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Genie in a blotter: A comparative study of LSD and LSD analogues' effects and user profile

Running head: LSD analogue effects and user profile

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Abstract

Objective: This study aimed to describe self-reported patterns of use and effects of LSD analogues (AL-LAD, 1P-LSD and ETH-LAD) and the characteristics of those who use them.

Methods: An anonymous self-selected online survey of people who use drugs (Global Drug Survey 2016; N=96,894) which measured perceived drug effects of LSD and its analogues.

Results: Most LSD analogue users (91%) had also tried LSD. The proportion of UK and US respondents reporting LSD analogue use in the last 12 months was higher than for LSD only. LSD analogue users described the effects as psychedelic (93%), over half (55%) obtained it online, and almost all (99%) reported an oral route of administration. The modal duration (8 hours) and time to peak (2 hours) of LSD analogues were not significantly different from LSD. Ratings for pleasurable high, strength of effect, comedown, urge to use more drugs, value for money and risk of harm following use were significantly lower for LSD analogues compared with LSD.

Conclusions: LSD analogues were reported as similar in time to peak and duration as LSD, but weaker in strength, pleasurable high and comedown. Future studies should seek to replicate these findings with chemical confirmation and dose measurement.

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INTRODUCTION

Since the first use of lysergic acid diethylamide (LSD) in 1943 by Albert Hofmann (Hofmann, 1980), many similarly structured compounds have emerged such as ALD-52, AL-LAD (or Aladdin), ETH-LAD, PRO-LAD, LSZ and 1P-LSD, to name just a few (Brandt et al., 2017; Brandt et al., 2016; Peyton & Shulgin, 1994; Watts, Mailman, Lawler, Neve, & Nichols, 1995). The increased speed of emergence of these new psychoactive substances (NPS) is partially driven by legislative processes chasing a synthesise-proscribe-synthesise model (Reuter & Pardo, 2017). For example, 1P-LSD use increased in popularity in the UK following prohibition of LSZ and AL-LAD in 2015 (Brandt, et al., 2016). Since May 2016, the UK Psychoactive Substance Act prohibited the supply of 1P-LSD and any other compounds deemed to cause a ‘psychoactive effect’ (Reuter & Pardo, 2017). Other countries now have similar blanket bans on all ‘psychoactive’ substances (such as Ireland, Poland, Romania, Australia: see Barratt, Seear, & Lancaster, 2017), or on analogues of psychoactive substances (United States: see Kau, 2008). While the effectiveness of these policies is yet to be fully established, they may result in a shift in purchase from ‘headshops’ or high street shops to surface web vendors, cryptomarkets and into ‘street’ markets (as discussed in Barratt & Lenton, 2017; Reuter & Pardo, 2017). The use of LSD analogues including 1P-LSD has been recently reported among nightclub attendees in the US (Palamar, Acosta, Sherman, Ompad, & Cleland, 2016) and social media and cryptomarket monitoring studies have also recently detected discussion of this class of drugs (Van Hout & Hearne, 2017; Vigna et al., 2016).

LSD analogues and LSD share the same lysergic backbone. However, they present slight variations in their chemical structure, such as AL-LAD’s modification at the N6-position (Brandt, et al., 2017). These lysergide derivatives act as an agonist of the 5-HT_{2A} receptor (Brandt, et al., 2016), generally considered the mediator of hallucinogenic effects behaviourally and subjectively (Geyer & Vollenweider, 2008). There are ethical barriers associated with the administration of hallucinogens to humans for research purposes: there is an unknown potential for harm associated with this class of drugs, and the subjectivity of individuals’ responses can vary significantly. Therefore, animal behavioural models are useful for investigating the pharmacology of these drugs. Hallucinogenic effects can be illustrated by measuring the head twitch response (HTR) in mice (Hanks & Gonzalez-Maeso, 2013). The HTR in mice is a side-to-side head movement elicited only by a hallucinogenic

5HT_{2a} agonist, which effectively discriminates between hallucinogenic and non-hallucinogenic 5HT_{2a} agonists. This response was found for mice that had been administered 1P-LSD (Brandt, et al., 2016), indicating that 1P-LSD is indeed likely to have hallucinogenic effects in humans. While lab-based evidence for human experience of 1P-LSD does not exist, detailed experiences reported by users (see Psychonaut Wiki, 2016a) include auditory and visual perceptual alterations following the consumption of 1P-LSD.

Research on mice regarding the potency of these compounds compared to LSD (ED₅₀=132.8 nmol/kg) indicated 1P-LSD (ED₅₀=349.6 nmol/kg) to be 38% the potency of LSD (Brandt, et al., 2016), AL-LAD slightly less potent (ED₅₀=174.9 nmol/kg) and LSZ equipotent (ED₅₀ = 114.2 nmol/kg, Brandt, et al., 2017). These varying potencies shown in mice do not reflect reported dosages in humans. The typical dosage of LSD is approximately 150 micrograms, however the dosage of AL-LAD ranged between 80–160 micrograms (Shulgin & Shulgin, 1997), LSZ between 100–300 micrograms (Erowid, 2014) and 1P-LSD between 50–300 micrograms (Psychonaut Wiki, 2016a). The duration of the effects of LSD analogues (AL-LAD and LSZ 6–10 hours, 1P-LSD 8–12 hours, Psychonaut Wiki, 2016a, 2016b, 2016c) are, however, comparable to that of typical LSD (6–12 hours).

What we currently know about the use of LSD analogues in humans is based on animal models plus the experience and effect reports posted to websites and wikis. In this paper, we use an anonymous web survey to describe the self-reported effect profile of LSD analogues, including AL-LAD, 1P-LSD and ETH-LAD, in humans, in comparison to the effect profile of the better-known drug, LSD. We also compare LSD analogue and LSD user profiles.

METHOD

An anonymous online survey on the use of psychoactive substances was designed and conducted by Global Drug Survey (GDS) (<http://www.globaldrugsurvey.com/archive/GDS2016/>) between November 2015 and February 2016. GDS runs the world's biggest drug survey and is conducted annually, in partnership with global media partners who promote the survey to their audiences. In 2016, the survey was translated into 10 languages. GDS enables rapid assessment and identification of novel drugs as well as new drug trends before their spread to the wider community (e.g., Kaar et al., 2016; Lawn, Barratt, Williams, Horne, & Winstock, 2014; Lawn, Borschmann, Cottrell, & Winstock, 2016). Ethical approval was received from King's College London

(PNM1415-18). Participation was voluntary and no incentives (payments or lotteries) were offered for participation.

A total of 100,711 responses were submitted to Global Drug Survey. After preparing the data, 3,817 records were excluded due to data capture glitches, duplicate entries, reporting no psychoactive drug use at all, reporting the use of a fake drug, and reported age over 100 years. Almost one-third of remaining 96,894 responses were from Germany (n=29,865, 31%), followed by Switzerland (n=8,173, 8%), New Zealand (n=7,633, 8%), UK (n=6,015, 6%) US (n=5,366, 6%), Netherlands (n=5,058, 5%) and Australia (n=4,931, 5%), with the remaining countries accounting for 31%. The average age of respondents was 28.7 years (SD=11.2, range=16–95), and the majority were male (64%; female, 34%; transgender, 1%). The sub-sample comprised 3,678 respondents who reported LSD analogues or LSD as their last new drug tried. The average age of the subsample was 23.4 years (SD=5.7, range=16–56), and the majority were male (74%; female, 25%; transgender, 1%).

Self-reported lifetime use and recent (last 12 month) use of LSD and LSD analogues were collected. The use of LSD analogues was measured separately for AL-LAD and also as a category, labelled ‘LSD Analogues (e.g. 1P-LSD, ETH-LAD)’. For this paper, variables relating to AL-LAD and ‘LSD Analogues (e.g. 1P-LSD, ETH-LAD)’ were combined, and hereon referred to as ‘LSD analogues’. While it is possible that respondents may have included others, the three LSD analogues named in the survey were AL-LAD, 1P-LSD and ETH-LAD. For both LSD and LSD analogues, profiling information was collected regarding route of administration, source of the drug, and effects such as type of effect, duration, time to peak, strength (scored from 1–10, 10=extremely strong), pleasurable high (scored from 1–10, 10=best ever had), comedown (scored from 1–10, 10=extremely strong), urge to use more drugs (scored from 1–10, 10=extremely strong), negative effects while high (scored from 1–10, 10=extremely strong), risk of harm following use of the drug (scored from 1–10, 10=extremely high risk) and value for money (scored from 1–10, 10=best experienced), where these drugs were identified as being the last drug tried for the first time. This profiling set of variables has been used previously by the GDS group to profile NPS, including Mephedrone (Winstock et al., 2011), the NBOMe series (Lawn, et al., 2014), DMT (Winstock, Kaar, & Borschmann, 2014) and methoxetamine (Winstock, Lawn, Deluca, & Borschmann, 2016).

Prior to running the multivariate analyses, missing value analysis on variables of interest showed no variables with less than 5% missing. Multicollinearity and singularity were also tested using a Pearson product moment correlation. All variables correlated in a meaningful way, ensuring the validity of the statistical analysis used (Tabachnick & Fidell, 2013). Normality and homoscedasticity assumptions for multivariate analyses were met. Linearity appeared to be violated however MANOVA is robust to this violation (Tabachnick & Fidell, 2013) therefore conducting a MANOVA was deemed acceptable. As described more fully in the results, the univariate assumption of equality of variance was not met for some variables. MANOVA was conducted to compare differences between LSD and LSD analogues on effects such as strength, pleasurable high, negative effects while high, comedown, risk of harm following use, and value for money. Independent samples t tests were conducted to determine differences in duration and time to peak. The alpha level was set at .05 and only valid percentages were used.

RESULTS

Patterns of use

Among the entire sample (N=96,894), 25,953 (27%) reported use of LSD compared with 2,349 (2%) that reported use of LSD analogues (see Table 1). Recent (last-12-month) LSD use was reported by 13% of the entire sample (n=12,491), whereas recent LSD analogue use was reported by 1% (n=1,431). Of the 2,202 respondents with available data who reported ever using LSD analogues, 2,004 (91%) reported lifetime use of LSD. Of the 1,249 with available data who reported using LSD analogues in the last 12 months, 1,055 (85%) also reported LSD use in the last 12 months.

[Insert Table 1 about here]

Demographics of LSD analogue users

Comparisons of demographic characteristics were performed between individuals who reported (a) use of LSD analogues in the last 12 months and (b) use of LSD in the last 12 months but not LSD analogues (see Table 2). There was a significantly higher proportion of recent LSD analogue users in the UK and the US compared with recent LSD users. Overall, recent LSD analogue users had a younger mean age and were more likely to be male compared with recent LSD users.

[Insert Table 2 about here]

Description by those whom a LSD analogue was ‘the last new drug tried’

Almost all participants reporting LSD analogues as their last new drug tried described the effects as mostly psychedelic (LSD/ketamine like; 93%), while 2% described it as mostly stimulant (cocaine/amphetamine like), 1% mostly cannabis like and 1% mostly empathogenic (MDMA/ecstasy like). Additionally 2% of the group described the effects as ‘other’. The most common source of LSD analogues was online (n=186, 56%), followed by a friend (n=111, 33%), then a dealer (n=28, 8%); these reported sources were significantly different from the ones reported for LSD, $\chi(5)=649.20$, $p < .001$, which was less likely to be sourced online (n=260, 8%) and more likely to be sourced from a friend (n=2,251, 68%). The majority of participants reported swallowing as the common route of administration (ROA) (n=278, 83%) while the 17% of ‘other’ ROA commonly reported ‘sublingual’, ‘blotter’ and ‘tab’ which are all oral routes. Only 1 participant reported snorting and 1 other reported injecting. Reported ROA for LSD did not significantly differ from LSD analogues ROA, $\chi(5)=7.69$, $p = .174$.

Comparison of effects of LSD and LSD analogues

The modal duration of effect for both LSD and LSD analogues was 8 hours. The results indicated no significant difference in duration between LSD and LSD analogue groups ($t(443)=1.50$) $p=.134$. The modal time to peak was 2 hours for both LSD and LSD analogues. There were no significant difference in mean times to peak for LSD and LSD analogues ($t(3601)=.85$) $p=.398$.

A multivariate analysis of variance was conducted to compare LSD (n=3,015) and LSD analogues (n=306) on pleasurable high, strength of effect, negative effects while high, comedown, urge to use more, value for money and risk of harm following use of the drug. The assumption of equality of variance was not met for pleasurable high, $F(1, 3,319)=7.37$, $p=.007$, negative effects when high, $F(1, 3,319)=10.41$, $p=.001$, comedown $F(1, 3,319)=4.94$, $p=.026$, urge to use more drugs, $F(1, 3,319)=13.39$, $p < .001$ and risk of harm $F(1, 3,319)=47.85$, $p < .001$. The MANOVA yielded significant findings on the combined variables measuring the effects of the last new drug used, $F(7, 3,313)=4.74$, $p < .001$, $\eta^2=.01$, power $\Rightarrow 1$. Results showed that ratings of LSD did not differ from ratings of LSD analogues on negative effects when high, $F(1, 3,319)=0.81$, $p=.368$. However, ratings of LSD were

significantly higher than ratings of LSD analogues on pleasurable high ($F(1, 3,319)=5.50$, $p=.019$, $\eta^2=.01$, $\text{power}=.65$), strength of effect ($F(1, 3,319)=5.51$, $p=.019$, $\eta^2=.01$, $\text{power}=.65$), comedown ($F(1, 3,319)=5.37$, $p=.021$, $\eta^2=.01$, $\text{power}=.64$), urge to use more drugs, $F(1, 3,319)=3.89$, $p=.049$, $\eta^2=.01$, $\text{power}=.50$), value for money ($F(1, 3,319)=10.78$, $p=.001$, $\eta^2=.01$, $\text{power}=.91$), and risk of harm ($F(1, 3,319)=27.32$, $p < .001$, $\eta^2=.01$, $\text{power}=.99$) (see Table 3).

[Insert Table 3 about here]

DISCUSSION

To our knowledge, this paper is the first to describe patterns of use and self-reported effects of LSD analogues (AL-LAD, 1P-LSD and ETH-LAD) in humans. In this sample, ‘typical’ users of these analogues were males aged in their mid-twenties, identifying as ‘White’, who were mostly full-time students or employed. These characteristics were similar to the demographics of other psychedelic drug users (e.g., Lawn, et al., 2014; Winstock, et al., 2014), although they may also reflect the bias of people inclined to complete the GDS. Nonetheless, some differences were identified between LSD and LSD analogue users. There were significantly higher proportions of respondents who reported LSD analogue use in the last 12 months compared to only LSD from the UK and the US. It should be noted that these survey data were collected during a period where 1P-LSD was still legal in the UK, so this trend may be subject to change in future years. The majority of participants who had used LSD analogues reported that they had obtained LSD analogues online, which significantly differed from methods used to obtain LSD, matching with previous reports on the ease of availability of NPS online (Brandt, King, & Evans-Brown, 2014; Van Buskirk, Naicker, Roxburgh, Bruno, & Burns, 2016). The most common route of administration was oral and the majority of participants reported the type of effect as psychedelic (LSD/ketamine like), which did not significantly differ from LSD. The modal duration of effect reported for LSD analogues (8 hours) as well as the time to peak (2 hours) were the same as for LSD. A comparison of the reports on perceived effects of LSD analogues and LSD showed that LSD was rated significantly higher for pleasurable high, strength, urge to use more drugs, value for money, risk of harm following use and comedown. These results suggest that LSD analogues are ‘weaker’ versions of LSD. This result is consistent with animal research showing LSD analogues such as 1P-LSD having a lower potency than LSD in mice (Brandt, et al., 2016).

This study has several limitations. The main weakness of this study was the possible drug reporting inaccuracies, both intentional and unintentional as well as manufacturer mislabelling. It is possible that users led to believe they were taking LSD were in fact consuming one of its analogues and vice versa. Also, it is plausible that the substances taken would be completely different from the LSD family such as the NBOMe series (Caldicott, Bright, & Barratt, 2013; Martins et al., 2017 under review). Future studies should seek to replicate these findings with chemical confirmation. In addition, future studies should investigate harms of LSD analogues, both short term and long term. Measuring additional detail regarding the experience such as dosage and whether or not other drugs were consumed concurrently should be considered to gain a better understanding of LSD analogue effects in humans. A further limitation is that the survey sample is self-selected and, therefore, it is not necessarily representative of a wider population of psychedelic users.

CONCLUSION

This is the first study to describe the self-reported effect profile of LSD analogues, including AL-LAD, 1P-LSD and ETH-LAD, in humans. The profile of LSD analogues was reported to be very similar to LSD in relation to duration, time to peak and route of administration (oral). However, LSD analogues were considered weaker with regard to strength, pleasurable high and comedown. Future research should monitor and test the substances subject to investigation and seek to replicate and confirm these initial findings.

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DECLARATIONS OF INTEREST

Adam Winstock is founder and director of Global Drug Survey Ltd, an independent data exchange hub. There are no other conflicts to declare.

AUTHOR CONTRIBUTIONS

LC conducted all statistical analyses and drafted the paper. MB supervised the analysis and critically revised the paper. LM, JF and AW critically revised the paper. JF, LM and MB managed data translation, preparation and cleaning. AW is principle director of the GDS project, managing its relationships with media partners and its scientific direction. All authors have contributed to, read and agreed to this manuscript.

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