.12537

Weighing the Risks vs. Benefits of Liraglutide for Children

No medications are currently approved for treating non-monogenic, nonsyndromic obesity in children under 12 years of age. The only FDA-approved medications for adolescent obesity are Phentermine and Orlistat. However, there still remains a treatment gap in severe pediatric obesity. Liraglutide, a GLP-1 analogue effective in adults, is being evaluated for safety and efficacy in children based on BMI, weight loss, and side effects.

The SCALE Kids trial was a phase 3a, double-blind, randomized, placebo-controlled study involving 82 participants over 56 weeks. In this trial, 56 participants were assigned to receive liraglutide, while 26 were given a placebo. This design aimed to assess the efficacy and safety of liraglutide in the target population. Eligible participants were children (6 to <12 years of age) with obesity, which was defined as an age-adjusted and sex-adjusted BMI in the 95th percentile or higher. Each participant received either once-daily subcutaneous liraglutide at a dose of 3.0 mg (or the maximum tolerated dose) or placebo, plus lifestyle interventions.

At week 56, the observed mean change from baseline in BMI was a 6.7% decrease with liraglutide and 2.1% increase with placebo; at week 82 (follow-up period), the change in BMI was a 0.8% decrease and 6.7% increase, respectively. At week 56, the observed mean change from baseline in body weight was a 0.8% increase with liraglutide compared to the 10.2% with placebo; at week 82, these figures had increased to 10.7% and 19.0%, respectively. Ultimately, the data indicate that liraglutide was more effective than placebo in reducing both BMI and body weight.

The majority of adverse events were mild to moderate, including nausea, vomiting, and diarrhea. Notably, 80% of participants in the liraglutide group experienced gastrointestinal disorders compared to 54% in the placebo group. Despite this, treatment completion rates remained high and participants could manage side effects with antiemetic agents. Importantly, no significant changes were observed in growth metrics or Tanner stages, indicating that liraglutide did not adversely affect growth and development over the 56-week treatment period.

Overall, the potential of liraglutide represents a hopeful advancement in decreasing childhood obesity by effectively reducing BMI in children. While caution is warranted, the results of this trial suggest that, with proper oversight and continued research, medications like liraglutide may become valuable tools in childhood obesity.

Written by: Abigail Ham
N Engl J Med 2024, doi: 10.1056/NEJMoa2407379

Conceived with Technology, Born with Risk: ART Babies and Heart Defects

By allowing the conception of over 10 million children worldwide through the in vitro manipulation of human eggs, sperm, and embryos, developments in assisted reproductive technology (ART) have significantly transformed the field of reproductive health. Despite these advances, research indicates that children conceived via ART face an increased risk of congenital heart defects (CHDs) compared to those born through spontaneous conception (SC). CHDs are structural cardiac abnormalities present at birth, and they account for about half of all significant birth defects.

By analyzing data from four Nordic countries, this study compared the risk of major CHDs in ART-conceived children with those born via SC through the first year of life. The Committee of Nordic ART and Safety (CoNARTaS) used logistic regression analysis to assess this risk, accounting for both single and multiple births. To ensure reliable findings, researchers considered various factors, including the child's birth year, maternal age, previous birth history, and maternal health.

Among the 7.7 million liveborn children analyzed over approximately 31 years (1984 to 2015), 171,735 (2.2%) were conceived through ART, while approximately 7.5 million (97.8%) were born via SC. Low birth weight (16.0% vs. 4.2%), as well as preterm birth (18.3% vs. 5.8%), were more common outcomes for children born with ART as compared to SC. Also, ART mothers were often older—40.4% were 35 years of age or older, compared to 16.3% in the SC group.

The study revealed that major CHDs were found in 1.84% of ART-conceived children, indicating a 36% higher risk compared to SC (1.15%) [Adjusted Odds Ratio (AOR) 1.36; 95% Confidence Interval (CI) 1.31-1.41]. Among singletons, 1.62% of those born via ART had major CHDs, while the rate for those conceived naturally was lower (1.11%) [AOR 1.19; 95% CI 1.14–1.24]. Regardless of the method of conception, multiples had the highest risk; however,

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CD19-CAR T-cell Therapy: Revolutionizing Autoimmune Disease Treatment

CD19-CAR T-cell therapy, initially approved for cancer treatment with products such as Breyanzi® (lisocabtagene maraleucel), has significant efficacy in sustained, medication-free remission for patients with autoimmune diseases (AIDs), particularly systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). The therapy's success comes from its ability to completely depleting B-cells across all body tissues, proving fundamentally superior to partial depletion through the elimination of residual B cells that perpetuate autoimmune responses and trigger disease relapse.

A clinical study in September 2024 conducted a comparison of CD19-CAR T-cell therapy with Gazyva® (obinutuzumab), an advanced anti-CD20 antibody. Through sequential lymph node biopsies, the study revealed that while obinutuzumab enhanced B-cell clearance compared to earlier treatments, it fell short of the comprehensive depletion achieved by CAR T-cells, which maintained their effectiveness regardless of Fcγ receptor polymorphisms that typically limit antibody-based treatments.

Another study in October 2024 compared CAR T-cell therapy directly with Rituxan (rituximab), the traditional B-cell-depleting treatment. Unlike rituximab's limited targeting of circulating blood B cells, CAR T-cells completely depleted B-cells in tissues, dissolved follicular structures, and depleted follicular dendritic cells (FDCs), indicating a fundamental immune system reset of tissue architecture.

These findings represent a paradigm shift in autoimmune disease therapy. While the current market offers various CAR T-cell products targeting different antigens—such as Abecma® (idecabtagene vicleucel) for B-cell maturation antigens and Carvykti® (ciltacabtagene autoleucel) for plasma cells in multiple myeloma—their successful application suggests potential treatments for various antibody-mediated diseases, from rheumatoid arthritis to multiple sclerosis.

While current treatments like rituximab and obinutuzumab require ongoing administration and rely on compromised Fc-dependent mechanisms, CAR T-cell therapy's unique approach offers lasting remission in a single treatment. This mechanism demonstrates that complete remodeling of lymphoid tissues and depletion of tissue-level B-cells is achievable, suggesting therapeutic potential beyond our current clinical options. As research advances, the development of next-generation CAR T-cells engineered for enhanced precision—perhaps "switchable" cells that can be regulated post-infusion, or versions targeting multiple antigens simultaneously—could shift autoimmune disease treatment from continuous immunosuppression to resetting the immune system itself, where cellular engineering provides sophisticated, potentially curative solutions for conditions once thought to require lifelong medication.

Written by: Amy Huynh
Ann Rheum Dis. 2024; doi:10.1136/ard-2024-226142

Machine Learning and Neural Networks: The Future of Clinical Pharmacy?

In our increasingly expensive healthcare system, it's not surprising that different technological methods are being used to decrease workload and associated cost. But these systems are also used to improve patient care. One such system, the FeelBetter machine learning system, has been used in emergency departments to optimize medication therapy management and transition of care. Adverse drug events are estimated to account for 10%-30% of hospitalizations[3] in older patients, largely due to their vulnerability to adverse reactions and complications arising from polypharmacy. Patients with multiple comorbidities and complex care plans require careful assessment to ensure their medication therapy is optimized for effectiveness and to minimize potential harm. Proper risk identification and therapy management recommendations can reduce time spent in the hospital and improve patient health. Pharmacist have been effectively filling this role, but this manual method is labor intensive, costly and prone to human error.

The FeelBetter system can manage a much larger workload and provide recommendations considering more factors than a pharmacist alone can. The program uses machine learning, logistics regression, decision trees, and graph neural networks to analyze nearly all aspects of the patient. Demographics, laboratory results, diagnosis, vital signs, social history (smoking, alcohol, and recreational drug use), insurance type, problem list, procedure history, previous ED and observation visits, estimated cost based on average Medicare reimbursements by length of stay, and health care utilization patterns are all considered. Patients are stratified into different risk groups based in those factors. Going beyond simple drug-drug interactions, the system takes all available aspects of the patient's situation into account and makes therapy recommendations for those deemed to be at high risk of health care utilization.

In the recent study performed at the Brigham and Women's hospital in Boston and published in the American Journal of Managed Care, pharmacist review of the system found the system accurate 99.3% of the time in providing the correct warning. One of the most significant benefits of the s ystem was found to be the identification and prioritization of high-risk patients with complex therapy regimens. Highlighting high risk patients and making therapy recommendations was found by clinicians to be helpful in making decisions 97.3% of the time. The study highlights the potential benefits of a system such as the FeelBetter system, which ensures patients receive the attention their complex care requires. An article titled Caregiver's Guide to Medications and Aging[2] posted by the Family Caregiver Alliance highlights the need for better management of patient's medication therapies. The FeelBetter system can reduce the burden on caregivers by reducing hospitalizations due to suboptimal medication management and adverse drug events. However, there is still a need for a pharmacist to ensure healthcare literacy and to address adherence issues. As of April 2024, the FeelBetter system has been deployed by Atlantic Health System to manage polypharmacy for the 420,000 patients they serve.[1] While the FeelBetter system is an exciting use of technology to improve the efficiency of the health system and reduce errors, ultimately the pharmacist still plays a crucial role in patient care.

Written by: Kevin Hatley
AJMC 2024; doi:10.37765/ajmc.2024.89592

ART: continued from pg 4

compared to singletons born via ART, multiples born via ART showed an even higher absolute risk of major CHDs at 2.47%. Additionally, severe CHDs were detected in 0.35% of ART children versus 0.26% of SC children [AOR 1.30; 95% CI 1.20–1.42].

Although most children with CHDs survive into adulthood, they frequently face ongoing health challenges, such as atrial fibrillation and congestive heart failure, before the age of 42. While the exact causes of CHDs remain largely unknown, both genetic and environmental factors may contribute to their development. This highlights the critical need for prenatal screening, particularly through fetal echocardiography, which can lead to timely interventions and specialized delivery planning.

Written by: Guneet Gill
European Heart Journal 2024; doi: 10.1093/eurheartj/ehae572

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