Abstract (word count 128)

Several prescription and non-prescription drugs are liable for abuse. However, oral hypoglycemic agents are among the most benign and low risk drugs in terms of abuse liability. This *Commentary* intends to raise awareness regarding the abuse of a particular type of oral hypoglycemic agent, namely sulfonylurea drugs, used to experience mental altering effects for its euphoric "*hypoglycemic rush*". Information is available on discussion fora online where people exchange their experiences. Moreover, several case reports have been published and described the liability for abuse of sulfonylurea drugs. This article intends to shed the light on this phenomenon in light of available literature, attempting to explain the possible scientific basis for it. In addition, it highlights the need for health professional awareness and vigilance for this form of drug diversion.

Impact on practice:

- Raising awareness of clinicians about the underestimated, under-researched issue of hypoglycemic drug abuse.
- Explaining the potential abuse of hypoglycemic rush in light of published scientific literature.
- Making recommendations to legislative authorities in some countries to limit access to sulfonylurea drugs to be available strictly on prescription.

Abuse of Sulfonylureas: Is Factitious Hypoglycemia a cause for concern?

Mayyada Wazaify,[1] Leen Abushams,[1] Marie Claire Van Hout[2]

1: Department of Biopharmaceutics and Clinical Pharmacy, School of Pharmacy, The University of Jordan

2: Public Health Institute, Liverpool John Moore's University, United Kingdom

Address for correspondence and reprints:

Professor Mayyada Wazaify

Department of Biopharmaceutics and Clinical Pharmacy

E-mail: m.wazaify@ju.edu.jo

Telephone: +962795494923

ORCID #: orcid.org/0000-0001-8724-6027

Keywords: euphoria, factitious hypoglycemia, prescription drug abuse, sulfonylurea

Abuse of Sulfonylureas: Is Factitious Hypoglycemia a cause for concern?

The aim of writing this Commentary is to shed the light on a briefly reported and dated form of intentional drug intoxication known as "*factitious hypoglycemia*" [1,2] which appears to be re-emerging in recent times [1,3]. We refer to the phenomenon of abuse of a particular type of oral hypoglycemic agents, namely sulfonylurea drugs, used to experience mental altering effects for its euphoric "*hypoglycemic rush*" [1]. We utilize the definition of abuse whereby intentional use of pharmaceutical medicines is for non-medical purposes, rather than accidental overdose [4]. Anecdotal web discussions [5] and case reports of Marchetti et al 1988 and Svirski and Edoute 1996 [6,7] center on the use of sulfonylurea drugs to experience a *"near coma*" state, which users describe as "*joyful*" or "*euphoric*". [3,5] Such mind altering effects are caused by the deliberate inducement of hypoglycemia or referred to as *"factitious hypoglycemia"* [6,7]. A narrative review was conducted and designed to present a broad perspective on abuse or misuse of oral hypoglycemic agents, and describe its history and development in terms of how common it is and its public health implications. A structured literature search was conducted based on the question; what is currently known about liability of sulfonylureas to abuse? Search terms include sulfonylureas, oral hypoglycemic agents, glibenclamide, glyburide, different brand names, and "*euphoria*","*high*","*hypoglycemic rush*". There was no restriction on date range, and all types of articles, including opinion pieces were included.

In general, oral hypoglycemic agents are among the most benign and low risk drugs in terms of potential abuse liability. However, on conducting this rapid review of

web discussions and extant literature, we wish to draw the readership's attention to this unique form of intoxicating and non-medical intentional use of sulfonylurea drugs. We know that those interested in alternative ways of getting *"high"* are constantly in search for new alternatives that are available, cheap and legal and replace those drugs which are harder to obtain, more expensive illicit drugs. [8,9] For example, more unusual forms of pharmaceutical medicinal diversion include those with little or no mental altering effects such as bisoprolol, table salt or menthol vapor rubs [8-10]. Hence, we report here on the case of abuse of sulfonylureas, whereby the reported intoxication effect is caused by adrenaline release [11,12]. Adrenaline is responsible for the feeling of *"rush"* and contribution to dependence type behavior [11,12].

Normally, the brain utilizes glucose as sole energy source, which makes it particularly sensitive to any decrease in blood glucose level. When blood glucose levels drop too low, the body tries to increase the amount of glucose available in the bloodstream by releasing hormones such as glucagon and epinephrine (also called adrenaline) that stimulate the release of glycogen from the liver [13]. Symptoms of hypoglycemia are caused by a combination of adrenaline release and low glucose in the brain. Adrenaline can cause anxiety, shaking, sweating, tachycardia, and emotional reactivity such as irritability, anger and tears, *"brain fog,"* fatigue and insomnia [14]. These symptoms are often called the *"warning signs"* of hypoglycemia [13]. Lack of glucose to the brain can cause difficulties in concentration, blurred vision, slurred speech, lack of coordination, headaches, dizziness, and drowsiness. Hypoglycemia can also cause changes in emotions and mood. Feelings of nervousness and irritability, becoming argumentative, showing aggression, and crying are common, although some people experience euphoria

and giddiness [14]. *"Factitious hypoglycemia"* occurs secondary to the surreptitious use of insulin or insulin secretagogues (sulfonylureas, meglitinides). It can be differentiated from fasting hypoglycemia caused by hyperinsulinaemia or injection of insulin, by an elevated (> 1.0) molar ratio of insulin to C-peptide [15]. When sulfonylurea preparations are consumed, the only way of distinguishing factitious hypoglycemia from insulinoma is by determining the drug in serum and urine [14].

We conducted a rapid assessment of web discussions and review of extant literature which describe this unique form of pharmaceutical medicinal abuse whereby consumers deliberately ingest large doses of glibenclamide (also known as Glyburide) of up to 50mg at once to cause hypoglycemia and induce associated euphoric effects [6,7,16]. We note that the maximum daily dose ranges between 12 mg (micronized form) to 20 mg (standard glibenclamide) [17]. Several cases of deliberate inducement of hypoglycemia [6,7,16] described varied reasons for such excessive consumption, either to experience drug induced euphoria [16], or in seeking attention caused by Munchasen syndrome [18]. Of note are that case reporting occurs in the majority in medical personnel, diabetics or members of their family [14,16]. There are several factors contributing to such increased risk of drug abuse among medical personnel, such as emotional stress at work and easy access to drugs. [19] In addition, healthcare professionals' over-confidence may lead them to believe that their medical competency will prevent problems relating to acute intoxication and misuse of such drugs.. [19] A survey of 60 adolescents (12-20 years old) with Type-1 diabetes mellitus revealed a 36.7% prevalence of substance (alcohol, tobacco, illicit drugs) use and 19% reported

insulin misuse. [20] In this study, self-harm intent was reported by one-third of insulin misusers. Substance use and insulin misuse were not related to glycemic control or diabetes self-management behaviors.[20]

Despite the low case reporting, web discussions register an interest in *"factitious hypoglycemia"* as evidence by the following comments; "*I like the feeling. until it starts getting crazy intense, then it's like I guess I should do something about this", "mild hypoglycemia feels good to me. I feel like I have been day drinking*", "*I know alot of people describe having a hypo like being drunk, but at least you know why you're drunk." "I bet if there was a way to safely get your levels down to a hypo level and keep them there people would use it as a drug."* [5].

Hence we wish to draw attention to this unique form of pharmaceutical medicinal abuse for intoxication purposes, and the need for health professional awareness of and vigilance for this form of diversion and patient misuse of their drugs. In addition medical and pharmacy practitioners are advised to be aware of symptomatologies of *"factitious hypoglycemia" and the need for* pharmacovigilance

Ethics Approval: N/A

Finding: N/A

Acknowledgements: N/A

References:

1. Suusman KE. The use and abuse of oral hypoglycemic agents. Rocky Mt Med J. 1967;64(2):56-9

2. Horwitz DL. Factitious and artifactual hypoglycemia. Endocrinol Metab Clin N Am. 1989;18(1):203-10.

3. Brown A. Feeling euphoric on a low-carb diet? The effect on your brain is similar to an illicit drug. In: The conversation website. 2017. http://theconversation.com/feeling-euphoric-on-a-low-carb-diet-the-effect-on-your-brain-is-similar-to-an-illicit-drug-76303. Accessed 2 Jul 2018.

4. Hughes GF, McElnay JC, Hughes CM, McKenna P. Abuse/misuse of non-prescription drugs. Pharm World Sci 1999; 21: 251-255.

5. Anonymous. Feeling some sort of high or euphoria from hypoglycemia. In: Reddit website. 2016. **https://www.reddit.com/r/diabetes/comments/4snzwp/feeling_some_sort_of_high_or_euphoria_from/**. Accessed 24 Jun 2018.

6. Marchetti P, Faloppa C, Zappella A, Navalesi R. A case of factitious hypoglycemia with unusual presentation. Minerva Med. 1988;79(12):1101-3.

7. Svirski B, Edoute Y. Sulfonylurea-induced factitious hypoglycemia. Harefuah. 1996;130(10):678-80.

8. Madae'en S, Bostamy B, Jaber D, Wazaify M. Death of a middle-aged man after long term abuse of a combination anticholinergic, beta blockers and narcotic drugs: A

suspected Münchausen syndrome case report. J Addict Neuropharmacol. 2015;2(1):7-9

9. Jaber D, Al-Awwa I, Wazaify M. Multiple prescription drug abuse and salt craving in a psychotic patient: A case report from a teaching hospital in Jordan. Int J High Risk Behav Addict. 2015;4(3):e22449

10. Blackwood GW. Severe psychological disturbance resulting from abuse of nasal decongestants. Scott Med J. 1982;27:175-176.

11. Schmidt KT, Weinshenker D. Adrenaline rush: the role of adrenergic receptors in stimulant-induced behaviors. Mol Pharmacol. 2014;85(4):640-50

12. Zaniewska M, Filip M, Przegalinski E. The involvement of norepinephrine in behaviors related to psychostimulant addiction. Curr Neuropharmacol. 2015;13(3):407-18.

13. Hieronymus L, O'Connell B. Understanding Hypoglycemia. In: Diabetes Self-Management. 2017. https://www.diabetesselfmanagement.com/managing-diabetes/blood-glucose-management/understanding-hypoglycemia/. Accessed Jun 24 2018.

14. Siegel EG, Mayer G, Nauck M, Creutzfeldt W. Factitious hypoglycemia caused by taking a sulfonylurea drug. Dtsch Med Wochenschr. 1987;112(41):1575-9.

15. Lebowitz MR, Blumenthal SA. The molar ratio of insulin to C-peptide: An aid to the diagnosis of hypoglycemia due to surreptitious (or inadvertent) insulin administration. Arch Intern Med. 1993;153(5):650-5.

16. Hasche H, Bachmann W, Haslbeck M, Mehnert H. Hypoglycaemia factitia: Three Case Descriptions. Self-inflicted hypoglycaemia (three cases). Dtsch Med Wochenschr. 1982;107(16):625-628.

17. Glyburide Dosage. www.Drugs.com. Can be obtained from URL: https://www.drugs.com/dosage/glyburide.html [last accessed on Oct 14th, 2018]

18. Jermendy G. Factitious hypoglycemia--Munchausen syndrome in diabetes mellitus. Orvosi Hetilap. 1995;136(1):31-3.

19. Kenna GA, Wood MD. Prevalence of substance use by pharmacists and other health professionals. J Am Pharm Assoc 2004;44(6):684-93.

20. Snyder LL, Truong YK, Law JR. Evaluating Substance Use and Insulin Misuse in Adolescents With Type 1 Diabetes. Diabetes Educ. 2016;42(5):529-37.