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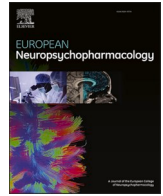


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REVIEW

GLP-1 agonists and risk of suicidal thoughts and behaviours: Confound by indication once again? A narrative review

Robertas Strumila^{a,b,c,*}, Aiste Lengvenyte^{a,b,c}, Sebastien Guillaume^{a,b}, Benedicte Nobile^{a,b}, Emilie Olie^{a,b}, Philippe Courtet^{a,b}^a Department of Emergency Psychiatry and Acute Care, CHU Montpellier, France^b IGF, University of Montpellier, CNRS, INSERM, Montpellier, France^c Psychiatric Clinic, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) agonists have been successfully used in clinical practice for the treatment of diabetes and obesity, offering significant clinical benefits. However, concerns regarding their potential link to psychiatric side effects, like suicidal thoughts and behaviours (STB) have emerged. This narrative review investigates the complex interplay between GLP-1 agonists and STB, focusing on the biological stress induced by rapid weight loss, psychological and social consequences, similar mechanism with addiction, and the evaluative lens of the Bradford Hill criteria on causality. While GLP-1 agonists can contribute to substantial health improvements, they also introduce biological and psychological stressors. Disruptions in homeostasis from quick weight reduction can elevate cortisol and norepinephrine levels, heightening the risk for, or exacerbation of STB. Psychological factors, including unfulfilled expectations and identity changes after significant weight loss, compound these risks. Utilizing the Bradford Hill criteria reveals insufficient evidence for a direct causal link between GLP-1 agonists and STB. Yet, the indirect effects related to the metabolic and psychological disturbances associated with rapid weight loss call for a cautious approach. Used carefully in targeted populations GLP-1 agonists may even emerge as protective agents against STB. Therefore, it is crucial to monitor patients during the treatment and screen for preexisting mental health conditions. If detected, appropriate clinical management should be applied. Future studies should aim at optimizing dosing schedules to mitigate the adverse effects of rapid weight loss and further investigate GLP-1 agonists in possible STB prevention.

Introduction

Glucagon-like peptide-1 (GLP-1) agonists are one of the most talked about innovations in medicine, changing the management of diabetes and obesity (Ahrén, 2023). The journal Science named them "Breakthrough of the Year" in 2023 (Thorp, 2023). Since the introduction of the first GLP1 agonist, Exenatide, in 2005 more and more medications with ever-increasing potency in this group are being approved. Until recently, liraglutide was the most prescribed medication in the GLP-1 agonists group. Nowadays, semaglutide and tirzepatide, the latter combining agonism of GLP-1 and glucose-dependent-insulinotropic polypeptide (GIP) receptors, are being increasingly used both on- and off-label. The paradigm-shifting clinical benefits of GLP-1 agonists have been repeatedly demonstrated in clinical trials and real-world data, and their popularity is reflected in media interest and shortages despite

access regulations (Mahase, 2024).

With the rapid adoption and expansion of every new drug, side effects are often noticed later. Recently, several commentaries started to investigate the possible link between GLP-1 agonists and suicidal thoughts and behaviours (STB) (Arillotta et al., 2023; McIntyre, 2024; McIntyre et al., 2023). For example, one of the studies pulled data from the FDA Adverse Event Reporting System and found disproportionate reporting of suicidal ideation. It prompted European regulators to open an investigation. The review was triggered by the Icelandic medicine agency following reports of suicidal thoughts and self-injury in people using liraglutide and semaglutide. In the European Medicines Agency report from July 11, 2023, it was stressed that "it is not yet clear whether the reported cases are linked to the medicines themselves or the patients' underlying conditions or other factors." In addition, recent real-world studies found no link between the use of GLP-1 agonists and

* Corresponding author at: Department of Urgent and Post Urgent Psychiatry, 371 Av. Du. Doyen Gaston Giraud, 34090, Montpellier, France.

E-mail addresses: r-strumila@chu-montpellier.fr, robertas.strumila@mf.vu.lt, drstrumilarobertas@gmail.com (R. Strumila).

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increased risk of STB, and a recent large population-based study has instead reported a lower risk of incident and recurrent suicidal ideation in obese and overweight individuals taking semaglutide compared with non-GLP-1 agonist anti-obesity medications (Chen et al., 2023; Wang et al., 2024). Also, recent pharmacovigilance studies based on the FDA and EMA Adverse Event Reporting System databases reported no evidence suggesting an association between GLP-1s and STB based on clinical characteristics, time-onset, and co-medication analysis (Guirguis et al., 2024; Ruggiero et al., 2024; Zhou et al., 2024).

Definitions matter

It is important to clearly define the terms when talking about STB with regard to the secondary outcomes. Suicidal thoughts are ideas that arise in a person's consciousness either willingly or unwillingly. They are very prevalent: it has been shown that around 21% of Europeans had such thoughts at some point in their life (Castillejos et al., 2021). A suicide attempt, on the other hand, is an actual attempt to end one's life. Death by suicide is the extreme, but rare outcome of the suicide attempt. It is important to note, that suicidal ideas and death by suicide, are weakly correlated (Klonsky et al., 2021; Lukaschek et al., 2015), and many people with suicidal ideation will go on to live their lives without attempting suicide. However, some people who never had suicidal ideation could experience a suicidal attempt in a moment of stress during their life, in fact about 20% of suicide attempters never had any psychiatric diagnoses before in their life (Klonsky et al., 2021; Oquendo et al., 2024). A historical example comes from the introduction of selective serotonin reuptake inhibitors, which have been reported to be associated with increased suicidal ideation risk in those under 25 years old (Olsson et al., 2006). Later analyses demonstrated that the observed associations were largely influenced by confounding by indication (Fornaro et al., 2019), and the reduction of prescription of selective serotonin receptor inhibitors ultimately led to increased rates of suicide attempts and deaths (Gibbons et al., 2007). Furthermore, a recent real-world study of more than half a million people, the biggest of this kind, showed that SSRI use actually reduced STB, including in youths (Lagerberg et al., 2022).

Other rapid weight loss interventions and STB

GLP-1 agonists are not the first weight loss interventions causing controversy regarding STB. Rimonabant, a selective cannabinoid receptor-1 (CB-1) antagonist, showed promising results in clinical trials ("Rimonabant Therapy for Obesity Results in Modest Weight Loss," 2007) and was approved in Europe for weight loss in 2006. However, in 2008 it was withdrawn from the market due to psychiatric side effects (Christensen et al., 2007). Data from clinical trials submitted to regulatory authorities showed that rimonabant caused depressive disorders or mood alterations in up to 10% of subjects and suicidal ideation in around 1% of subjects. In a large RCT comprising more than 9000 patients, the rate of psychiatric adverse events (anxiety, depression, depressed mood, or insomnia) was greater than 30%. The later discovered antagonism of the opioid mu receptor (Seely et al., 2012) has been proposed to be involved in these effects, since the opioid system is implicated in mood regulation, and the use of opioids may predispose to depression and STB (Jelen et al., 2022; Pecina et al., 2019; Stanley et al., 2010).

A widely used intervention associated with a rapid weight loss is the bariatric surgery. It is well-documented that some people have increased rates of STB after bariatric surgery OR 1.9 when compared with the general population and OR 3.8 when compared to matched controls. (Castaneda et al., 2019). In a landmark study from 2007 which evaluated long-term mortality after bariatric surgery it was found that Even though all-cause mortality during a mean follow-up of 7.1 years, adjusted long-term mortality from any cause in the surgery group decreased by 40%, mortality from suicide and accidents were 58%

higher in the surgery group than in the control group (Adams et al., 2007). For instance, a study of veterans who underwent bariatric surgery found that the hazard ratios for increased ideation was 1.12, and for suicidal attempts 1.62 (Hung et al., 2023), emphasizing the need for careful monitoring of psychological states before and after the surgery. However, a significant confounder for the association between bariatric surgery and increased STB risk was found in one study – 93% of events occurred in people who had a history of mental health problems in the past (Bhatti et al., 2016), even though they were asymptomatic before the surgery, weakening the hypothesis that rapid weight loss itself as a causal mechanism, but might rather be an important stressor in vulnerable individuals. This is supported by a recent study where 133 formerly obese adults were investigated before and 2 years after bariatric surgery (Custers et al., 2024) which found that "cognitive function, inflammatory biomarkers, comorbidities, physical activity, and depressive symptoms were still improved 2 years after bariatric surgery". It is known, that improvement in these factors does indeed reduce suicidality (Cáceda et al., 2018). So, this also points to the more probable explanation – confound by indication, where people with clinical obesity were already at higher risk for suicide to begin with. Since cardiovascular deaths are reduced by GLP-1 therapy, and all people die from other causes nevertheless, the relative increase in suicides is a natural consequence of this trajectory.

Biological stress associated with rapid weight loss

Suffering from obesity is associated with higher morbidity, lower quality of life, higher utilization of healthcare services, and comorbid cardiovascular, psychiatric, and endocrinological conditions (Brochu, 2020; Leutner et al., 2023; Pi-Sunyer, 2009). In most cases, treatment with GLP-1 agonists does lead to increased quality of life (Kosiborod et al., 2024), however, the question is what goes wrong, when it doesn't. One of the possible explanations could be the concept of allostasis, which describes the process by which the body responds to stressors to regain homeostasis (McEwen and Wingfield, 2003). People with obesity often have decreased metabolic rate, and increased insulin resistance resulting in ineffective use of existing energetic resources, as well as increased hunger signalling, and decreased satiety signalling (Singla, 2010). Their "normal" weight threshold, controlled by the hypothalamus, is increased and the body actively works to present this homeostasis (Schwartz et al., 2017).

Rapid reduction in food intake and weight loss disrupts this carefully regulated system and results in overall biological stress, exemplified by rapid and marked increases in cortisol secretion and norepinephrine levels. Resulting hormonal changes can create so-called allostatic load and put the organism on a high level of stress. This can cause increases in cortisol (Dolores Parra et al., 2006; Tomiyama et al., 2010; Zauner et al., 2000). Cortisol system dysregulation has been implicated in STB (Herzog et al., 2023) and a rapid increase in norepinephrine levels is associated with anxiety and suicidal ideation (Montoya et al., 2016). Another example could be the tests performed on starvation subjects – their norepinephrine levels increased more than 2 times in 4 days (Zauner et al., 2000). Rapid two-fold increase in norepinephrine levels causes anxiety, and can indeed lead to suicidal ideation (Montoya et al., 2016). Future studies will have to show whether slower dose escalation of GLP-1 agonists would be less likely to cause excessive stress, possibly resulting in negative psychiatric outcomes. A real-world study comparing 10,690 GLP-1 agonist users with diabetes mellitus type 2 and 42,766 propensity score-matched patients without GLP-1 agonist use found that the risk of anxiety disorder diagnoses was decreased (Tsai et al., 2022).

Another biological stressor associated with rapid weight loss could be associated with the loss of the fat tissue, which stores various toxic compounds. A rapid reduction of the fat tissue can result in excessive amounts of fat-stored molecules in the circulation, ultimately resulting in negative effects on health. For instance, studies show increases in

peripheral blood levels of pesticides and other toxic organic pollutants in people who underwent caloric restriction or bariatric surgery (Chevrier et al., 2000). While any associations are speculative at best, pesticide exposure has been associated with STB (Wu et al., 2023).

Addiction as a GLP-1 agonism target

STB is also strongly associated with other addictions, such as alcohol and substance use disorders (Conner et al., 2019). In particular, chronic alcohol consumption may impair emotional regulation, and coping behaviours, ultimately increasing the risk of STB (Conner et al., 2019; Strumila et al., 2023). Interventions targeting alcohol use disorder are therefore key to reducing the STB risk.

Recently, several animal and human studies showed promising results on the GLP-1 agonists' effectiveness in treating alcohol addiction. In a mice study, Semaglutide reduced alcohol intake and relapse-like drinking in both female and male mice (Aranäs et al., 2023). A social media analysis found that around 71% of posts of semaglutide users mentioning alcohol, indicated reduced cravings, desire and other negative effects related to alcohol (Quddos et al., 2023). A review that analysed all the available papers concluded that the effect is probably centrally mediated in part through dopamine signalling, but exact mechanisms are still elusive (Klausen et al., 2022). While these results remain to be confirmed, they reiterate an old observation that obesity and addiction share many similarities, with obesity being conceptualized as a complication of food addiction (Kenny, 2011). Dopamine signalling impairment might underline these associations since people with binge eating disorders with or without obesity have enhanced dopamine release during food stimulation (Wang et al., 2011). In neuroimaging studies, the availability of dopamine D2 receptors was decreased by around 18% in obese individuals - 2.47 SD 0.36 vs. 2.99 in controls SD0.41; $p < 0.0075$ (Wang et al., 2001). Meanwhile, after bariatric surgery and resulting weight loss, D2/D3 receptor availability increased by around 16% (0.76 to 0.88, $p=0.031$). (van der Zwaal et al., 2016). High fat -high carbohydrate food, often consumed in high quantities in people with obesity, is associated with attenuated phasic dopamine release (Estes et al., 2021), as well as gene expression changes in dopamine and opioidergic systems (Reyes, 2012). GLP-1 receptor agonists have also been shown to alter brain activity related to highly desirable food cues (Farr et al., 2016), and to control stress response and behaviours associated with it (Holt, 2021). Not surprisingly, experts in the field have been proposing the use of GLP-1 agonists in various psychiatric conditions like mood disorders and addictions (Camkurt et al., 2018). Lastly, a recent neuroimaging study found that there was no change in resting state functional connectivity in participants who received semaglutide compared to controls (Verovnik and Vovk, 2024).

Neurobiologically, GLP1 receptors are expressed in the brain directly, mostly in the hypothalamus, hippocampus and brainstem. There, they decrease food intake, reduce inflammation and apoptosis, modulate reward behaviour (which is important for addiction), and promote neurogenesis, cell survival, learning and memory (Diz-Chaves et al., 2022; Kopp et al., 2022; Pelle et al., 2023). Given all these beneficial actions it becomes even more unlikely that suicidal thoughts and behaviours risk would be increased.

While all of these ideas remain speculative, if GLP-1 agonists prove to be effective in treating addictive processes, GLP-1 agonists can emerge as protective agents for STB, especially in people prone to addiction. Future interventional studies should examine these effects.

Psychological and social aspects of GLP-1 agonist use possibly linked to mental health

GLP-1 agonists are often portrayed as a revolution in medicine that rapidly changes people's lives. Unsurprisingly, the use of this medication might be associated with elevated expectations for improvements in body composition and overall well-being. However not everyone reacts

to these medications in this way, and some people do not respond or respond minimally. A failure of medication-induced changes to meet high expectations might result in deceptions and, in extreme cases, possibly in suicidal ideation. For instance, individuals who did not respond to psilocybin had increases in STB, which was suggested to be at least partly associated with the loss of hope following a lower-than-expected response to a hyped intervention (Lengvenyte et al., 2023). In support, as it is often stated in psychology research: "the secret to happiness is low expectations" (Rutledge et al., 2014). When expectations are not met, frustration, anger, and deception can rise in a person's consciousness, and this can give way and lead to suicidal ideation. Giving support for this notion, a study involving more than 6000 Korean adults found that not losing as much weight as wanted during a weight loss intervention was associated with an increased risk for suicidal ideation in women (Ju et al., 2016). Expectation management and approaches such as mindfulness or dialectical behaviour therapy might be a useful integral part of the care of individuals undergoing GLP-1 treatment, pending clinical studies. These interventions usually lead to happier states, but the path to get there is accepting the situation and learning to live with it despite its emotional valence (Keng et al., 2011; Wojnarowska et al., 2020).

On the other hand, if the intervention is successful, it might rapidly change not only the body image but also the social identity and value system. At an extreme end of the spectrum, body image problems are pervasive phenomena in anorexia nervosa, in which food and other rewards become less rewarding than perceived social and personal rewards from body image (Kaye et al., 2013). In people who rapidly lose weight, there might be changes in lifestyle (such as increased participation in physical activities and reduced participation in hedonic and food-related activities), possibly resulting in shifts in personal networks (Greaves et al., 2017). On the other hand, body weight is strongly associated with social identity (Hunger et al., 2015) and rapid weight loss could result in identity disturbance, which has been associated with suicide attempts in borderline personality disorder (Yen et al., 2021). Regret and blaming oneself for the previous obesity might lead some people to STB if not properly supported.

Bradford Hill criteria of causality

The Bradford Hill criteria, developed by Sir Austin Bradford Hill in 1965, are a group of nine principles that can be useful in establishing epidemiologic evidence of a causal relationship between a presumed cause and an observed effect (Fedak et al., 2015). While not providing definitive proof of causality, these criteria may guide the assessment of the likelihood of a causal relationship. In Table 1, we applied the Bradford Hill criteria of causality to the possible association between GLP-1 agonists and STB.

Discussion and conclusions

There seems to be insufficient empirical evidence to support the hypothesis that GLP-1 agonists directly increase the risk of STB. However, indirect effects associated with the GLP-1-associated rapid weight loss may be associated with STB. They include allostatic load and temporary increases in catecholamine concentrations and restriction in serotonin levels, resulting in exacerbation of pre-existing mental disorders, endotoxemia due to the release of biological molecules stored in diminishing fat tissue, as well as phenomenological changes in perception of self, life evaluation, possible emergence of feelings of guilt and/or regret.

The better explanation for the observed phenomenon of suicidality in the context of glp1 agonist use seems to be the type of bias sometimes observed in research called "confound by indication" (Andrade, 2024; Ilzarbe and Vieta, 2023). In this scenario, it is easy to mix the cause and effect of intervention, because of the underlying condition. The often-cited example is the similarity of the situation with

Table 1
Assessing a possible causal link between GLP-1 agonists and STB using Bradford Hill criteria.

Criteria	Comment	Directionality
1. Strength of Association	The association is very weak. Suicidal events are very rare occurrences in clinical trials and in real-world settings. In a recent study, the real-world incidence of de novo suicidal ideation was 0.11% for first-time suicidal ideations, and approximately 7% for people with a previous history of suicidal ideation (Wang et al., 2024).	Negative
2. Consistency	The emergence of suicidal ideation is not consistent in people treated with GLP-1 agonists. It is impossible to predict which patients will develop STB during the treatment with GLP-1.	Negative
3. Specificity	The observed effect is non-specific – STB is also common in people not exposed to GLP-1.	Negative
4. Temporality	The difference between the de novo suicidal ideation and reactivation of past suicidal ideation is about 63 times (0.11% vs 7%). This does not suggest causality but implies the need for careful evaluation in people with a prior history of SI.	Negative
5. Biological Gradient (Dose-Response Relationship)	To date, there is no evidence that a higher dose of GLP-1 agonist causes more STB than a lower dose.	Negative
6. Plausibility	There are no preclinical studies that would suggest that GLP-1 agonism causes STB. GLP-1 is a natural hormone, and current medications increase the effectiveness of a naturally existing mechanism.	Negative
7. Coherence	No biomarker study to date mentioned GLP-1 anomalies in people with STB.	Negative
8. Experiment	Some human studies showed a reduction in depression in people treated with GLP-1 agonists [53,54]. Preclinical studies on STB are not possible, but animal models on depression showed improvements in depressive-like behaviours after liraglutide administration [55].	Negative
9. Analogy	Although rimonabant could be considered as an analogy – an effective weight loss drug associated with suicidal thoughts and behaviours, the recent discovery that it also blocks opioid receptors negates this finding – the weight loss effect was probably stemming from CB-1 inhibition, and STB from the Mu Opioid receptor inhibition (Seely et al., 2012).	Negative

antidepressants, where it was observed, that people taking antidepressants are at a higher risk of suicide. The human brain is an explanation machine and always tries to find the easiest answer first (system 1 vs system 2 type of thinking (Shleifer, 2012)). A more logical and correct answer is that people who are prescribed antidepressants are already at high risk of suicidal thoughts and behaviours (Lee and Chang, 2022). While FDA issued a black box warning, reacting to the pressure from the public, subsequent analyses actually showed a protective effect of SSRI on suicidal thoughts and behaviours when used as intended (Lagerberg et al., 2022), and also there are no data, that they would cause STB's in people prescribed SSRI's for other things, like heart disease (Angermann et al., 2016) or COVID19 (Stewart et al., 2023).

More important than the studies of mechanistic and psychosocial explanations of why some people might suffer from STB during the treatment with GLP-1 agonists, the real concern is patient safety. Given the positive effects of GLP-1 agonists on many health-related outcomes, including body weight, inflammation, heart disease, diabetes, addiction, and suicidal ideation (Wang et al., 2024). Furthermore, given the significant reduction in the risk factors that are known to predispose to suicidal behaviour and death by suicide (Brundin et al., 2017; Chen et al., 2023; Lengvenyte et al., 2021), GLP1 agonists used chronically can even turn out to be protective in this regard and join the short list of medicines that are effective in suicide prevention. Yet, a balanced view of benefits and risks is needed, and cause for caution and increased surveillance in people with pre-existing psychiatric conditions, and psychological support in individuals undergoing drastic and rapid weight reductions. We also call for studies on dose adaptation in people at risk, possibly reducing the speed of weight loss.

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CRedit authorship contribution statement

Robertas Strumila: Visualization, Methodology, Writing – original draft, Writing – review & editing. **Aiste Lengvenyte:** Writing – review & editing. **Sebastien Guillaume:** Supervision, Validation, Conceptualization. **Benedicte Nobile:** Writing – review & editing. **Emilie Olie:** Supervision, Validation, Conceptualization. **Philippe Courtet:** Supervision, Validation, Conceptualization.

Declaration of competing interest

None of the authors have any conflicts of interest regarding the content of this work.

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