TEN DAYS OF GLP-1 FACTS

Are you interested in GLP-1 drugs and would like to better understand what they are and how they work? NorCal is excited to share 10 DAYS OF GLP-1 FACTS starting tomorrow and hope to answer many of the questions you may have about them, whether you are completely new to this class of medications or already know the basics and want to learn more.

Glucagon-like peptide 1 (GLP-1) receptor agonist medications are revolutionizing the treatment of diabetes, obesity and cardiorenal disease. **They are now recognized by the ADA as a first line treatment for overweight conditions and for lowering A1C to goal of 7% in people with type 2 diabetes who are overweight.**

As a leading clinical endocrinologist and primary investigator in Marin, Dr. Linda Gaudiani was involved in both the earliest research trials and development of the first drugs in the GLP-1 class, approved and introduced in 2005. as well as many since. As Medical Director of NorCal she leads a team of experienced physicians and coordinators who continue to actively conduct state-of -the-art clinical trials on the GLP-1 family of new pharmaceuticals, making the newest drugs available to the community. Stay tuned for the next 10 days for her GLP-1 facts!

Make sure to LIKE OUR PAGE to make sure you don't miss any of them!

Disclaimer: This information is for general knowledge and educational purposes only and does not constitute medical advice.

#glp1weightloss #ClinicalTrials #clinicalresearch #diabetesmanagement #NorCalMedicalResearch

DAY ONE OF GLP-1 FACTS

What Are GLP-1s?

GLP-1 agonists are a class of medications that were first investigated to help manage blood sugar (glucose) in people with type 2 diabetes. GLP-1 agonists were shown to not only be very effective in lowering A1C levels but also in promoting significant weight loss by several newly discovered intestinal and neurological pathways. Subsequent drugs in this class are producing unprecedented weight loss in increasing numbers of people. It is estimated that over 9 million prescriptions have been written for GLP-1s and one in eight Americans have tried GLP-1s. They can be life-changing for people whose weight increases their health risks, from diabetes to heart, kidney and liver disease, sleep apnea, osteoarthritis and especially for patients who have struggled for years with obesity and found that changes to diet and exercise just aren't sustainable on their own.

As an endocrinologist and clinical researcher here in Marin since the mid 1980's, I was very involved in the early research trials and development of the first drug in the GLP-1 class and I continue as a primary investigator participating in numerous multi-site GLP-1 clinical trials as newer formulations of these drugs have become available. The previous "eat fewer calories and exercise more" advice is now understood to be inadequate for treating significant weight disorders in most people. Regaining weight lost by just "dieting" has been almost universal and frustrating. We now see obesity not as a patient failure but as a very complex chronic disease which can finally be treated successfully in many individuals by addressing underlying gut hormone imbalances in the GLP-1 gut hormone levels and this can be achieved safely with a fairly low risk profile of adverse effects.

FDA approved available GLP-1 agonists are most often injectable medications and initially were taken as a daily or twice daily shot, but new injectables like Ozempic are weekly and practically painless. Recently oral formulations have also become available and additional improved oral and injectable formulations are now in clinical trials which will provide more treatment options for many patients who cannot tolerate the current medications.

There is also a similar class of medication called dual GLP-1/GIP receptor agonists, including tirzepatide (Mounjaro) currently on the market but also being further studied in combination with other compounds to enhance benefit and tolerability and reduce risks. Combinations of GLP-1s and other glucoregulatory gut hormone supplements are also in current study.

This is why we perform clinical trials at NorCal: to advance knowledge and bring forth new safe and effective traetments for chronic diseases.

DAY TWO OF GLP-1 FACTS

How Do They Work?

To understand how GLP-1's work, it helps to understand how the naturally occuring GLP-1 hormones work.

GLP-1 is a **hormone** that your small intestine makes. It has several roles, including:

- **Triggering insulin release from your pancreas:** Insulin is an essential hormone that allows your body to use the food you eat for energy and lowers the amount of glucose (sugar) in your blood. If you don't have enought insulin, your blood sugar increases, leading to diabetes and the cells are deprived of nutrition
- **Blocking glucagon secretion:** Glucagon is a hormone your body uses to raise your blood sugar levels when necessary. By blocking glucagon secretion, GLP-1s prevent more glucose from going into your bloodstream.
- **Slowing stomach emptying:** Slower digestion means that your body releases less glucose (sugar) into your bloodstream from the food you eat.
- **Increasing satiety:** GLP-1's affect areas of your brain that process hunger and satiety (how full you feel after eating) and other expressions of fullness.

GLP-1 agonist medications work by mimicking this naturally occuring hormone. If you have overweight condition, obesity or pre diabetes or type 2 diabetes, these medications help manage your blood sugar, **lower your A1C** and enhance weight loss as follows:

- by triggering your pancreas to release more insulin
- by slowing digestion which also helps decrease blood sugar spikes
- by increasing the feeling of satiety which reduces your food intake, appetite and hunger, often resulting in weight loss.

By lowering your A1C, these medications significantly reduce all the major diabetes complications and also reduce cardio-vascular risks and kidney disease.

DAY 3 OF GLP-1 FACTS

GLP-1s For Persons With Type 2 Diabetes

GLP-1s are now recognized by the ADA as a first line treatment to help manage type 2 diabetes by lowering A1C to goal of 7% in people with type 2 diabetes and overweight. An A1C test measures the average amount of sugar in your blood over the past few months. There are a few conditions in which the A1C may not reflect the actual average glucose control due to anemia, renal disease and other variations in hemoglobin but physicians know to evaluate for these discrepancies. Healthcare providers use the A1C to help diagnose prediabetes and type 2 diabetes (T2D) and to monitor how well your diabetes treatment plan is working.

The results of many well-designed trials have clearly proven that getting the A1C to 7% lowers the risks of diabetic eye disease, nerve disease and kidney disease 50 to 76%!!! And the benefits of getting the A1C to goal of 7% persist for decades. Lowering the A1C to goal of 7% has also been shown to reduce cardiovascular risks such as heart attacks and strokes.

There are several other types of diabetes medications, including metformin, which are often the first medication for treating T2D. But your healthcare provider may recommend a GLP-1early on if:

- metformin is not helping manage T2D
- if it's unsafe for you to take metformin due to side effects of kidney insufficiency
- you have an A1C higher than your target
- you haven't reached your target A1C within 3 months of treatment and you have additional conditions, like atherosclerosis, heart failure or chronic kidney disease
- if you are overweight

Our current GLP-1 clinical studies may be right for you if your A1C is higher than 7%. Visit our website for information on these studies.

It's important to remember that the most effective management of T2D usually involves several therapies and medications, ongoing lifestyle and dietary modifications, regular exercise, improved sleep, stress reduction and psychosocial support.

DAY 4 OF GLP-1 FACTS

GLP-1s For Obesity

Obesity defined as BMI (body mass index) of 30% or more affects roughly 42% of U.S. adults, according to the Center for Disease Control and Prevention (CDC) estimates, a number which has been on the rise for the past 2 decades and skyrocketed during and after COVID. Significant overweight as BMI over 27% with associated risk factors affects another huge percent of the US population including children and adults, so the cardio-metabolic disease prevalence in our country is epidemic. The FDA currently approves the use of semaglutide (Novo-Nordisk) in various formulations and high-dose liraglutide and tirzepatide to help treat obesity. Health care providers may also prescribe these medications for people who have overweight along with other health conditions such as kidney and heart disease and sleep apnea since losing weight can help manage coexisting conditions. Tirzepatide (Eli Lilly) is also FDA approved for treating type 2 diabetes and results in very significant weight loss.

The weight loss potential of these drugs took center stage only in the past four to five years, after an early clinical trial of Ozempic confirmed a surprising benefit; in addition to improved diabetes control those taking it could lose as much as 15% or more of their body weight. Social media caught on, use of these drugs by celebrities like Elon Musk and Oprah and active marketing by Novo Nordisk, Ozempic's manufacturer, did the rest. The new generation of GLP-1 agonists on the market, Novo Nordisk's Ozempic, Wegovy, and Rybelsus (the pill form) and Eli Lilly's Mounjaro and

Zepbound (also pill form), have now become household names and are producing unprecedented weight loss in increasing numbers of people. While Ozempic, Rybelsus and Mounjaro are approved to treat diabetes, in practice doctors also prescribe these drugs to patients who do not have diabetes looking to lose weight.

Wegovy, Rybelsus and Ozempic contain the compound semaglutide, which stimulates levels of the body's hormone GLP-1, and they work by slowing down gastric and bowel activity, by reducing the appetite centers in the brain, and by stimulating insulin production by the pancreas. They make people feel full faster, and for longer. Mounjaro and Zepbound work similarly, but they use tirzepatide which stimulates both GLP-1 and a second similar gut hormone, GIP.

Semaglutide and tirzepatide target the brain directly and curb hunger, appetite and craving signals, silencing what many users have called "food noise."

NorCal has GLP-1 weight loss studies for persons with and without diabetes, so please stay tuned! One of them may be right for you!

DAY 5 OF GLP-1 FACTS

What About the Side Effects?

Patients tend to experience most side effects when they first start treatment or as they increase their doses over the first few months. The most common issues are gastrointestinal: nausea, vomiting, diarrhea, constipation, acid reflux, stomach pain and discomfort. People can also experience fatigue, dizziness and headaches.

To avoid nausea, we advise patients to eat more slowly and halve their portion sizes immediately upon starting the drug and not wait until they are feeling "full" to stop eating. This helps tolerate the delayed gastric emptying and decreased motility, giving the gastrointestinal tract a chance to adjust. Also, not all patients require the maximum doses, so starting on a low dose and slowly increasing to an effective dose will help reduce chances of getting nausea. Occasionally antinausea meds are helpful; dose reduction or drug holidays can also be used to help patients adjust. Avoiding fatty rich foods may also improve tolerance.

Regarding constipation, increasing fiber and fluid intake can be very helpful. Occasionally other supplements like psyllium and softeners are helpful.

Patients may need to increase their Vitamin B12 intake (consume fish, lean meat, eggs and dairy daily), calcium intake (increase dairy products, dark green leafy vegetables, tofu and sardines and consider taking a calcium supplement) and Vitamin D intake (consume fatty fish, eggs, mushrooms and vitamin D-fortified dairy/milks and take a supplement) to minimize a decrease in bone mineral density associated with weight loss. Regular monitoring through bloodwork can be helpful in assessing nutritional status while losing weight.

Losing a lot of weight quickly can also have ripple effects. Some patients note hair loss, although this can happen with large weight loss from any causes as well. Some patients note looser skin or more wrinkles with any kind of weight/fat loss and also there is a statistical risk of pancreatitis and gallbladder disease with weight loss but these are rare.

Concern has also arisen about the proportion of the lost weight that is fat mass vs lean body mass in patients taking these drugs who lose large amounts of weight. This is being studied more closely, and new drugs are being designed that might reduce muscle mass loss. The quality of foods that are eaten is also important with focus on adequate protein intake.

For more information about muscle mass loss make sure to read tomorrow's post.

DAY 6 OF GLP-1S FACTS

Minimizing the Loss of Muscle Mass

With GLP-1s now inducing weight loss at levels only seen before through surgical intervention, obesity specialists say patients on these drugs are experiencing complications similar to those seen after weight loss surgery, including muscle mass loss.

It is important to note that **loss of lean mass** is expected with all weight loss interventions, including drugs, bariatric surgery or even intense lifestyle interventions and is attributed to the magnitude of weight lost rather than an independent effect of GLP-1s. It is impossible to lose weight from the fat compartment of the body only.

Two approaches are key to addressing muscle mass loss in patients losing weight with GLP-1s: increased protein intake and physical activity.

The recommended dietary allowance for protein is 0.8g/kg for most adults, but is not sufficient for older, obese patients, who need closer to 1.0-1.2g/kg bodyweight to maintain muscle mass. For example, for a 250 lb. patient, 114-136 g protein per day might be necessary. This is equivalent to roughly 15 oz of cooked animal protein; a 4-oz chicken breast has about 35 g of protein but the protein should come from a variety of sources stressing lean lower cholesterol foods and supplements. Research shows that consuming more protein than recommended offers a skeletal muscle preservation benefit. Practical nutrition strategies like aiming for 20-40 g of protein at every meal can help patients increase their protein intake. Focusing on high-quality protein sources and emphasizing both protein and vegetables will result in maximum stimulation of muscle protein syntheses. It's important to note, though, that individuals with kidney disease must limit their protein intake to 0.6-0.8 g/kg bodyweight per day to avoid overtaxing their kidneys.

It's not clear what long-term effect loss of muscle mass may have on physical function, bone density, and longevity, and is of greatest concern in older adults with age-related low muscle mass obesity who are at risk of further muscle atrophy and frailty.

Refraining from incrementing patients' doses of GLP-1s too rapidly or on any set regimen ie "every four weeks" and increasing the dose only when patients start to plateau on the same dose may prevent overly rapid weight loss and rapid muscle loss. Body composition is often measured during a clinical trial to track and study this.

In addition to a high-protein diet, strengthening exercise is highly recommended. The higher a patient's body mass index, the more likely they are to injure themselves with weight-bearing aerobic exercises at first. But resistance training, even in a sitting position, is an exercise everyone can do early in their program and continue to preserve muscle. While exercise will not contribute greatly to weight loss, it's very important for cardiovascular health, mental health, weight maintenance, and preventing excess muscle mass loss with weight loss.

150 minutes of cardiovascular exercise per week and an appropriately designed resistance training program is encouraged for most patients in a graded approach and even higher goals of 200 to 300 minutes per week result in further benefit as patients become more fit. Exercise recommendations should be highly individualized for safety and efficacy.

DAY 7 OF GLP-1 FACTS

Cost and Availability Issues

When GLP-1 drugs work, they can be life-changing for people whose weight increases their health risks, from diabetes to heart, kidney and liver disease. Yet Novo Nordisk and Lilly can't make enough GLP-1s to meet demand and mostly sell them in a few of the world's wealthiest countries. Since so many people are turning to these drugs for weight loss, there are now shortages and insurance hurdles for the patients with diabetes who also need them for glucose control (lowering their A1C levels) as well, frustrating both doctors and patients.

In addition to the shortage of these medications, U.S. prices, often set above $1,000 per month without insurance, place them beyond the reach of many patients who need them and are not covered by their insurances or don't have insurance. Hopefully, prices will come down in the near future, and Medicare and other insurers will broaden insurance coverage as more data shows risk and disease prevention.

As patients and practitioners contend with shortages and sky-high prices, compounded drugs have flooded the market. Find out more about these compounded drugs in tomorrow's post.

DAY 8 OF GLP-1

Compounded Drugs: Safe or Not? The Value of Medical Guidance

The recent surge in demand for GLP-1 medications has led to significant shortages and supply chain challenges and thus a growing use of compounded drugs. Both cost and scarcity have forced many patients to explore alternatives to FDA approved and physician prescribed products, including compounded versions of these drugs.

Making Ozempic, Mounjaro, Wegovy, Rybelsus and Zepbound involves highly complex processes using specialized equipment in unique manufacturing settings. This means that increasing supply for skyrocketing global demand is taking some time. The supply shortages are not related to a quality defect or safety issue.

What is a compounded drug? According to the FDA (US Food and Drug Administration), a drug may be compounded for a patient who can't be treated with an FDA-approved medication.

The quality and safety of compounded medications can vary widely however, depending on the pharmacy's adherence to regulations and quality control standards. The efficacy and safety of all compounded drugs have not been systematically studied. Therefore, there may be issues with purity, safety and efficacy of some and not others, but problems have been reported.

Many obesity medicine physicians caution their patients about taking compounded weight loss drugs. Practitioners want to provide the most effective and safe treatments and usually recommend treatments that have been rigorously studied in controlled clinical trials. Compounded medications have not been studied in large control trials and are not FDA approved, and some compounding pharmacies are not licensed or accredited. Compounded drugs can present variability in quality and potency and an increased risk of contamination or adverse effects (with subcutaneous injections, any impurities from a non-sterile drug can reach the bloodstream quickly).

If you find you can get medication without a prescription, without a medical exam or consultation or without lab testing or if you're sourcing your GLP-1 online, from a spa, a weight loss clinic or your local gym **without** medical supervision, be aware of these risks and get more information.

In addition to possible safety and quality issues, taking compounded drugs without medical supervision, counseling and a comprehensive plan puts people at a greater risk of weight loss complications and usually reduces the tolerability. Make sure to monitor your side effects, be vigilant for any adverse reactions and report them to your healthcare provider immediately for guidance.

Finally, as mentioned in our Day 6 Post, rapid weight loss without medical supervision can result in excess muscle mass loss, which can lead to a host of other problems including malnutrition, sarcopenia and falls with injury.

Manufacturers are working to increase production capacity as demand for these medications grows but shortages may persist for some time. New approved drugs are on the horizon but it's important to stay informed and to consult with healthcare professionals for personalized advice.

Remember, while compounded medications may offer a solution during shortages, they should be used with caution and careful monitoring by a qualified practitioner. Participating in a highly monitored clinical trial is another way to obtain access to treatment!

DAY 9 OF GLP-1 FACTS

The Future of GLP-1s – What Do We Still Need to Know That We Might Find Out from Clinical Studies?

- How **durable** are the results of GLP1 weight loss and what will happen if people discontinue use after some time? How should one safely taper or discontinue them?
- How about the results from **combinations** of GLP-1 meds with other glucoregulatory hormones that have since been discovered like GIPR, glucagon, amylin and others. Will they yield even better results? Will the side effects be reduced?
- Can we develop safer and more effective **oral** preparations?
- What is the **long-term safety** profile of these preparations? Will they be found to have serious adverse events over time?
- Can new formulations **improve tolerability,** especially reducing the gastrointestinal side effects that some 50% of people experience on these meds?
- What about preservation of **lean body mass** and avoidance of **muscle wasting** (sarcopenia)?
- Will this group of drugs be useful to treat **other conditions**, like addictions, neurologic diseases?
- What about safety in **other populations**, children, adolescents, women of childbearing potential, the elderly, hospitalized persons?
- Are the cheaper **compounded products** effective? Safe?

Lastly, it is hoped that an **expanded choice** of effective GLP-1 medications will drive the **cost** of these drugs down so that their full potential can be realized globally and that newly developed formulas will improve effectiveness and minimize side effects.

It's important to keep in mind that, when you lay out the countless known benefits of blood sugar management and weight loss, including the lower risk of high blood pressure, heart disease, stroke, sleep apnea, metabolic syndrome, fatty liver disease, several cancers and more, the advantages of GLP-1s seem very worthwhile.

So, there's a lot of work we must do carefully as a medical community, but our success depends on the generous participation of patients in very meticulous, well designed and medically monitored clinical trials.

Participants in well conducted clinical trials may benefit from the investigational product itself, as well as from the nutritional, exercise and lifestyle counselling that may be part of the protocol. No medical insurance is required, and personal identity and results are highly protected by codes. There is no cost at all to a participant in a clinical research study. Labs, medical visits, monitoring, and study drugs are free, and stipends are provided for patient travel and time. Protocols are very carefully explained to interested persons as well as the possibility of receiving placebo (inactive comparators) in some study protocols as part of Informed Consent procedures. Investigator physicians can communicate results and progress with primary care doctors as requested.

We're very excited to be screening people now for two new GLP-1 type weight loss studies. Please visit our **website** for more information on participation.

DAY 10 OF GLP-1 FACTS

Weight Regain After Withdrawal

We face many unknown questions about whether these drugs need to be continued permanently to maintain lost weight or whether some patients may be able to eventually be taken off these drugs with continued weight maintenance. This is an area of active clinical research.

A study published in April 2022 which sought to examine changes in body weight and cardiometabolic risk factors upon the termination of Ozempic found that after a year people had regained two-thirds of the weight they had lost. The positive changes they had seen in cardiometabolic risk factors had similarly reversed. The rebound occurs quite simply because the drug does not cure the underlying issues that led to weight gain in the first place.

These findings confirm the chronicity of obesity and suggest ongoing treatment is required to maintain improvements in weight and health. Just like treatments for other long-term conditions, such as high-cholesterol or blood pressure, it is not really surprising that these drugs don't continue to work after people stop taking them.

There is good evidence that suddenly stopping a medication is not ideal unless there are significant side effects. A combination of ongoing support in making lifestyle changes and slow dose tapering or intermittent therapy may allow some patients to avoid regaining weight after coming off these medications.

I am confident additional data that will come from a range of clinical studies like the ones we are running right now at NorCal and others, chart review studies and even narrative reviews.

Achieving health goals is a journey with ever-changing terrain but we keep walking it together.