Is approving esketamine as an antidepressant for treatment resistant depression associated with recreational use and risk perception of ketamine? Results from a longitudinal and cross-sectional survey in nightlife attendees

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Word count: 3551

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Background Esketamine was licensed for use in treatment resistant depression by the European Medicines Agency in December 2019. It is unclear whether this new approval has lowered the risk perception of recreational ketamine use. This is important given a recent increase in recreational ketamine use.

Methods This study expanded on an existing longitudinal online study of the nightlife scene, by adding an additional longitudinal assessment as well as a new cross-sectional sample. Participants had to be aged 18-34 years, reside in the UK and have attended at least 6 electronic music events in the past year. The likelihood of increasing recreational ketamine use due to the approval, attitudes towards and risk perception of medical ketamine use and experiences resulting from recreational ketamine use were collected after the approval. Changes in ketamine use and frequency were assessed longitudinally before and after the approval.

Results The overall sample size was 2415: 414 longitudinal (57% retention rate) and 2001 new cross-sectional participants. The majority indicated no change in their likelihood of using recreational ketamine due to the approval of esketamine (87%). Longitudinal participants did not indicate an increase in past 12 month use or frequency after the approval. Only one-third of participants reported being aware of the approval. Participants previously aware showed greater overall support for medical use of ketamine than participants previously unaware of the change. However, an equally high risk was assigned to the recreational use of ketamine in both groups. Ketamine users indicated both increases as well as decreases in depression and anxiety as a result of ketamine use.

Conclusion The introduction of esketamine as an antidepressant was not associated with a change in the risk perception of recreational ketamine use in most participants, nor was it longitudinally associated with increased use. Potential negative effects of recreational ketamine use on mental health, as users in this sample reported, should be clearly communicated when discussing the benefits of (es-) ketamine in a therapeutic context.

Keywords: ketamine, esketamine, policy change, nightlife, attitudes, risk

Declaration of Interest

HVC is also supported by grants from the UK MRC and by the National Institute for Health Research UCLH Biomedical Research Centre; she has consulted for Janssen Research and Development.

Funding

This paper is based on independent research commissioned and funded in England by the National Institute for Health Research (NIHR) Policy Research Programme (project ref. PR-ST-0416-10003). ALAMA-nightlife is a collaborative project supported by the European Research Area Network on Illicit Drugs (ERANID). The views expressed in this article are those of the authors and not necessarily those of the national funding agencies or ERANID.

Introduction

Two decades of research into ketamine as a treatment for major depressive disorder have culminated in the approval of esketamine, an enantiomer of ketamine, as a medication for treatment resistant depression (TRD) by the Federal Drug Administration (March 2019) and the European Medicines Agency (December 2019) in intranasal formulation (currently branded as SPRAVATO^{TM}). Furthermore, in the years before the approval of esketamine an increase in the recreational use of ketamine had been recorded (Flatley, 2018; Grabski et al., 2021; Smith, 2017; Stripe, 2020; Van Laar et al., 2020). Even though recreational use of ketamine is still relatively low (3% in adults in England & Wales aged 16-24, <1% in adults in England and Wales aged 16-59), chronic use can have serious consequences such as cystitis, cognitive impairments and addiction (Morgan & Curran, 2014).

Attitudes towards the introduction of esketamine and its acceptability as an antidepressant have been investigated in potential patients and carers (Jilka et al, 2021; Veraart et al., 2018) but very little is known about attitudes of recreational ketamine users. There is currently limited evidence on whether this approval might lead to the perception of ketamine as being less dangerous in a recreational context. Some evidence comes from a recent cross-sectional study conducted in New York City of 209 nightlife attendees: about 10% of participants indicated that media coverage of the medical benefits of ketamine would increase their likelihood to use more recreationally, yet in recent users of ketamine the likelihood was much higher (Palamar & Le, 2021). However, longitudinal data are currently lacking.

One study suggested that the introduction and commercialisation of medical cannabis in certain states in the United States of America (USA) was correlated with a lower risk perception of recreational use in adolescents in those states (Schuermeyer et al., 2014). However, it is unclear if this translated to an increase in recreational cannabis use (Sarvet et al., 2018). The approval of esketamine as a medicine for TRD is certainly different to the introduction of medical cannabis, as ketamine has been used medically for many decades for induction and maintenance of anaesthesia. But there are also crucial differences between ketamine for anaesthesia and esketamine for TRD: firstly, esketamine is administered at a subanaesthetic dose, more similar to dosing in recreational use; and secondly, the nasal spray formulation enables the user (in theory) to use it “ad-hoc” without medical supervision and outside a hospital setting, which has never been a possibility with ketamine for anaesthesia. Given the potentially serious consequences of chronic recreational ketamine use, assessing whether the recent approval of esketamine affects risk perception in individuals prone to recreational drug use is important. Furthermore, given the lack of up to date data, risk perceptions of consequences of ketamine use in users versus non- users and experiences of risky behaviours after ketamine use in users was assessed.

Data from the Eletronic Music Scene Survey United Kingdom (EMSS UK), an extension of the EMSS survey (Feltman et al., 2021; Waldron et al, 2020; Grabski et al., 2021) were used in order to address the following questions: 1) whether the risk perception of recreational ketamine use decreased following esketamine's approval as an antidepressant, 2) whether past 12 month use and frequency of ketamine use changed after esketamine's approval in a longitudinal sample, 3) attitudes towards medical and recreational ketamine, 4) risk perception of experiences as a result of ketamine use and actual experiences following ketamine use in this nightlife sample.

Methods

Sample and procedure

The EMSS UK survey was an extension of the EMSS survey, which assessed different aspects of nightlife and drug use behaviours in 5 European countries at two timepoints in 2017 and 2018 online (Grabski et al., 2021). The EMSS UK extension was conducted in 2020, inviting EMSS participants from the UK to complete a third survey as well as recruiting a new sample of participants from the UK. This enabled the researchers to assess changes in use longitudinally before and after the approval of esketamine in 2019 and provided us with greater statistical power to assess attitudes and risk perceptions of ketamine.

The survey was administered online. Questions were based upon previous EMSS surveys, but to account for the Covid-19 pandemic participants' drug use variables were assessed twice: once assessing use before March 2020 (start of Covid-19 pandemic and associated lockdown measures in the UK) and once assessing use after March 2020. All data presented here relate to use in the 12 months before March 2020. Furthermore, questions covering recent policy changes relating to ketamine, attitudes about ketamine as an antidepressant, perceived risk of ketamine experiences and actual ketamine experiences were added to the EMSS UK.

All longitudinal UK participants who completed both previous EMSS surveys were invited to take part. Eligibility criteria at baseline were residing in the UK, being between 18-34 years old and having attended at least 6 dance/electronic music events during the past 12 months. Baseline recruitment was mostly online using convenience sampling through Facebook and Instagram advertisements. A small proportion (3%) of longitudinal participants was recruited offline at clubs and festivals. Longitudinal participants were invited to a third survey in June 2020 via email, the only contact information stored. Longitudinal survey completers were reimbursed with a £10 Amazon voucher.

Cross-sectional participants were recruited between June and September 2020, utilizing the same inclusion criteria and online sampling methods as for the longitudinal sample at baseline, except that past 12 month attendance in at least 6 nightlife events was assessed before the start of Covid-19 measures in the UK (March 2020). They were included in a lottery to win electronic gadgets (2 MacBooks and 7 bluetooth speakers). This lottery was independent of previous lotteries held for the EMSS survey.

Written informed consent was obtained digitally from participants before the start of the survey and the study was approved by the University College London ethics committee (Ethics Project ID: 10437/003).

Measures

Demographic information

This included age, gender, education, employment status, relationship status, and urbanicity.

Ketamine use

Ketamine use variables were past 12 month use ('Have you used ketamine in the past 12 months?') and frequency ('How often did you use this drug in the last 12 months?', with response options 'Three times a week or more' [6], 'Weekly' [5], 'Fortnightly' [4], 'Monthly' [3], 'Every two or three months' [2], and 'Three times or less in the year' [1]).

Ketamine policy changes

Participants' knowledge of the policy change regarding ketamine was assessed ('Are you aware that (Es)ketamine has been approved as a treatment for treatment resistant depression by the European Drug Agency?'). Participants then responded to two further items on a 5-point Likert scale assessing whether this change made them more or less likely to use recreational ketamine or street ketamine for medical purposes ('much less likely' – 'much more likely'). To avoid bias, these three items were presented after those assessing ketamine use, attitudes and risk perception.

Attitudes towards ketamine as an antidepressant

Participants responded to 11 items on a 5-point Likert scale to statements relating to the risk of the use of medical and recreational ketamine for therapeutic as well as recreational purposes ('strongly disagree' to 'strongly agree').

Risk perception of experiences after ketamine use

Participants assessed the risk of 14 potential experiences as a result of ketamine use on a 5-point Likert scale ('extremely unlikely' to 'extremely likely').

Experiences after ketamine use

Participants, who had indicated lifetime use of ketamine, responded to a list of 14 items to indicate which they had experienced as a result of ketamine use.

Data analysis

Differences between participants aware and unaware of the policy change were calculated using Wilcoxon rank sum tests. Differences between participants' assessment of ketamine as an antidepressant now and 2 years ago were calculated using Wilcoxon signed rank tests. A subset analysis of longitudinal participants assessing differences in past 12 month use between the three EMSS assessment timepoints was calculated using McNemar's chi square tests. An analysis of longitudinal participants assessing differences in frequency of use between the three EMSS assessment time-points was carried out using Wilcoxon signed rank tests.

All analyses were conducted using R statistical software (Foundation for Statistical Computing, Vienna, Austria).

Results

Participants

In all, 414 longitudinal participants (57% retention rate) and 2,001 new participants completed the EMSS UK survey. Differences between the longitudinal and cross-sectional sample are displayed in tables S1, S2 and S3 (supplementary materials). The participants' mean age was 24.46 years (SD 4.02), 47% identified as female, 51% as male and 2% as other. The majority had completed a university degree (65%) and lived in an urban area (71%). 63% indicated lifetime use of ketamine and 52% indicated past 12 month use. Most ketamine users indicated a frequency of use between '3 times or less' to 'every 2-3 months' in the past 12 months. Less than 20% of ketamine users indicated using fortnightly or more in the past 12 months (see Table 1). A comparison of longitudinal and cross-sectional participants shows a comparable sample when taking the age difference into account (Supplementary materials, S1).

<Insert Table 1 here>

Effect of approval of esketamine as an antidepressant

All participants (N=2415) were included in this analysis, and answers were split into participants aware versus not aware of the approval. The majority (77%) indicated not being aware that ketamine had been approved as a treatment for TRD by the European Medicines Agency.

The majority indicated no change in their likelihood to use recreational ketamine based on these policy changes (87%), while 12% indicated being more likely to use recreational ketamine. There was a statistically significant difference in the likelihood of using recreational ketamine between participants previously aware and unaware of these policy changes (Z=-2.61, p=0.004), with those unaware indicating a slightly higher likelihood of using recreational ketamine. However, the effect size was very small (*d*=0.05).

The majority indicated no change in likelihood of using street ketamine for medical purposes (82%), while 16% indicated being more likely to use street ketamine for medical purposes. There was no statistically significant difference in the likelihood of using street ketamine for medical purposes between participants previously aware and unaware of these policy changes (Z=-0.57, p=0.291, *d*=0.01) (see Table 2).

<Insert Table 2 here.>

A subset analysis of longitudinal participants across all study timepoints (2017, 2018, 2020 – pre Covid-19) revealed no significant increase in past 12 month use between TP1 and TP2, however the lower bound of the confidence interval only marginally includes the null hypothesis ($\chi 2[1]= 3.24$, OR= 1.54, 95% CI 0.97 to 2.52, p=0.071). There was no significant difference in past 12 month use pre and post policy change between TP2 and TP3 ($\chi 2[1]= 0.05$, OR= 0.92, 95% CI 0.56 to 1.50, p=0.815). There was furthermore no difference in past 12 month use in longitudinal participants aware of the change (N=149, 36%) between TP1 and TP2 and no difference between TP2 and TP3. There was no difference in past 12 month use in longitudinal participants not aware of the change (N=265, 64%) between TP1 and TP2 and no difference between TP2 and TP3. There was a significant increase in frequency between TP1 and TP2 and a decrease between TP2 and TP3 in the overall sample (Table 3).

<Insert Table 3 here.>

Attitudes about ketamine as an antidepressant

All participants were included in this analysis (N=2415), and answers were split into participant aware versus not aware of the approval of esketamine. Of participants aware of the approval 61% endorsed the belief that ketamine was a safe and effective treatment for depression, whereas only 31% stated they believed so two years ago. The difference between the current and the past attitudes was statistically significant ($Z=-15.31$, $p<0.001$, $d=0.55$). In contrast, only 23% of participants unaware of the approval currently endorsed the belief that ketamine was a safe and effective treatment, and 10% stated they believed so two years ago. The difference between the current and the past attitudes was statistically significant ($Z=-17.82$, $p<0.001$, $d=0.44$).

The majority agreed that antidepressant use of ketamine was only acceptable when prescribed by a medical professional. Generally, participants unaware of the approval assigned a higher risk to medical use of ketamine for depression as well as other mental health indications than participants aware of the change. The risk of recreational ketamine use on the other hand was considered high in both groups, with 74% of aware participants and 71% of unaware participants agreeing that use was risky.
The majority in both groups agreed that people who used street ketamine for medical purposes should not be prosecuted, but the agreement was much more pronounced in participants aware of the policy change (72%) than in those unaware (54%) (see Table 4).

<Insert Table 4 here.>

Risk perception of experiences after ketamine use

All participants (N=2415) were included in this analysis, and answers were split by lifetime ketamine use versus never use. The highest overall probability was assigned to experiencing cognitive impairments such as confusion (78%) and memory impairments (71%). High risks were also assigned to experiencing physical accidents (69%), being in a 'K-hole' (68%), and experiencing sleeping problems (53%). For sleeping problems, a much higher risk was assigned by never users (70%) than by ketamine users (30%).

The risk assessments about the effect of ketamine on mental health were mixed: more participants indicated a higher likelihood of being less depressed (43%) than of being more depressed after ketamine use (33%). In particular, the risk assigned to feeling more depressed was higher in non-users (45%) than in users (26%). For anxiety, the risk of feeling less anxious (41%) was rated similarly to

the risk of feeling more anxious (40%) after ketamine use. The likelihood of developing cystitis, a known side-effect from chronic ketamine use, was rated 32% (see Table 5).

<Insert Table 5 here.>

Experiences after ketamine use

Only participants indicating lifetime use of ketamine were included in this analysis (N=1520). The most common experience following ketamine use was being in a 'K-hole' (53%). Forty-eight percent indicated experiencing confusion and 32% indicated experiencing memory impairments.
Regarding effects on mental health, more participants indicated feeling less depressed after use (32%) than feeling more depressed (18%). For anxiety, similar numbers of participants indicated feeling less anxious after use (30%) and more anxious (26%). As for physical effects, 22% indicated having experienced sleeping problems, 13% having experienced abdominal cramps, 10% physical accidents, 6% cystitis, and less than 1% hypothermia. 13% indicated the experience of flashbacks and 9% indicated difficulties in reducing or stopping use (see Table 6).

<Insert Table 6 here.>

Discussion

This is the first study to assess changes in use behaviour and attitudes towards recreational ketamine use in the context of the recent approval of esketamine for TRD by the European Medicines Agency. The majority of participants indicated no greater likelihood to increase their recreational ketamine as a result of the approval. A subset analysis of longitudinal participants showed no increase in past 12 month use in the sample before and after the policy change (2018 - 2020), nor an increase in frequency of ketamine use during this period. This is promising, as half of the sample indicated use of ketamine in the past 12 month, thus representing a group open to recreational ketamine use and therefore potentially especially prone to a lower risk perception of ketamine use following policy changes.

However, despite the high number of ketamine users in the sample, only one-third were aware of the introduction of esketamine as a medication for TRD. Those aware of the change differed from those not aware: more than half of participants aware of the introduction of esketamine had a favourable opinion towards ketamine as an antidepressant, compared to only a quarter of the participants unaware of the change. Both groups, however, indicated that this opinion was more favourable now than it would have been before the policy change. Generally, participants unaware of the approval

rated the risk of medical ketamine use higher than those aware of it: for example, they were less in favour of the use of prescribed ketamine to treat other mental health conditions and assigned a higher probability to the risk of prescribed ketamine leading to the use of harder drugs. One important exception, however, was the risk of using recreational ketamine which was rated equally high by both groups. Taken together, these findings suggest that even though awareness of the introduction of esketamine as a medication for TRD lowers the risk perception of the medical use of ketamine, it does not seem to translate to recreational ketamine use. This result aligns with a recent study from New York City in which the majority of participants indicated no greater likelihood to use ketamine as a result of greater media coverage of its therapeutic benefits (Palamar & Le, 2021). Assessing the relationship of recreational ketamine use and media coverage in a UK population might be an important avenue for further research, especially as a recent study found local differences in how frequently medical ketamine was reported on and a frequent lack of a discussion of the risk of unregulated ketamine use (Gallagher et al., 2021)

The greatest risk of recreational ketamine use was assigned to cognitive impairments and physical accidents. Only a third of participants assigned a high risk to the development of cystitis, a known and well documented side effect of chronic ketamine use (Morgan & Curran, 2014). One reason for this finding might be that this is not a common experience in young nightlife attendees: only 6% of ketamine users in this sample indicated having experienced cystitis as a result of ketamine use. A previous study in recreational ketamine users in the nightlife scene found a much higher rate of urinary symptoms (27%), however ketamine dependence was also higher in this sample (Winstock et al., 2012). This current sample was comprised of mostly low to moderate users and cystitis is typically associated with chronic ketamine use. However, given the gravity, and often irreversibility, of this side effect, increased health warnings of risks specific to ketamine use escalation in populations prone to recreational use might be needed.

Findings concerning the effects of ketamine on mental health were mixed: participants rated the possibility of increased as well as decreased anxiety similarly highly. The possibility of a decrease in depression was rated only slightly higher than the possibility of an increase in depression. These results were mirrored in the actual experiences of users in this sample. These ambiguous experiences have the potential to lead to confusion and might lead to the perception in some users, depending on the experiences of their peers and their information channels, that recreational ketamine is mostly beneficial for mental health. It is therefore important to communicate the risks of recreational ketamine use on mental health effectively, especially when reporting on the benefits of esketamine and ketamine prescribed in a medical context.

The current study has several limitations. First, in order to minimize the effect of the Covid-19 pandemic and associated restrictions participants were asked about their ketamine use and frequency in the 12 months before March 2020. Most participants filled in the survey in June 2020 which might subject the ketamine use results of timepoint 3 to some degree of recall bias. Second, even though ketamine use in this sample was high, most users indicated low to moderate frequency of use. It is unclear whether a sample of mostly heavy users would be more likely to be influenced by the policy change. Third, actual changes in use could only be assessed in longitudinal participants (17% of the sample). Even though this seems to be comparable to the cross-sectional sample it might differ on unobserved variables and thus potentially introduce bias. Fourth, the longitudinal assessment of the third (post policy timepoint) assessed past 12 month use and frequency of ketamine before March 2020. As esketamine was approved by the EMA in December 2019 the assessed period does not completely fall into the post policy timepoint. However, it can be expected that the results would pick up initial changes in consumption. Furthermore, we are confident that this time window provides the best available data to assess our overall empirical question, because estimates from March 2020 onwards would have been strongly confounded by the impact of the COVID-19 pandemic. Fifth, the eligibility criteria for the longitudinal sample were assessed at timepoint one, whereas for the cross sectional sample they were assessed at timepoint three. However, when taking this two year difference in age into account the sample are similar enough to be combined (see Tables S1, S2 & S3).

Conclusions: Our findings suggest that that the introduction of esketamine as an antidepressant was not associated with risk perception of recreational ketamine use or use behaviour in the majority of this sample of young adults with a high prevalence of recreational and experimental substance use. This is particularly encouraging in light of a recent increase in recreational ketamine use in some countries (Flatley, 2018; Grabski et al., 2021; Smith, 2017, Stripe 2020,; Van Laar et al., 2020). However, our findings on risk perception and risk of ketamine use suggest that more information on the potential negative effects of recreational ketamine use, such as cystitis, should be communicated to users at the risk of escalation. Furthermore, negative effects of recreational ketamine use on mental health, as users in this sample reported, should be clearly communicated when discussing the benefits of (es-) ketamine in a therapeutic context.

References

Feltmann, K., Elgán, T. H., Strandberg, A. K., Kvillemo, P., Jayaram-Lindström, N., Grabski, M., … & Gripenberg, J. (2021). Illicit drug use and associated problems in the nightlife scene: a potential setting for prevention. International journal of environmental research and public health, 18(9), 4789.

Flatley J. (2018) Drug Misuse: Findings from the 2017/18 Crime Survey for England and Wales. London: Office for National Statistics.

Gallagher, B., Neiman, A., Slattery, M. C., & McLoughlin, D. M. (2021). Online news media reporting of ketamine as a treatment for depression from 2000 to 2017. Irish journal of psychological medicine, 1-9.

Grabski, M., Waldron, J., Freeman, T. P., Mokrysz, C., van Beek, R. J., van der Pol, P., ... & Curran, H. V. (2021). Drug Use Changes at the Individual Level: Results from a Longitudinal, Multisite Survey in Young Europeans Frequenting the Nightlife Scene. *European Addiction Research,* 1-6.

Jilka, S., Odoi, C. M., Wilson, E., Meran, S., Simblett, S., & Wykes, T. (2021). Ketamine treatment for depression: qualitative study exploring patient views. *BJPsych open*, *7*(1).

Morgan, C. J., Curran, H. V.(2012). Ketamine use: a review. *Addiction*, *107*(1), 27-38.

Palamar, J. J., & Le, A. (2021). Media coverage about medical benefits of MDMA and ketamine affects perceived likelihood of engaging in recreational use. Addiction Research & Theory, 1-8.

Sarvet, A. L., Wall, M. M., Fink, D. S., Greene, E., Le, A., Boustead, A. E., ... & Hasin, D. S. (2018). Medical marijuana laws and adolescent marijuana use in the United States: a systematic review and meta-analysis. Addiction, 113(6), 1003-1016.

Schuermeyer, J., Salomonsen-Sautel, S., Price, R. K., Balan, S., Thurstone, C., Min, S. J., & Sakai, J. T. (2014). Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003–11. Drug and alcohol dependence, 140, 145-155.

Smith K. (2017) Drug Misuse: Findings from the 2016/17 Crime Survey for England and Wales. London: Office for National Statistics, 2018.

Stripe N. (2020) Drug Misuse: year ending March 2020. London: Office for National Statistics.

Van Laar, M.W., Cruts, A.A.N., Van Miltenburg, C.J.A., Strada, L., Ketelaars, A.P.M., Croes, E.A., Beenakkers, E.M.T., & Meijer, R.F. (2020). *Nationale Drug Monitor; Jaarbericht 2019 [Netherlands National Drug Monitor; 2019 Annual Report; with Summary in English].* Utrecht/Den Haag: Trimbos-instituut/WODC.

Veraart, J. K., Smith-Apeldoorn, S. Y., Trueman, H., de Boer, M. K., Schoevers, R. A., & McShane, R. (2018). Characteristics of patients expressing an interest in ketamine treatment: results of an online survey. BJPsych open, 4(5), 389-392.

Waldron, J., Grabski, M., Freeman, T. P., Mokrysz, C., Hindocha, C., Measham, F., ... & Curran, H. V. (2020). How do online and offline sampling compare in a multinational study of drug use and nightlife behaviour? International Journal of Drug Policy, 82, 102812.

Winstock, A. R., Mitcheson, L., Gillatt, D. A., & Cottrell, A. M. (2012). The prevalence and natural history of urinary symptoms among recreational ketamine users. BJU international, 110(11), 1762-1766.

Tables 1-6.

Table 1. Demographic characteristics of the sample

		Total sample: n (%)	Had used ketamine: n (%)	Had not used ketamine: n (%)
N completers		2415	1520	895
Age; mean (SD)		24.5 (4.01)	24.5 (3.9)	24.4 (4.2)
Gender				
	Female	1141 (47)	675 (44)	466 (52)
	Male	1231 (51)	820 (54)	411 (46)
	Other	43 (2)	25 (2)	18 (2)
Uni degree completed		1565 (65)	1012 (67)	553 (62)
Occupation	*Full-time work*	1085 (45)	683 (45)	402 (45)
	Part-time work	298 (12)	197 (13)	101 (11)
	Student	1001 (41)	597 (39)	404 (45)
	NEET	212 (9)	154 (10)	58 (6)
Urbanicity	*Large town/city*	1720 (71)	1132 (74)	588 (66)
	Small to mid-sized town	479 (20)	262 (17)	217 (24)
	Rural/ countryside	216 (9)	126 (8)	90 (10)
Relationship status	*Single*	1205 (50)	743 (49)	462 (52)
	Married/ CP	72 (3)	38 (3)	34 (4)
	Divorced/ separated	9 (0.3)	3 (0.2)	6 (1)
	In relationship/ not cohabiting	563 (23)	367 (24)	196 (22)
	In relationship/ cohabiting	565 (23)	369 (24)	196 (22)
	Widow(er)	1 (0.04)	0 (0)	1 (0.1)
LT ketamine use		1520 (63)	1520 (100)	0 (0)
Past 12 month ket use		1267 (52)	1267 (83)	0 (0)
Frequency ket use	*Not in the last 12 months*	-	253 (17)	-
	3 times or less in the year	-	457 (30)	-
	Every 2 to 3 months	-	342 (23)	-
	Monthly	-	206 (14)	-
	Fortnightly	-	158 (10)	-
	Weekly	-	90 (6)	-
	3 times a week or more	-	14 (1)	-

NEET: Not in education, employment or training, CP: Civil Partnership, LT: lifetime; Ket: ketamine

Table 2. Endorsement of statements regarding ketamine policy changes*

	Total sample: n (%)	Aware of policy change: n (%)	Not aware of policy change: n (%)
N	2415	788	1627
Based on these changes in legislation are you more or less likely to use recreational ketamine?	301 (13)	70 (9)	231 (14)
Based on these changes in legislation are you more or less likely to use recreational ketamine for medical purposes?	398 (16)	118 (15)	280 (17)

*indicating “more likely” or “much more likely” on a 5-point Likert scale.

Table 3. Sensitivity analysis ketamine use longitudinal sample (N=414)

		TP1 (2017)	TP2 (2018)	TP3 (2020)	TP1 vs TP2			TP2 vs TP3		
12 months use		n (%)	n (%)	n (%)	χ^2	OR	p	χ^2	OR	p
	Total sample	174 (42)	191 (46)	188 (45)	3.24	1.54	0.071	0.05	0.92	0.815
	Aware	81 (54)	86 (58)	86 (58)	0.46	1.33	0.499	0	1	1
	Not aware	93 (35)	105 (40)	102 (38)	2.75	1.75	0.097	0.10	0.86	0.749
12 months freq		Med; M (SD)	Med; M (SD)	Med; M (SD)	Z	*d*	p	Z	*d*	p
	Total sample	0; 0.86 (1.27)	0; 0.98 (1.32)	0; 0.89 (1.26)	-2.21	0.11	0.027	2.07	0.10	0.038
	Aware	1; 1.16 (1.39)	1; 1.32 (1.43)	1; 1.22 (1.44)	-1.48	0.12	0.139	-1.48	0.12	0.138
	Not aware	0; 0.69 (1.17)	0; 0.79 (1.21)	0; 0.71 (1.11)	-1.60	0.10	0.110	-1.34	0.08	0.180

Total sample: N=414, Aware: N=149, not aware: N=265, TP = timepoint, freq = frequency, OR=odds ratio, Med=Median, M=Mean, SD=Standard deviation

Table 4. Endorsement of statements regarding ketamine as an antidepressant*

	Total sample: n (%)	Aware of policy change: n (%)	Not aware of policy change: n (%)
I currently believe ketamine is a safe and effective treatment for depression	856 (35)	482 (61)	374 (23)
Two years ago, I believed ketamine is a safe and effective treatment for depression	417 (17)	248 (31)	169 (10)
The use of ketamine as an antidepressant is only acceptable when prescribed by a medical professional	1563 (65)	571 (72)	992 (61)
The use of prescribed ketamine as an antidepressant is risky	985 (41)	265 (34)	720 (44)
Using prescribed ketamine as an antidepressant leads to the use of harder drugs	509 (21)	83 (11)	426 (26)
The use of recreational ketamine as an antidepressant is acceptable	573 (24)	263 (33)	310 (19)
Recreational ketamine use is risky	1775 (74)	563 (71)	1212 (74)
Using recreational ketamine leads to the use of harder drugs	1164 (48)	327 (41)	837 (51)
I'm in favour of the medical provision of ketamine for other mental health conditions	1286 (53)	597 (76)	689 (42)
I'm in favour of the medical provision of ketamine to treat drug addictions, such as problematic alcohol use	1268 (53)	594 (75)	674 (41)
People who use recreational ketamine as an antidepressant should not face legal prosecution	1443 (60)	568 (72)	875 (54)

* indicating “somewhat agree” or “strongly agree” on a 5-point Likert scale.

Table 5. Estimated likelihood of experience after ketamine use*

	Total sample: n (%)	Had used ketamine: n (%)	Had not used ketamine: n (%)
Confusion	1874 (78)	1221 (80)	653 (73)
Memory impairments	1710 (71)	1026 (66)	684 (76)
Physical accidents	1673 (69)	993 (65)	680 (76)
Being in a 'K-hole'	1645 (68)	1003 (66)	642 (72)
Sleeping problems	1270 (53)	464 (30)	624 (70)
Feeling less depressed	1048 (43)	731 (48)	317 (35)
Abdominal pains/ cramps	1007 (42)	595 (39)	412 (46)
Feeling less anxious	993 (41)	684 (45)	309 (35)
Difficulty reducing or stopping use	993 (41)	487 (32)	506 (57)
Feeling more anxious	970 (40)	529 (34)	441 (49)
Feeling more depressed	793 (33)	393 (26)	400 (45)
Cystitis	771 (32)	507 (33)	264 (29)
Flashbacks	689 (29)	350 (23)	339 (38)
Hypothermia	598 (25)	240 (16)	358 (40)

* indicating "likely" or "very likely" on a 5-point Likert scale.

Table 6. Experiences after ketamine use in lifetime users (N=1520)

	Had used ketamine: n (%)
Being in a 'K-hole'	809 (53)
Confusion	722 (48)
Feeling less depressed	481 (32)
Memory impairments	480 (32)
Feeling less anxious	460 (30)
Feeling more anxious	400 (26)
Sleeping problems	333 (22)
Feeling more depressed	280 (18)
Flashbacks	204 (13)
Abdominal pains/ cramps	191 (13)
Physical accidents	147 (10)
Difficulty reducing or stopping use	138 (9)
Cystitis	92 (6)
Hypothermia	7 (0.8)