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Wazaify, M, Abushams, L and Van Hout, MC (2019) Abuse of sulfonylureas: Is factitious hypoglycemia a cause for concern? International Journal of Clinical Pharmacy, 41 (3). pp. 3-5. ISSN 2210-7703

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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.

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

2

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

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

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

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

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

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

77
78 We conducted a rapid assessment of web discussions and review of extant literature
79 which describe this unique form of pharmaceutical medicinal abuse whereby consumers
80 deliberately ingest large doses of glibenclamide (also known as Glyburide) of up to
81 50mg at once to cause hypoglycemia and induce associated euphoric effects [6,7,16].
82 We note that the maximum daily dose ranges between 12 mg (micronized form) to 20
83 mg (standard glibenclamide) [17]. Several cases of deliberate inducement of
84 hypoglycemia [6,7,16] described varied reasons for such excessive consumption, either
85 to experience drug induced euphoria [16], or in seeking attention caused by Munchausen
86 syndrome [18]. Of note are that case reporting occurs in the majority in medical
87 personnel, diabetics or members of their family [14,16]. There are several factors
88 contributing to such increased risk of drug abuse among medical personnel, such as
89 emotional stress at work and easy access to drugs. [19] In addition, healthcare
90 professionals' over-confidence may lead them to believe that their medical competency
91 will prevent problems relating to acute intoxication and misuse of such drugs.. [19] A
92 survey of 60 adolescents (12-20 years old) with Type-1 diabetes mellitus revealed a
93 36.7% prevalence of substance (alcohol, tobacco, illicit drugs) use and 19% reported

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

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

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

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111 **Ethics Approval: N/A**

112 **Finding: N/A**

113 **Acknowledgements: N/A**

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