Simerdip Kaur takes a look at the latest ophthalmology-related news stories and asks which are based on facts and which are 'fake news'.

Headline: Another plant-based remedy for the eye?

What do the nicknames Mary Jane, tea, and 420 all have in common? They refer to marijuana of course! If, like me, you were oblivious then perhaps this article is worth a read.

Marijuana is a mixture of the dried flowers, leaves and tops of the cannabis plant indigenous to eastern Asia. For centuries, it's been used in religious and spiritual ceremonies, for healing purposes and as a form of psychotropic diversion. Of the many hundred compounds in the plant, delta-9-Tetrahydrocannabinol (δ^9THC) and Cannabidiol (CBD) are the two main opioid-like chemicals known as cannabinoids, i.e. they are solely composed of carbon, oxygen and hydrogen molecules [1]. The former is known for its psychoactive, whilst the latter for its relaxant, effects on the nervous system. The human body also produces its own endogenous cannabinoids which are lipid derivatives such as anandamide (arachidonoyl ethanolamide) and 2-arachidonoyl glycerol (2-AG) and 2-arachidonyl glyceryl ether (noladin) that act as neurotransmitters [1]. Both endogenous and exogenous cannabinoids act on the endocannabinoid receptors consisting of cannabinoid 1 (CB1R) and cannabinoid 2 receptor (CB2R). CB1 is mainly found in the central nervous system (CNS) but also in the lung, heart, urogenital, gastrointestinal, peripheral neurons and the eye [1]. In the eye, CB1R have been isolated from the cornea, ciliary epithelium, trabecular meshwork, Schlemm's canal, ciliary muscle, ciliary body, blood vessels and in the retina. CB2R on the other hand are involved in modulating cytokine release as part of the immune system and can be found on leucocytes, tonsils and the spleen [1]. It is unsurprising then that numerous researchers have sought to investigate the therapeutic effects of cannabis on the human body alongside the parallel illicit trials by its recreational users.

In 1971, the use of marijuana for lowering intraocular pressure (IOP) was first described by Hepler and Frank [2]. They recruited 11 healthy young men between the ages of 21 to 43 without glaucoma and provided each of them with 2g of marijuana containing 0.9% THC through ice-cooled water pipe and demonstrated a decrease in IOP between 16% and 45% in nine of them, with one subject experiencing a 4% increase in IOP and another with no change [2]. However, these effects were short lasting, between three to four hours, and further hindered by the development of tolerance. Moreover, a patient would have to smoke up to 3000 joints per year at a significant cost of several thousand pounds, notwithstanding the side-effects of lung damage from the smoke inhalation but also the detriment to cognitive function and the risk of drug-induced psychosis [3,4]. Nevertheless, this preliminary publication led to the victory for a patient in Washington several years later against the supreme court to be the first legal user of marijuana for his glaucoma. The medical marijuana movement is believed to have stemmed from here [5].

Numerous other studies soon followed, exploring various methods of administering marijuana to examine its effect on IOP, including tablets and intravenous routes. Even cannabis eye drops which would seem the most obvious route of delivery was unsuccessful due to its lipophilic nature, rendering it unsuitable for water-based administration. Oil based vehicles have been trialled with no success and instead cause irritation of the ocular surface. Neither of these modes of administration produced sustainable effects and were inferior compared to the other pharmaceutical agents available at the time. Concurrently, research on this topic has since dwindled away.

There is, however, potential for its use in ocular surface pain and inflammation. In a mouse model of autoimmune uveitis (Xu et al. 2017), a synthetic CB2R selective agonist was delivered systemically and initiated antigen suppression, impaired leucocyte response and generation of pro-inflammatory cytokines in. In another mouse model, topical application of a different CB2R agonist decreased intraocular inflammation by more than conventional steroids and non-steroidal anti-inflammatories (NSAIDs) [6]. Additionally, a separate group demonstrated application of δ^8THC (instead of δ^9THC as it is more stable) and CBD reduced the pain score following capsaicin induced hyperalgesia on mice corneas via modulation at CB1R and serotonin 1A receptor (5-HT_{1A}) [7]. More promisingly, a potential breakthrough for cornea neuropathic pain sufferers comes in the form of perfluorohexyloctane (F6H8). It is from a family of semifluorinated alkanes (SFAs) characterised by their colourless and inert non-aqueous lipophilic liquid nature, low surface and interface tension, is naturally preservative free and a non-blurring wetting agent. Professor Steven from Cologne, Germany and his team of researchers trialled the use of F6H8, marketed as NovaTears®, in a prospective observational study of 25 patients with evaporative dry eye disease (DED) [8]. They reported a satisfactory safety profile and improvement in patients with mild to moderate disease. The researchers hope that the success of F6H8 in DED will result in its use as part of a phase 1 study for Dronabinol – a synthetic δ^9THC, so that both compounds form one semifluorinated alkane, comprising a liquid vehicle and a cannabinoid receptor binding ligand to treat neuropathic pain associated with DED [8].

In the UK, cannabis is a class B drug and banned from recreational use, however, cannabis-based products for medicinal use can be prescribed by doctors on the specialist register on a named patient basis following a legislative change in 2018 [9]. Subsequently the National Institute for Health and Care Excellence (NICE) has approved Nabilone, a synthetic δ^9THC for intractable chemotherapy-induced nausea and vomiting; Sativex (Nabiximol), an oral mucosal spray with equal ratios of δ^9THC to CBD for multiple sclerosis related spasticity; and Epidyolex (CBD), an oral solution for children with Lennox-Gastaut and Dravet syndrome related epilepsy [10]. These developments represent a small but significant step towards the acceptance of medical cannabis as a treatment and will likely propel more research in this area of pharmacotherapy.

References

1. Tomida I, Pertwee RG, Azuara-Blanco A. Cannabinoids and glaucoma. *Br J Ophthalmol* 2004;**88**:708-13.
2. Hepler RS, Frank IR. Marihuana smoking and intraocular pressure (letter). *JAMA* 1971;**217**:1392.
3. Lieberman MF. "Recredicinal" Marijuana. *Am J Ophthalmol* 2017;**177**:xv-xviii.
4. Novack GD. Cannabinoids for treatment of glaucoma. *Curr Opin Ophthalmol* 2016;**27(2)**:146-50.
5. Graul TA. Marijuana and Glaucoma. *Glaucoma Today* March/April 2018 [online].
6. Toguri JT, Caldwell M, Kelly MEM. Turning down the thermostat: modulating the endocannabinoid system in ocular Inflammation and pain. *Front Pharmacol* 2016;**7**:304.
7. Thapa D, Cairns EA, Szczesniak A, et al. Cannabinoids δ^8THC, CBD, and HU-308 Act via distinct receptors to reduce corneal pain and inflammation. *Cannabis and Cannabinoid Research* 2018;**3(1)**.
8. Steven P, Scherer D, Krösser S, et al. Semifluorinated alkane eye drops for treatment of dry eye disease—a prospective, multicenter noninterventional study. *J Ocul Pharmacol Ther* 2015;**31(8)**:498-503.
9. NHS England and NHS Improvement. Cannabis-based products for medicinal use. 31 October 2018: https://www.england.nhs.uk/wp-content/uploads/2018/10/letter-guidance-on-cannabis-based-products-for-medicinal-use.pdf (Last accessed April 2020)
10. National Institute for Health and Care Excellence (2019). Cannabis-based medicinal product (NICE guideline NG144): https://www.nice.org.uk/guidance/ng144 (Last accessed April 2020)

SECTION EDITOR

Simerdip Kaur,

Ophthalmology Specialty Trainee Year 3,
KSS Deanery, UK.

E: simerdip.kaur@hotmail.com