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Starting GLP-1 therapy may induce impulse control disorders.

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4 **Starting GLP-1 therapy may induce impulse control disorders.**
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3 Glucagon-like peptide 1 (GLP-1) agonists are being increasingly used globally. Clinical
4 indications have expanded from treatment of diabetes and obesity with associated pathologies,
5 to obese individuals without co-morbidities and more worryingly, are being used by non-obese
6 media celebrities and “internet influencers” for rapid life-style weight loss.
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10 Current warnings about GLP-1 agonists mainly relate to gut motility issues. Effects on cognition
11 has received scant attention, with the few studies published focusing on longer term outcomes,
12 rather than during the immediate phase of rapid weight loss.¹ The authors of this article (a
13 gastroenterologist and a psychiatrist) have become aware of individuals (not their patients)
14 who have started on GLP-1 medication and made major life changing decisions regarding their
15 domestic situation (such as divorce, house moves) within the first few months of starting
16 treatment. Without knowing the details underlying these events, the rationale for some of
17 them appears reckless. This led us to consider that starting GLP-1 agonists may result in
18 cognitive changes in decision making through the combination of metabolic changes resulting
19 from calorie deficit/rapid weight loss, in combination with direct effects of GLP-1 on brain
20 function.
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24 GLP-1 agonists can cross the blood brain barrier, GLP-1 receptors are widely distributed
25 throughout the brain and central GLP-1 receptor activation affects several neurotransmitters
26 including elevating dopamine turnover in the amygdala.¹ Cognitive changes may occur on
27 initiation of several medicines including dopamine agonists (e.g. levodopa and Capergoline).
28 Dopamine agonists increase the risk of impulse control disorders, including pathological
29 gambling and hypersexuality, with the British National formulary advising that patients need to
30 be warned about this risk. However, there is no equivalent advice for GLP-1 agonists in patient
31 information leaflets or from government regulatory agencies. The NICE (*Semaglutide*) website
32 advises doctors to warn patients about potential impairment of driving and performance of
33 skilled tasks, particularly during dose escalation period, and in the USA, FDA advice (*Wegovy*)
34 focuses on potential development of psychosis and suicidal ideation, advising doctors to warn
35 patients to be alert to sudden changes in mood, behaviors, thoughts, or feelings.
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40 The psychological and physiological state of patients taking GLP-1 agonists is relatively new and
41 underexplored. Patients are undergoing rapid breakdown of body energy stores but without
42 the higher function signals of severe hunger. This distinguishes them from patients with forced
43 calorie restriction where heightened arousal, agitation, additional acquisition of non-food items
44 and reduced cognitive flexibility occurs.² The psychological profile of patients taking GLP-1
45 agonists also differs from subjects with anorexia nervosa.³ Studies of cognitive changes in
46 patients undergoing bariatric surgery suggest this procedure may improve some executive
47 function.⁴ However, assessment usually occurs many months after surgery, rather than within
48 the first few months where some of the most extreme weight loss changes, and in the case of
49 GLP-1 agonists when dose escalation, are taking place. Patients with cancer-related cachexia
50 also have reduced appetite, despite weight loss, and exhibit cognitive impairment⁵ but have the
51 confounding issue of psychological changes due to cancer diagnosis. Based on this evidence, we
52 recommend research should be conducted to explore this risk and in the interim, patients
53 starting GLP-1 agonists should be cautioned about making rapid life changing decisions.
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