Original Paper

Risk of emergency medical treatment following consumption of cannabis or synthetic cannabinoids in a large global sample

Journal of Psychopharmacology
1–6

DOI: 10.1177/0269881115574493
jop.sagepub.com

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Abstract

Background: Synthetic cannabinoids (SCs) have become increasingly popular in recent years. Diverse in chemical structure, many have been subjected to legislative regulation, but their availability and use persists. Often marketed to reflect their similar effects to cannabis, their use has been associated with a range of negative health effects. We sought to determine the relative risk of seeking emergency medical treatment (EMT) following use of SCs and natural cannabis.

Methods: We utilized an anonymous online survey of drug use, obtaining data from 22,289 respondents. We calculated the relative risk of seeking EMT between the two substances using an estimate for days used in the past year.

Results: Thirty-seven cannabis users (0.2%) and 21 SC users (1.0%) had sought EMT during the past year following use. The relative risk associated with the use of SCs was 30 (95% CI 17.5–51.2) times higher than that associated with cannabis. Significantly more symptoms (p=0.03) were reported by respondents seeking treatment for SCs than for cannabis.

Conclusions: Whilst these findings must be treated with caution, SCs potentially pose a greater risk to users' health than natural forms of cannabis. Regulation is unlikely to remove SCs from the market, so well-informed user-focused health promotion messages need to be crafted to discourage their use.

Keywords

Cannabis, synthetic cannabis, emergency medical treatment

Introduction

The last decade has seen an unprecedented growth in novel psychoactive substances (NPSs), with 73 new substances reported to the EU early warning system in 2012 compared with 14 in 2005 (EMCDDA, 2013b). Although many NPSs such as the cathinones and piperazines appeared as a result of declining availability and purity of popular illicit psychostimulants such as MDMA (EMCDDA, 2013a), synthetic cannabinoids (SCs) did not. Available since 2004, SCs represent a diverse group of compounds that vary widely in potency and pharmacological structure (EMCDDA, 2013c), and are the most numerous in terms of new notifications to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (EMCDDA, 2013a, 2013c). Although the Centre was aware of 84 different SCs as of May 2013 (EMCDDA, 2013c), the prevalence of their use is largely unknown. However, Global Drug Survey (GDS) has previously shown the lifetime prevalence amongst a self-nominating sample of drug users to be 16.8% (Winstock and Barratt, 2013b).

Dissolved in acetone then sprayed onto inert herbal carrier materials, SCs have enjoyed wide and inventive marketing (EMCDDA, 2013c). Although typically sold as herbal incense and in packaging marked not for human consumption, their promotion relies upon encouraging consumers that, when smoked, their effect profile is similar to natural cannabis (EMCDDA, 2013a). However, consumers are clearly able to differentiate between the two products, and previous work by GDS (Winstock and Barratt, 2013b) reported that 93% of users indicated a preference for natural cannabis, with SCs scoring more highly on a range of negative effects.

As with other NPSs, the last few years have seen SCs being subjected to legislative regulation around the world (EMCDDA, 2013a). However, even with analogue legislation, such is their disparate chemical structure that newer, potentially more potent compounds are synthesized in response to groups of SCs becoming illegal (Dargan et al., 2011; EMCDDA, 2013a). Their use has been reported globally, from the UK, Europe and Scandinavia (EMCDDA, 2013a, 2013c; Hermanns-Clausen et al., 2013) to the USA (Alverio et al., 2012; Spaderna et al., 2013) and Australasia (Every-Palmer, 2011; Tung et al., 2012). As consumers and authorities have become more familiar with their use, unwanted

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psychological effects including paranoia, anxiety, psychosis and extreme agitation have been reported following SC consumption (Benford and Caplan, 2011; Every-Palmer, 2011; Cohen et al., 2012; Seely et al., 2012; Harris and Brown, 2013; Hermanns-Clausen et al., 2013; Spaderna et al., 2013). Physical side effects including seizures, acute renal injury, palpitations and even death have also been reported (Cohen et al., 2012; Bhanushali et al., 2013; Harris and Brown, 2013; Hermanns-Clausen et al., 2013; Murphy et al., 2013; Schneir and Baumbacher, 2012; Shanks et al., 2012; Spaderna et al., 2013). Data from an earlier cohort of GDS respondents suggested that the risk of serious untoward experience associated with SC use was high, with one in 40 last-year users reporting the need to access emergency medical treatment (Winstock and Barratt, 2013a). Using public hospital records, the prevalence of adverse events amongst regular cannabis users has been estimated to be 1.2–3.2 per 1000 (Jouanjus et al., 2011), but the relative risk between the two drugs has not previously been explored.

In the current study, we sought to determine the relative risk of seeking emergency medical treatment (EMT) amongst users of SCs and natural cannabis. Such investigation was deemed important in order to inform users and public health organizations of the potential harms of SCs, particularly at a time when there has been significant change in cannabis legislation in many parts of the world.

Method

Design

Global Drug Survey annually designs and conducts anonymous, online surveys to investigate trends in illicit drug use. In collaboration with our media partners, including MixMag, Fairfax Media and *The Guardian*, the survey is actively promoted via social networking sites such as Twitter, Facebook and Reddit for a period of approximately five weeks from its launch in mid-November each year. During this period in 2012, when the data used in this paper were collected, our strategy recruited 22,289 participants from 123 countries around the world. The research tool and methodologies of current studies have been developed from previous work carried out by the group, which have been successful at identifying emerging trends and patterns of drug use before they become apparent in the wider community (McCambridge et al., 2005b; Winstock and Barratt, 2013a, 2013b; Winstock et al., 2001, 2011). Questions to elicit prevalence, patterns of use, cost, associated harms and a range of specialist topics are formulated each year by the GDS expert advisory group and academic network.

Ethical approval was granted by the Joint South London and Maudsley and Institute of Psychiatry NHS Research Ethics Committee.

Measures

A wide range of demographical information was collected for participants in the survey. Prevalence of use was determined by individuals completing an extensive substance use screen, enquiring into their ever, last-year and last-month use (number of days used in the last 30) of over 130 drugs and medications, including cannabis and SCs. Individuals were then redirected to questions about each drug, including availability, route of use, cost and perceived value for money.

All last-year users of cannabis and SCs were asked if they had sought EMT in the last year in association with the use of either drug. Information about multiple individual events was not captured, as participants indicated whether they had or had not sought EMT and not on how many occasions. EMT seekers were asked to select which symptoms they had experienced from a list based on the available literature (see Table 3). Respondents were also asked whether they had required hospitalization and how long their symptoms had persisted.

Analysis

Chi-squared (χ^2) analyses were conducted to determine whether there were any differences in prevalence of EMT by gender, country of residence, last-month use, mental health diagnosis and being in receipt of mental health medication. A Mann–Whitney test was employed to ascertain if there was a significant association between age and EMT.

The primary measure of effect was the relative risk of requiring EMT following SC versus cannabis use. In order to take into account the difference in levels of exposure between cannabis and SCs, an estimate for the total days used in the last year was used as the denominator and number of participants reporting EMT as the numerator in calculating the risk for each drug. To calculate the days used in the last year, last-year users were effectively divided into two groups and the two estimates added together to give an overall estimate. Firstly, for last-month users who provided the number of days that they had used, the total number of days was calculated and multiplied by twelve to give an annual total. As the number of days used was not captured for the remaining last-year users, the remaining *N* was multiplied by the median days last-month use as a best estimate of the difference in exposure amongst this group between the two drugs. The relative risk was thus calculated as:

$$\text{Risk} = \frac{\text{N participants reporting EMT}}{\left(\text{Total days monthly use X } 12\right) + \begin{pmatrix}\text{N remaining yearly users X}\\ \text{monthly median days use}\end{pmatrix}}$$

$$\text{Relative Risk} = \frac{\text{Risk of EMT due to SC use}}{\text{Risk of EMT to cannabis use}}$$

This analysis was performed for all last-year users of either SCs or cannabis, and also on two smaller sub-groups of last-year users. The first of these was restricted to include only those who had provided the number of days used in the last month. Thus an exact number of days could be calculated and no estimate using median levels of exposure was required. Secondly, the relative risk was calculated for all last-year users of both cannabis and SCs. This allowed us to address the question as to whether the observed relative risk was due to differences between the two drugs, or a result of inherent differences between the individuals who choose to use them. By accounting for the differences in individuals in this way, we have effectively controlled for individual factors which could have an effect on the relative risk.

Due to relatively low levels of missing data, we used available case analysis, including all individuals with observed values in the variable of interest in the analysis. All analyses were performed using STATA 13 (College Station, TX 77845, USA).

Results

Demographic profile of cannabis and synthetic cannabis users

The majority of the sample (97.2% *n*=21,656) reported lifetime cannabis use and 21.7% (*n*=4835) lifetime use of SCs. A total of 87.9% (*n*=19,024) of cannabis users and 45.0% (*n*=2176) of SC users had used in the last year, henceforth known as past-year users. The demographic profile of both past-year cannabis and SC users can be found in Table 1.

Prevalence of emergency treatment seeking

Cannabis. Thirty-seven past-year cannabis users (0.2%) had sought EMT following cannabis use in the previous 12 months. Although the median age of treatment seekers was slightly lower than that of non-seekers, it was not a statistically significant association (median 25 years IQR 23–37 vs 27 years IQR 21–37, Mann–Whitney test z=0.34, p=0.73). No difference was observed in the prevalence of EMT between women and men (0.19% vs 0.16%; χ^2 1 d.f.=0.22, p=0.64). A statistically significant association existed between country of residence and EMT, with the lowest proportion observed in those from Australia (0.07%) and the UK (0.19%), and the highest in those from the USA (0.29%) and other countries (0.35%; χ^2 3 d.f.=8.76, p=0.03). EMT was not more prevalent amongst last-month users (0.22%) than amongst those who had not used in the previous month (0.15%; χ^2 1 d.f.=1.14, p=0.29). A non-significantly higher proportion of past-year users who had a mental health diagnosis sought EMT (0.26%) than those without (0.17%); (χ^2 1 d.f.=1.59, p=0.21). A non-significantly higher proportion of EMT seekers (0.34%) were receiving a current prescription for mental health medication than those who were not (0.17%); (χ^2 1 d.f. = 3.57, p=0.06). Of those seeking EMT following cannabis use, 15 (40.5%) reported use of other drugs with alcohol the most commonly reported (n=10).

Synthetic cannabinoids. Amongst past-year SC users, 21 (0.97%) had sought EMT following use of the drug in the previous year. Past-year SC users who sought EMT were significantly older (median 31 years, IQR 25-41) than those who did not (median age 25 IQR 20–34; Mann–Whitney Test z=2.12, p=0.03). A greater proportion of EMT was observed amongst women (1.68%) than men (0.77%), but this fell short of statistical significance (χ^2 1 d.f.=3.07, p=0.08). There was no significant association between country of residence and EMT (χ^2 3 d.f.=0.8, p=0.85), with similar proportions from the UK (0.86%), Australia (0.91%), the USA (0.84%) and other nations (1.37%). No difference was observed in the prevalence of EMT between those who used in the last month (0.84%) and those who did not (1.03%; χ^2 1 d.f.=0.18, p=0.67). As with cannabis, there was no difference in the prevalence of EMT among those who had a mental health diagnosis (0.95%) and those who did not (0.97%; χ^2 1 d.f.=0.002, p=0.97). No difference was observed in EMT prevalence according to being in current receipt of a mental health prescription (1.23%) or not (0.92%; χ^2 1 d.f.=0.29, p=0.59). Of those seeking EMT following SC use, nine (42.8%) reported use of other drugs and this proportion was not significantly different to that reported by those seeking EMT following cannabis use (z=0.17, p=0.87). Again, alcohol (n=5) was the most commonly reported substance used in conjunction prior to EMT seeking.

Table 1. Past year user demographic profile.

	Cannabis	SCs
***N* (% of ever used)**	19,024 (87.9)	2176 (45.0)
Median age (IQR)	27 (21–37)	25 (20–34)
Median age first used (IQR)	16 (15–18)	21 (18–28)
Gender *N*[a]	17,657	2031
Male n (%)	12,457 (70.6)	1554 (76.5)
Female n (%)	5200 (29.4)	477 (23.5)
Country of residence *N*[a]	17,113	1975
UK ***n*** (%)	5737 (33.5)	584 (29.5)
Australia ***n*** (%)	5394 (31.5)	547 (27.7)
USA ***n*** (%)	2795 (16.4)	479 (24.3)
Other ***n*** (%)	3187 (18.6)	365 (18.5)
Median drugs ever used (IQR)	10 (6–16)	13 (8–19)
Mental health diagnosis *n* (%)	4162 (21.9)	526 (24.2)
Depression[b] ***n*** (%)	3298 (17.3)	411 (18.9)
Anxiety[b] ***n*** (%)	2060 (10.8)	270 (12.4)
Bipolar disorder[b] ***n*** (%)	458 (2.4)	74 (3.4)
Psychosis[b] ***n*** (%)	147 (0.8)	27 (1.2)
ADHD[b] ***n*** (%)	472 (2.5)	86 (4.0)
Other[b] ***n*** (%)	531 (2.8)	77 (3.5)
Ever prescribed mental health medication	3309 (17.4)	410 (18.8)
Currently prescribed mental health medication	2675 (14.1)	324 (14.9)
Use patterns		
Last month users ***N*** (%)	11,557 (60.8)	716 (32.9)
Daily users ***N*** (%)	2011 (10.6)	20 (0.9)
Median days monthly use (IQR)	10 (3–25)	3 (1–10)

[a]*N*: number of users responding to question.
[b]Users were able to indicate more than one diagnosis, hence the total number being larger than above row.

Relative risk of seeking EMT following cannabis or SC use

The relative risk of EMT following use of SCs versus cannabis is shown in Table 2. We estimated that the combined sample of 10,511 past-month cannabis users and the remaining 8513 past-year users had used cannabis on a total of 1,843,130 days in the past year. Thirty seven individuals reported accessing EMT in relation to their cannabis use giving an estimate of the per event risk of EMT of 0.0000201. The 2176 past-year SC users were estimated to have used SCs on 34,899 days in the past year and 21 reported EMT. Thus, the per-event risk of EMT was 0.0006017 and the risk of requiring emergency medical treatment associated with the use of SCs was 30 (95% CI: 17.5–51.2) times higher

Table 2. Relative risk per days use of treatment seeking following use of SCs vs cannabis.

	All past-year users	Last-month users	Past-year users of both
SCs			
Sought EMT ***N***	21	6	20
Days use per year	34,899	29,424	33,753
Risk	0.0006017	0.0002039	0.0005925
Cannabis			
Sought EMT ***N***	37	25	8
Days use per year	1,843,130	1,758,000	264,270
Risk	0.0000201	0.0000142	0.0000303
Relative risk (95% CI)	**30.0 (17.5–51.2)**	**14.3 (5.9–34.9)**	**19.6 (8.6–44.4)**

Table 3. Self-reported symptoms by treatment seekers following cannabis and SC use.

Cannabis			SCs		
Symptom	*N*	%	**Symptom**	*N*	%
Panic and anxiety	22	59.5	Panic and anxiety	17	81.0
Paranoia	13	35.1	Paranoia	13	61.9
Confusion	12	32.4	Scared	13	61.9
Palpitations	12	32.4	Agitation	10	47.6
Breathlessness	11	29.7	Breathlessness	8	38.1
Agitation	8	21.6	Sweating	8	38.1
Nausea	8	21.6	Auditory hallucinations	7	33.3
Other	8	21.6	Chest pain	7	33.3
Chest pain	6	16.2	Other	7	33.3
Loss consciousness	6	16.2	Visual hallucinations	7	33.3
Memory loss	6	16.2	Mood problems	6	28.6
Sweating	6	16.2	Unable to talk	6	28.6
Visual hallucinations	6	16.2	Nausea	4	19.0
Headache	5	13.5	Seizure/fits	4	19.0
Self harm	5	13.5	Accident	3	14.3
Mood problems	4	10.8	Aggression	2	9.5
Accident	3	8.1	Bladder problems	2	9.5
Aggression	3	8.1			
Seizure/fits	3	8.1			

than the corresponding risk associated with cannabis use. When restricting the analyses to last-month users, the relative risk was 14.3 (95% CI: 5.9–34.9).

To account for potential differences between individuals choosing to use cannabis and SCs, a further analysis was conducted in which the sample was restricted to the 2127 participants who reported past year use of both cannabis and SCs. Within this sample, the risk of EMT associated with SC use was 19.6 (95% CI: 8.6–44.4) times higher than that associated with cannabis use.

Self-reported symptoms

The most commonly reported symptoms amongst both cannabis and SC EMT seekers were panic, anxiety and paranoia, as shown in Table 3. These symptoms were, however, reported by a greater proportion of SC than cannabis EMT seekers. Significantly more symptoms (Mann–Whitney test z=2.14, p=0.03) were reported by individuals seeking EMT for SCs (median 5 IQR 4–8; range 1–17) than for cannabis (median 3 IQR 2–6; range 1–12).

Table 4. Time to recovery of cannabis and SC treatment seekers.

	Cannabis		SCs	
	N	**%**	***N***	**%**
Hospitalized	18	48.7	10	47.6
Time to recovery				
6 hours	15	40.5	10	47.6
12 hours	5	13.5	1	4.8
24 hours	6	16.2	2	9.5
48 hours	2	5.4	0	0.0
72 hours	1	2.7	0	0.0
96 hours	1	2.7	2	9.5
1–2 weeks	2	5.4	0	0.0
2–4 weeks	1	2.7	1	4.8
>4 weeks	3	8.1	2	9.5
Not yet	1	2.7	3	14.3
Total	37	100	21	100

Time to recovery

Table 4 shows the proportion of EMT seekers who reported being admitted to hospital, and the time to recovery of those accessing treatment. There was no difference observed between the percentages of EMT seekers admitted to hospital following cannabis or SC use (z=0.08, p=0.94) and the majority of both groups reported full recovery within 24 hours. A higher proportion of SC EMT seekers (28.6%) reported a recovery time of two weeks or greater than did cannabis EMT seekers (13.5%), although this difference was not statistically significant (z=1.30, p=0.19).

Discussion

Using the largest self-report survey into patterns of drug use, which included specific questions relating to SC use and associated harms, we have estimated the risk of requiring EMT to be 30 times greater following the use of SCs than following cannabis. This is the first direct comparison of the two drugs, and shows that SCs expose users to a significantly greater risk of short term harm than natural cannabis. This supports previous research (Winstock and Barratt, 2013b) showing a greater range of negative effects following use of SCs compared to cannabis, and lends weight to the growing concerns that SCs are more dangerous, at least acutely, than natural forms of cannabis (Dargan et al., 2011; Every-Palmer, 2011; Fattore and Fratta, 2011; Alverio et al., 2012; Seely et al., 2012; EMCDDA, 2013c; Hermanns-Clausen et al., 2013; Spaderna et al., 2013; Winstock and Barratt, 2013b).

SC users also reported a greater number of symptoms than cannabis users, suggesting increased symptom-clustering. Further research is needed to determine the differences between the two drugs with regard to time to recovery, but our data tentatively suggest increased symptom duration following SC use. Our finding

that agitation was more prevalent amongst SC EMT seekers complements previous findings (Cohen et al., 2012; Seely et al., 2012; Harris and Brown, 2013; Spaderna et al., 2013).

In contrast to our previous work (Winstock and Barratt, 2013a), past-year SC users who sought EMT were older than those who did not. Reasons for this change are not clear from our data, and may well be a phenomenon of our sampling strategy. The association between age and EMT following SC use requires further monitoring to contribute to the understanding of those most at risk. The smaller proportions of monthly and daily users observed amongst past-year SC users than cannabis users may be attributable to a number of factors. However, as 97.8% of past-year SC users were also past-year cannabis users, it may be that the effect profile of SCs is less favourable than natural cannabis. This supports previous work by GDS (Winstock and Barratt, 2013b) in which the effect of cannabis was deemed preferable by 93% of users.

Limitations

When judged against traditional epidemiological criteria for monitoring public health, the authors fully acknowledge that our methods have potentially significant limitations. These have been fully discussed in previous publications utilizing the same research tool (Winstock et al., 2001, 2011, 2012; McCambridge et al., 2005a, 2005b). The main limitation of our methodology lies in our sampling strategy, which is an example of purposive sampling (McCambridge et al., 2005b). We acknowledge that this has significant limitations, most notably with respect to response bias, whereby there will be inherent differences between those who participate and those who do not (Friedman and Wyatt, 2006). It is more likely that individuals will respond to surveys if they see topics or items that are of interest to them, and thus by definition will differ from those who do not participate (Eysenbach and Wyatt, 2002). Therefore, as participants in our survey may have a greater interest in or experience with drugs, they may not be representative of the wider population. However, purposive sampling that seeks to include a wide cross-section of users and a large overall sample size can result in a sample of drug users that may be considered sufficiently representative to make reasonable inferences for the general population (Topp et al., 2004).

However, as our interest is in identifying emerging substances of abuse and new trends in drug use, rather than highlighting current trends in the general population, the 'volunteer effect' our sampling strategy encourages may be helpful. Moreover, it is unlikely that our sampling method would have affected the validity of our estimates of per-episode risk of EMT. It is unlikely that our sample would have been biased with respect to risks of EMT specific to use of cannabis or SCs. Indeed, our estimates may be specific to sentinel drug users and thus may underestimate the risk for less experienced users. This effect is likely to be similar for cannabis and SCs so would not bias our estimate of the relative per episode risk.

All measures were reliant on self-report without cross referencing external sources of data. We were thus unable to verify the level of exposure of cannabis and SCs. We could not explore potency, and thus the magnitude of the difference in observed risk may, in part, be explained by the fact that SCs are often much more potent than natural cannabis. Furthermore, we were unable to examine the specific SC compounds individuals were exposed to, and were reliant on the accurate reporting of exposure to SCs, rather than other compounds that theoretically could be sprayed onto inert herbal material. We were also unable to verify contact with emergency treatment services, symptoms or duration. Moreover, we could not determine that EMT could be directly attributable to SCs or cannabis use, and not to other factors such as poly-drug use. However, it could be argued that sentinel drug users are best placed to determine the subjective effects of substances they use.

Our relative risk estimate carries potential limitations. The extrapolation of days used in the last month to the previous year makes the assumption that each individual's use was constant. The lack of a measure for days used for last-year users necessitated the use of the median days monthly cannabis and SC use as a best estimate for differences in exposure. This does not take into account that levels of use are likely to vary considerably between users in the last year. While this may have decreased the precision of our estimates, it is likely that it would have limited estimates of cannabis and SC use similarly, and therefore will not have biased our estimate of the relative risk of EMT following the use of either drug. To account for this, a measure of days used in the last year has been included in the 2014 survey. As our survey asked whether past-year users had or had not sought EMT in the previous year, and not on how many occasions, we could not explore whether individuals had sought EMT on more than one occasion as a result of SC or cannabis use.

One strength of our methodology is that it permitted us to restrict the analysis to users of both substances. While controlling for a range of possible individual factors, we were still able to show a dramatic increase in risk of EMT following SC use. It is also possible that our research underestimated the true incidence of adverse effects from either drug, as only episodes deemed serious enough to prompt EMT were considered.

Despite these limitations, GDS has previously shown our methodology to be a valid and effective tool for detecting new drug trends and effect profiles (Winstock et al., 2001, 2011; Winstock and Barratt, 2013b). Online surveys are increasingly being used as a research tool to access large drug-using populations (Miller and Sønderlund, 2010), and GDS is the largest annual survey of drug use in the world. In conjunction with sources of information from healthcare providers, law enforcers and policy makers, rapid and large scale population studies make an important contribution to the planning and implementation of the most beneficial public health strategies.

Conclusion

Our findings indicate that SCs expose users to a far higher risk of acute intoxication related harm than natural forms of cannabis. Although further research is needed, this is an important public health message as SC use shows no sign of abating (EMCDDA, 2013a). At a time where cannabis regulation is undergoing serious review in many countries, it might be useful to reflect that some currently available alternatives are potentially far more dangerous. Regulation is unlikely to remove synthetic cannabinoids from the market place, so well-informed and credible user-focused health promotion messages need to be crafted to discourage use of these substances.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: AW is the founder and owner of Global Drug Survey. AW, ML and RB are employed by the Institute of Psychiatry, King's College London. JW has just completed a MSc at IoP and London School of Hygiene and Tropical Medicine.

Funding

Global Drug Survey Ltd is an independent self-funded organization. The authors received no financial support for the research, authorship, and/or publication of this article.

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