Science Note 7: Should we be worried about the long-term use of GLP-1s?

The Bottom Line: The available evidence suggests that GLP-1 receptor agonists have a favourable long-term safety profile, supported by extensive clinical use and large safety databases. Nevertheless, some uncertainties remain, particularly regarding newer agents and aspects of their neurological effects that are not yet fully understood. As with all long-term therapies, continued research and post-marketing surveillance remain important.

What We Know

One perspective on this topic is certainly pragmatic. If we take, for example, liraglutide, which is specifically indicated for the treatment of obesity, it has been on the market since 2014 and has been used by a large number of people. Researchers argue that if there were major previously unrecognised adverse effects associated with its use, they would likely have become apparent by now.[3]

More broadly, GLP-1 receptor agonists have an extensive safety record in the treatment of Type 2 diabetes. Since their introduction in 2005, more than 20 million people worldwide have used them. Druker (2022) specifically reviewed concerns relating to pancreatitis, pancreatic cancer, thyroid cancer, cardiovascular risk and other unforeseen toxicities. His conclusion was that the available evidence supports both the effectiveness and safety of GLP-1 receptor agonists in the treatment of Type 2 diabetes, cardiovascular disease, obesity and multiple co-morbidities.

Druker (2022) further concluded:

"The well-defined mechanisms of GLP-1 action through a single G protein-coupled receptor, together with the extensive safety database of GLP-1 receptor agonists in

people with Type 2 diabetes, provide reassurance surrounding the long-term use of these agents in people with obesity and multiple co-morbidities."

From this perspective, the long-term safety profile of GLP-1 receptor agonists appears reassuring, particularly for conditions where substantial long-term data already exist.

What We Know Less About

Semaglutide, on the other hand, was only approved for the treatment of obesity in 2021.[3] While semaglutide itself has been studied and used in Type 2 diabetes for longer than this, its use specifically for obesity is more recent.

Consequently, some clinicians argue that newer GLP-1 medications should continue to be monitored carefully so that any unexpected long-term effects can be identified as early as possible.

The Brain Question

One of the more interesting unanswered questions relates to the brain.

GLP-1 receptors are found throughout the central nervous system. However, naturally produced GLP-1 is rapidly broken down in the body and acts over relatively short periods of time. Synthetic GLP-1 receptor agonists remain active for much longer, resulting in more prolonged receptor stimulation. As a result, researchers continue to investigate which brain regions may be affected and whether some of the benefits and side effects of these medications are mediated through pathways that are not yet fully understood.[1]

Despite the remarkable weight-loss results seen with these medications, scientists still don't fully understand exactly why some people lose as much weight as they do on

them.[3] The existence of unanswered questions about brain function does not automatically imply that a medication is harmful.

However, because GLP-1 receptors are present in multiple brain regions involved in reward, motivation, appetite and behaviour, researchers continue to investigate their broader neurological and psychological effects.

Putting Risk Into Context

A useful way to think about long-term safety is that every medical treatment involves a comparison between two risks:

1. The risks associated with taking the medication.
2. The risks associated with not treating the condition.

For a person with obesity, Type 2 diabetes or significant cardiovascular risk factors, the consequences of leaving the disease untreated may be substantial.

The question therefore becomes not whether a GLP-1 medication is completely risk-free, but whether its known and potential risks are outweighed by its known and potential benefits.

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References

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