

# Poppers: legal highs with questionable contents?

## A case series of poppers maculopathy

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### ABSTRACT

**Background** Poppers are volatile alkyl nitrite compounds that are inhaled to enhance sexual experience and for their psychoactive effects. A less well-known side effect is foveal maculopathy, which has emerged following changes in their chemical composition. It is unclear if certain individuals are more susceptible to retinal damage or if there is a relationship between pattern of inhalation and brands used.

**Methods** A case series of 12 patients presenting to Sussex Eye Hospital, Brighton, with poppers-related visual impairment. Follow-up data were available in 10 cases, at a median time interval of 5 months (range 0–31 months). Eight samples of poppers were analysed using proton nuclear magnetic resonance spectroscopy.

**Results** Patients presented with disrupted central vision occurring soon after inhalation. All demonstrated disruption of the inner segment/outer segment junction on spectral domain optical coherence tomography. Six of the brands implicated in causing visual symptoms contained isopropyl nitrite, while Jungle Juice Plus varieties, used without side effects in one case, contained amyl nitrite, 2-methyl butyl nitrite and isobutyl alcohol. In general, symptomatic resolution, alongside partial, if not full, recovery of foveal architecture was observed following abstinence.

**Discussion** On the basis of the products tested here, it seems that isopropyl nitrite is toxic to the fovea and can cause significant visual disturbance. The production of poppers is unregulated and their popularity is concerning, particularly given their exemption from the Psychoactive Substances Act 2016, which might suggest that they are harmless chemicals.

### INTRODUCTION

Poppers are typically colourless liquids with strong odours, composed of volatile aromatic nitrites. They were originally developed from amyl nitrites, used in the treatment of angina for their vasodilatory action.<sup>1</sup> Poppers can cause a reduction in blood pressure, headache, flushing, tachycardia, dizziness and involuntary muscle relaxation, including the vagina and anal sphincter.<sup>2</sup> They are popular for their psychoactive effects and when inhaled, users experience transient euphoria and sexual arousal. While initially more common among the homosexual community,<sup>2</sup> with 60% of Australia's male homosexual population admitting to trying poppers,<sup>3</sup> their use as a party drug is increasing among heterosexual and younger people.<sup>4</sup> About 1.1% of the general population in the UK use poppers at least once a year, making them the fourth most popular recreational drug after cannabis, cocaine and ecstasy.<sup>5</sup>

Poppers are illegal to sell for human consumption under the Medicines Act 1968 and so they are often sold in the guise of household items such as air fresheners. When ingested, they are highly toxic; 12 deaths have been attributed to alkyl nitrites in the last two decades.<sup>6</sup> The main component, isopropyl nitrite, replaced isobutyl nitrite following legislative changes in 2006 that classified the latter as a class II carcinogen.<sup>7–9</sup> It is unknown how the toxicity of isopropyl nitrite compares to the carcinogenic isobutyl nitrite, but it has been suggested that it might be at least as harmful.<sup>8</sup> The psychoactive substances bill was due to outlaw the production and selling of all legal highs in the UK from April 2016.<sup>10</sup> Poppers, however, have since been exempted on the basis that they do not directly stimulate or depress the central nervous system.<sup>11</sup>

Since the change in chemical composition of poppers, maculopathy has emerged as a serious side effect, with several case reports describing poppers-related visual impairment,<sup>7 12–15</sup> even after single use.<sup>7 13</sup> It is unclear whether the rise in incidence is related to particular nitrites or their ratio in poppers, more widespread use or better detection on high-resolution optical coherence tomography (OCT). Except for ceasing use, there is no treatment for popper-related retinal damage.

Here, we present 12 cases of visual disturbance associated with poppers use, report on their medium-term follow-up and include chemical analysis of popper products used by patients.

### MATERIALS AND METHODS

#### Clinical assessment

Twelve patients, all male, presented to Sussex Eye Hospital between 2013 and 2016, with symptoms that were subsequently linked to poppers. Mean age was 48 years (range 31–59 years). Four cases were in HIV-positive individuals, all well-controlled on antiretroviral medication. No clear link between poppers and immunodeficiency has emerged so far, although it has been suggested that inhaled nitrites could increase the risk of HIV transmission during unprotected anal intercourse.<sup>16</sup>

All patients were assessed by a retinal specialist and underwent fundus photography and spectral domain OCT (SD-OCT, spectral domain Topcon OCT 3000 and/or Heidelberg Spectralis) at baseline and follow-up visits. Fundus autofluorescence (short wavelength autofluorescence imaging, Heidelberg Spectralis) was performed in four cases. Follow-up data were available for 10 patients, with a median interval of 5 months (range 0–31 months).

#### Chemical analysis

Eight products were analysed: Platinum, Hard-on, Rush, Berlin XXX Hardcore, Liquid Gold, Jungle



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Juice (yellow label) and two Jungle Juice Plus (silver label, referred to as sample 1 and sample 2). All samples were sealed except for Jungle Juice Plus sample 1. Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were recorded using a Bruker Avance III 500 NMR spectrometer equipped with a room temperature broad band probe. Products and standards were diluted 5%–10% with deuterated acetone ( $\text{CD}_3\text{COCD}_3$ ) or, if not miscible with acetone, a deuterated water ( $\text{D}_2\text{O}$ ) coaxial insert was used with the neat liquid.  $^1\text{H}$  chemical shifts were determined by internal referencing to the lock solvent.

## RESULTS

Brand and pattern of poppers use along with clinical findings at presentation and follow-up assessments are summarised in [tables 1](#) and [2](#), respectively. Two cases were first-time users of poppers, while the remainder were occasional ( $n=3$ ) or regular ( $n=4$ ) users. The most frequently reported ocular symptom was impairment of central vision (blurriness or scotoma). Onset of symptoms relative to inhalation was fairly acute, occurring within hours or days.

Examination of the anterior segment and intraocular pressures was normal in all cases. Fundoscopy frequently showed subtle yellow-coloured foveal deposits, suggestive of poppers maculopathy. Fundus autofluorescence, performed in cases 1, 3, 4 and 7, showed a subtle area of foveal hyperfluorescence, corresponding with the yellow spot on fundus photography ([figure 1](#)). SD-OCT imaging revealed characteristic disruption of the inner segment/outer segment (IS/OS) junction in the subfoveal region in all cases, with varying amounts of retinal elevation ([figure 1](#) and [2](#)).

The findings on imaging, however, were not always symmetrical, with two cases (5 and 8) showing a unilateral poppers maculopathy. Case 5, an occasional user of poppers, presented with a central scotoma in the left eye only, with the

corresponding retinal disturbance confined to that eye. At 11 months, imaging and visual acuity (VA) improved, but had not fully resolved. Similarly, case 8 reported distortion only in the left eye—which correlated with the OCT findings—but in this instance, the abnormalities resolved within 3 months.

[Table 3](#) shows the main components identified in the popper products (see online supplementary appendix for details of the chemical shifts). Six of the products gave almost identical  $^1\text{H}$  NMR spectra. This was identified as an approximate 50:50 mixture of isopropyl nitrite and isopropyl alcohol. In the presence of water, nitrites easily convert to their corresponding alcohols. Isopropyl alcohol is commonly found in household products and inhalation of its vapours can cause headache, dizziness and drowsiness.<sup>17</sup> Two samples of Jungle Juice Plus were analysed. Sample one was a mixture of compounds tentatively identified as having amyl, 2-methyl butyl and isobutyl structure, but the nitrite functional group was absent as confirmed by Raman spectroscopy. Sample two of Jungle Juice Plus did contain nitrite and was identified as a mixture of amyl nitrite, 2-methyl butyl nitrite and the corresponding alcohols.

## DISCUSSION

### Symptoms linked to brands

In three of the above cases, the patient had used poppers for 20 years or more, only noticing symptoms on switching to a new brand. The first of these cases (case 7) developed a progressive central scotoma after using Jungle Juice, containing isopropyl nitrite. This followed a binge on the product in question, inhaling at approximately 5 min intervals during the course of 30 min. Previous and ongoing use of Jungle Juice Plus, containing amyl, 2-methyl butyl and isobutyl compounds (with no isopropyl nitrite, however) was not associated with visual side effects. Isobutyl alcohol, found in sample 1 of Jungle Juice Plus, is not a banned substance, and it evaporates slowly at room

**Table 1** Clinical summary at presentation

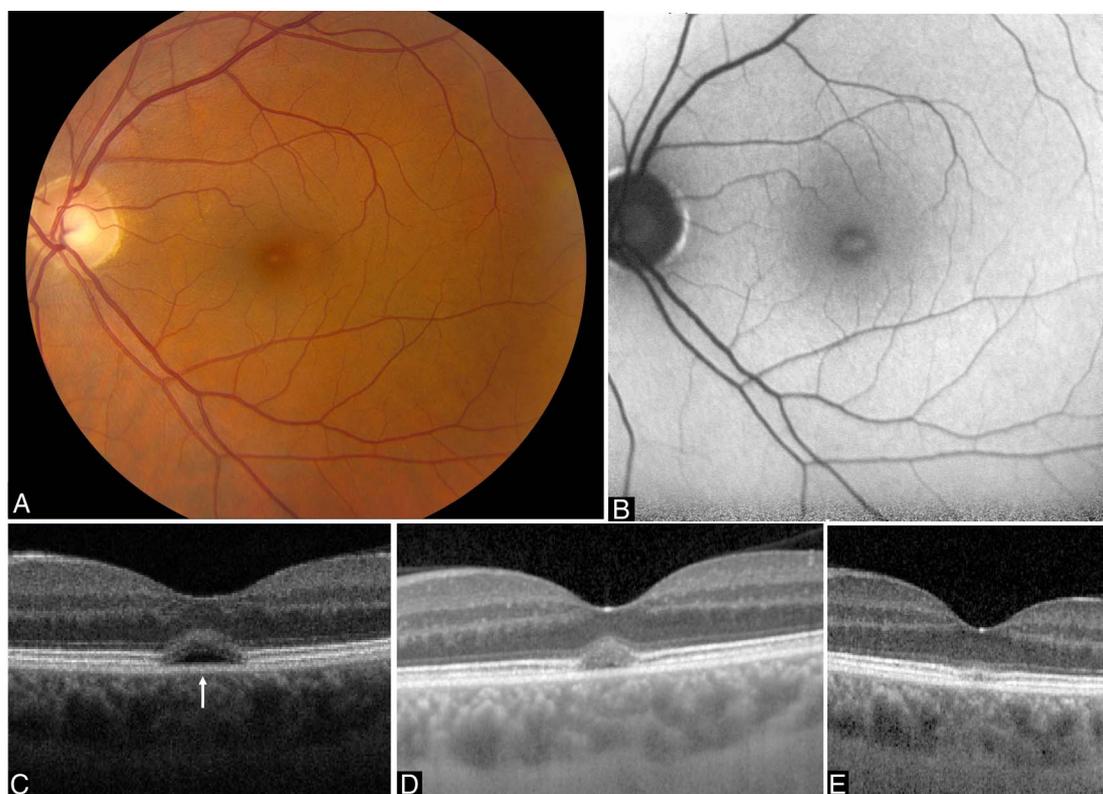
Case	Age, years	Brand	Pattern of use	Symptoms	Speed of onset	BCVA			Other
						OD	OS	OCT	
1	46	Liquid Gold	Once	Central visual disturbance for 6 months	Within 24 hours	6/6	6/6	Bilateral IS/OS disruption	–
2	56	–	Regular	Visual disturbance for 18 months	–	6/12	6/9	Bilateral IS/OS disruption	HIV positive
3	45	Berlin XXXX	Regular for years, problems switching brand	Central scotoma for 7 months	Within 24 hours	6/9	6/9	Bilateral IS/OS disruption	HIV positive
4	37	Rush, Hard-on	Occasional, problem with new brand	Central scotoma	2 days after switching brand	6/9	6/9	Bilateral IS/OS disruption	–
5	59	Old English, Liquid Gold	Occasional	Central scotoma (left eye)	Patient unsure	6/6	6/12	Left eye IS/OS disruption	Squint surgery
6	31	–	–	Central visual disturbance	–	6/6	6/9	Bilateral IS/OS disruption	–
7	42	Jungle juice (yellow label)	Regular for years, occasional binges	Central scotoma for 1 month	Within 24 hours	6/9	6/6	Bilateral IS/OS disruption	–
8	50	Amsterdam	Regular for years, with occasional heavy use	Central visual disturbance for 10 days (left eye)	4 days	6/36	6/6	Left eye IS/OS disruption	Right amblyopia
9	44	Jungle juice	Occasional for 18 months	Central disturbance with phosphenes	–	6/9	6/9	Bilateral IS/OS disruption	–
10	57	–	Weekly for 1 year	Central visual disturbance for 3 months	–	6/18	6/12	Bilateral IS/OS disruption	HIV positive
11	50	–	–	Central scotoma with phosphenes	–	6/9	6/6	Bilateral IS/OS disruption	HIV positive
12	55	–	One recent episode, over 5 days	Central visual disturbance for 6 months	–	6/6	6/9	Bilateral IS/OS disruption	–

BCVA, best corrected visual acuity; IS/OS, inner segment/outer segment; OCT, optical coherence tomography; OD, oculus dexter; OS, oculus sinister.

**Table 2** Clinical summary at longest follow-up

Case	Age, years	Follow-up (months)	Ongoing use	Symptoms	BCVA		
					OD	OS	OCT
1	46	31	Stopped	Resolved after 4 months	6/4	6/4	Resolved
2	56	16	Rare	Some improvement	6/12	6/7	Left improving, right stable
3	45	14	Stopped	Asymptomatic (within 7 weeks)	6/9	6/9	Improving
4	37	12	Monthly	Asymptomatic	6/6	6/6	Resolved
5	59	11	Stopped	Asymptomatic	6/4	6/9	Improving
6	31	6	–	–	6/6	6/6	Resolved
7	42	4	Occasional	Improving	6/5	6/5	Slight improvement
8	50	3	Stopped	Asymptomatic	6/36	6/4	Resolved
9	44	2	Stopped	–	6/9	6/9	Improving
10	57	1	Stopped	Asymptomatic	6/9	6/3	Improving
11	50	0	–	–	–	–	–
12	55	0	–	–	–	–	–

BCVA, best corrected visual acuity; OCT, optical coherence tomography; OD, oculus dexter; OS, oculus sinister.



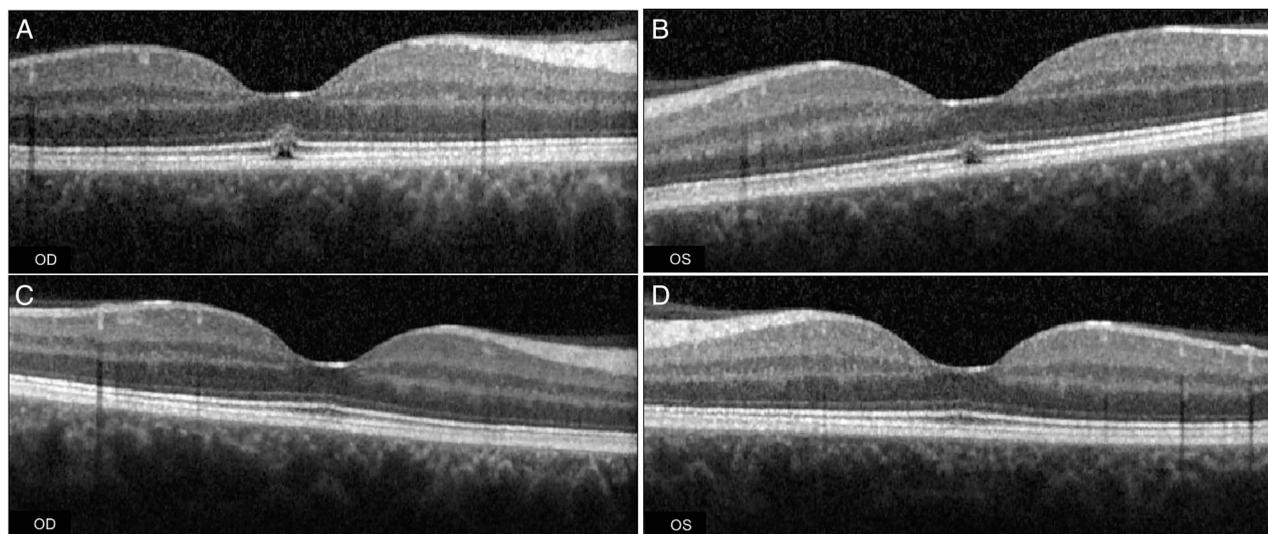
**Figure 1** Typical yellow foveal spot on fundal photography (A), with corresponding fundus autofluorescence (B) at presentation. Horizontal optical coherence tomography (OCT) scans through the left fovea showing inner segment/outer segment disruption (arrow) at presentation (C, Topcon), 5-month follow-up (D, Spectralis) and 14-month follow-up (E, Spectralis) (case 3).

temperature, with a potential to cause mild toxicity on inhalation (headache and drowsiness).<sup>17</sup> That said, its detection is concerning, given that isobutyl nitrite is a banned carcinogen and a potential source of isobutyl alcohol. This was the only bottle that had been opened and used by the patient, and so it is possible that any nitrites could have degraded to their corresponding alcohols before testing. Chemical analysis, however, could not confirm whether the product originally contained isobutyl nitrite.

The second case (case 3) noticed symptoms after using Berlin XXX, containing isopropyl nitrite, for the first time, having

previously suffered no ill effects with other brands. On using Berlin XXX again months later, he developed the same symptoms, again occurring over a similar time course. The third case (case 8) had frequently used isobutyl nitrites in the 1980s with no visual side effects, but after heavy use (sniffs at roughly 5–10 min intervals during a 5-hour period) of Amsterdam (not tested here) for the first time, he developed a central scotoma.

While there is likely to be a degree of variation in individual susceptibility to poppers maculopathy, the fact that several users give a clear history of visual disturbance originating on changing brands, suggests that different poppers exhibit differing toxicity



**Figure 2** Optical coherence tomography (OCT) images at presentation (A and B) and 1-year follow-up (C and D), showing complete resolution (case 4). OD, oculus dexter (right eye); OS, oculus sinister (left eye).

**Table 3** Main substances identified in the popper products by  $^1\text{H}$  NMR analysis

Product name	Identified components
Platinum	Isopropyl nitrite (~48%) and isopropyl alcohol (~52%)
Hard-on	Isopropyl nitrite (~49%) and isopropyl alcohol (~51%)
Rush	Isopropyl nitrite (~48%) and isopropyl alcohol (~52%)
Berlin XXX Hardcore	Isopropyl nitrite (~52%) and isopropyl alcohol (~48%)
Liquid Gold	Isopropyl nitrite (~49%) and isopropyl alcohol (~51%)
Jungle Juice (yellow label)	Isopropyl nitrite (~47%) and isopropyl alcohol (~53%)
Jungle Juice Plus (sample 1)	Amyl alcohol (~40%), 2-methyl butyl alcohol (~21%), isobutyl alcohol (~38%) (nitrites absent)
Jungle Juice Plus (sample 2)	Amyl nitrite (~49%), 2-methyl butyl nitrite (~28%), amyl alcohol (~15%), 2-methyl butyl alcohol (~8%)

$^1\text{H}$  NMR, proton nuclear magnetic resonance.

profiles. Nonetheless, with several brands and manufacturers involved, there is significant potential for varying strengths and contaminants.

### Evolution of maculopathy

In general, both symptoms and imaging abnormalities tended to improve over time. Six cases abstained from poppers use after diagnosis and most were asymptomatic within a few months, with improvements in measured VA. OCT abnormalities, although resolving, persisted after symptomatic resolution in three cases (3, 5 and 10), with mild ongoing disturbance evident at 11 and 14 months after cessation of use in cases 5 and 3, respectively (figure 1).

Full resolution was also observed after chronic use; for example, case 8 (who had a history of popper use spanning 30 years) stopped using poppers after diagnosis, and both imaging and symptoms were found to be normal at 4 months. This supports previous findings; a patient with a 12-year history of poppers use demonstrated complete restitution on OCT 6 months after cessation.<sup>18</sup> One of the few exceptions to this was a case who had used poppers regularly for years and who showed no improvement at 3 months, objective or subjective,

following cessation.<sup>12</sup> It would be interesting to know the outcome after a longer period of follow-up.

We observed a range of outcomes with continued poppers use. These were consistent with previous observations that chronic use does not lead to cumulative impairment or extrafoveal extension.<sup>7 13</sup> In case 4, where switching to a new brand was implicated in causing the maculopathy, the patient was symptomatic with evidence of OCT disturbances at 5 months. Despite approximately monthly use of another brand, symptoms and images normalised at 1 year (figure 2). In case 7, where Jungle Juice was implicated, there was some symptomatic and imaging improvement at 4 months, despite the occasional use of other brands, although it remains to be seen whether full resolution will occur. However, case 2, who initially improved after stopping popper use, soon developed a drop in acuity and further OCT changes after resuming inhalation. Whether the variability in outcome relates to patterns of use, brand of poppers, other behaviours or individual susceptibility remains unanswered.

### Mechanism of popper toxicity

The pathological mechanism of popper toxicity remains to be determined, and there is no obvious reason why isopropyl nitrite should be more toxic than isobutyl nitrite. It is postulated that nitric oxide donors, like nitrites, induce the upregulation of nitric oxide synthase, thereby prolonging nitric oxide production. Nitric oxide may be directly toxic to the macula, and it has been shown that photoreceptors are among the most sensitive retinal neurons to its toxic effects.<sup>19</sup> Nitric oxide also activates guanylate cyclase,<sup>20 21</sup> which is expected to decrease light sensitivity and experimentally, in rat retinas without foveas, nitric oxide potentiates the light responses of cones and decreases that of rods.<sup>22</sup> This effect could explain why some patients see phosphenes. Further theories for nitric oxide toxicity include interference with the protective macular pigment, zeaxanthin,<sup>23</sup> which could potentiate light toxicity.

The similarity between poppers maculopathy and photic injury, with both causing a yellow foveal lesion and disruption of the IS/OS junction on OCT, has been highlighted previously, but its significance is unclear.<sup>24</sup> Although clinical history seems to differentiate the conditions (none of the patients questioned here could link popper use to bright light exposure), this

observation may contribute towards understanding the pathological mechanism for popper-related toxicity. In addition, it is unclear why two cases (5 and 8) were unilateral. It is possible that toxicity in the fellow eye was subclinical and below threshold for detection on OCT.

## CONCLUSION

The cases presented here suggest that certain brands of poppers may be more toxic to the retina than others, with users anecdotally identifying a link between specific brands and the onset of their visual symptoms. Chemical analysis of the products tested suggests that isopropyl nitrite is responsible for poppers maculopathy, although the mechanism of this is unknown.

We suspect a high rate of poppers usage among the Brighton population; this is of increasing concern, both because of the mounting body of evidence suggesting that poppers can have serious effects on central vision and because of users and healthcare professionals who may be unaware of the risk. The notion that they are largely harmless chemicals might have been reinforced by the exclusion of poppers from the Psychoactive Substances Act 2016. While macula changes often resolve on cessation of use, symptoms can be prolonged and the visual effects of chronic use of the newer brands of poppers are unknown. For these reasons, it seems appropriate that the level of harm associated with poppers should be reassessed.

## Limitations and further work

Most of the products tested were not the exact bottles used by patients, but the brands they used were sourced from the same supplier where possible. Nevertheless, the composition of the poppers might have been different to that inhaled by the patients. We also relied on patients' recollection of their patterns of popper use. In some cases, it either was not possible to contact patients to collect follow-up data or they did not attend appointments. Longer-term follow-up will be required for chronic users of isopropyl nitrite compounds. Further analysis of popper products, particularly those used without visual side effects, could also be helpful as we demonstrated some variation in content, and there is quite a large range of products available. The background rate of poppers maculopathy is unknown and it would be interesting to determine whether there is a large subclinical cohort, with a French report having demonstrated OCT changes in asymptomatic users.<sup>25</sup> The pathological mechanism of popper toxicity remains to be elucidated and will be useful in clarifying the role of nitric oxide in the retina.

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