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Title: The Misuse and Abuse of Ophthalmic Preparations: A Scoping Review of Clinical Case Presentations and Extant Literature.

Abstract

The emergent trend of misuse and abuse of ophthalmic drugs is a public health concern. Common ophthalmic preparations contain anticholinergics, antihistamines, decongestants, anaesthetics, and vasoconstrictive and topically applied nonsteroidal anti-inflammatory drugs. Misuse and abuse relates to their effect in causing euphoria, relaxation, hallucination, and reduction of depression symptoms. A scoping review of literature was conducted using Arksey and O'Malley's (2005) framework for mapping extant literature on the current knowledge of the issue. Four themes emerged: abuse of cycloplegics and mydriatics, misuse and abuse of topical ophthalmic anaesthetics, misuse of topical ophthalmic vasoconstrictive and topically applied nonsteroidal anti-inflammatory drugs (NSAIDs), and public and pharmacist views on ophthalmic drug abuse/misuse. The review underscores the complex motives for misuse and abuse, availability of ophthalmic products, self-medication practices, presence of co-morbidities, and low public awareness which harms the important role of health professionals regarding suspected misuse of these common products.

Running Title: A scoping review of the abuse of ophthalmic eye drops

Keywords: Ophthalmic preparations; abuse, misuse, community pharmacy

Introduction

The use of over-the-counter (OTC) and prescription medication for non-clinical use and self-medication is a global public health challenge (Casati et al. 2012; Norman et al. 2016; Wazaify et al. 2017). OTC medications are those that do not need a prescription while prescription medications are those that cannot be dispensed unless a prescription is written by a physician (Lessenger and Feinberg 2008; Van Hout and Norman 2015; Foley et al. 2015). Whilst OTC medications purchased from community pharmacies can help individuals to self-treat minor ailments and are therefore convenient for patients and physicians, some carry risks regarding habit-forming use, abuse, and dependence (Cooper 2013; Van Hout 2014; Van Hout and Norman 2015; Bergin et al. 2015; Parry et al. 2015). Common drugs of misuse and abuse have analgesic, anaesthetic, stimulant, or anxiolytic properties (Wazaify et al. 2017). Ability to understand and measure the nature of public misuse of OTC medicines are complicated and challenged by retail environments and the hidden and heterogeneous nature of therapeutic and non-therapeutic forms of misuse (Lessenger and Feinberg 2008; Cooper 2011; Casati et al. 2012; Cooper 2013; Van Hout and Norman 2015). Complexities also centre on varied terminology used in the literature to define misuse and abuse. Misuse has been broadly defined as “problematic consumption outside of acceptable medical practice or medical guidelines, when self-medicating at higher doses and for longer than is advisable, for intoxicating purposes and when risks and adverse consequences outweigh the benefits” (Casati et al. 2012; Shei et al. 2014; Van Hout and Norman 2015).

This report is about the emergent trend of misuse and abuse of ophthalmic drugs, which is relatively rare and under-researched in comparison to the abuse of OTC drugs (Wazaify et al. 2017). Early warning reports and mini-reviews have highlighted the issue of recreational and self-medicating misuse of these drugs (Kadri et al. 2010; Bersini et al. 2013; Prilutskaya and Kuliev

2014; Bersini et al. 2015). Most commonly reported ophthalmic preparations are those containing anticholinergics, antihistamines, and/or decongestants, such as tropicamide, cyclopentolate, naphazoline, and antazoline (Darcin et al. 2011; Wazaify et al. 2016; Ponté et al. 2017). Other ophthalmic drugs liable for abuse are the topical anaesthetic drugs (TADs), such as proparacaine, lidocaine, benoxinate (oxybuprocaine), cocaine and tetracaine, and topically applied non-steroidal anti-inflammatory drugs (NSAIDs) (Rapuano 1990; Flach 2001; Erdem et al. 2013; Sharifi et al. 2013).

Given the early warning trends around this novel form of OTC drug misuse and abuse, the aim of this scoping review was to understand what is currently known about the misuse and abuse of ophthalmic drugs.

Methods

Scoping review methods are increasingly popular as an accepted approach for mapping the extant literature on a topic (Arksey and O'Malley 2005; Anderson et al. 2008; Levac et al. 2010; Hidalgo Landa et al. 2011; Daudt et al. 2013; Pham et al. 2014). Given the lack of extensive review around the topic (Hidalgo Landa et al. 2011), the scoping review as defined by Daudt et al. (2013:8) is to “map the literature on a particular topic or research area and provide an opportunity to identify key concepts, gaps in the research, and types and sources of evidence to inform practice, policymaking, and research.” This scoping review was used as part of a larger project (Arksey and O'Malley 2005; Levac et al. 2010) to provide a descriptive review of available literature on the topic of misuse and abuse of ophthalmic drugs.

The scoping review was underpinned by the primary research question: “What do we know about ophthalmic abuse?” Our review process adhered to the five stage method as adapted by

Arskey and O'Malley (2005) which involved: 1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) charting the data, and (5) collating, summarizing, and reporting the results. A rigorous and transparent method was used to locate and analyse all relevant literature (Arksey and O Malley 2005; Rumrill et al. 2010).

Search terms linked the terms “ophthalmic” with “abuse,” “eye drops,” “misuse,” and “over-the-counter” and were agreed upon by a team who have pharmacy, pharmacovigilance, and addiction expertise. Searches were conducted on the databases PubMed, Science Direct, Google Scholar, Electronic Library of Medicine, Hinari, and Cochrane Library. Limitations were set to human studies with no limitations on the language applied. Eligibility criteria centred on whether studies broadly described misuse or abuse of ophthalmic drugs. Reference lists in records were manually searched to identify any further studies not captured in the initial database search. Records were managed using the bibliographic software manager EndNote (Thomson Reuters 2012) with duplicates removed manually. The title and abstract of each citation were crosschecked to agree with the inclusion criteria reached within the team. The final data set was then created by procuring full text versions (Levac et al. 2010). The flowchart illustrating the process is presented in Figure. 1.

Insert Figure 1 about here

The search identified 4,483 citations, of which 54 were identified to directly relate to the misuse and abuse of ophthalmic drugs. These were then charted into themes by the team.

Results

Four themes emerged: abuse of cycloplegics and mydriatics, misuse and abuse of topical ophthalmic anaesthetics, misuse of topical ophthalmic vasoconstrictive and topically applied nonsteroidal anti-inflammatory drugs (NSAIDs), and public and pharmacist views on ophthalmic drug abuse/misuse. See Table 1.

Abuse of Cycloplegics and Mydriatics

The abuse of cycloplegics and mydriatics was observed in the case literature, with the first reported case in 1973 where a 25-year-old male with bilateral epithelial keratitis was initially treated with topical antibiotics, steroids, tropicamide, and cyclopentolate 1%. Drug induced toxicity was speculated to have contributed to keratitis, with the patient reporting application of 100-200 drops of cyclopentolate and tropicamide many times a day (Ostler 1975). Weight loss and continual sleep were reported. On cessation, keratitis resolved within four days but with withdrawal symptoms of excessive salivation, tremors, rigidity, nausea, vomiting, and anxiety. Darcin et al. (2011) reported the case of a 28-year-old male patient who abused cyclopentolate hydrochloride. He said that he liked the burning effect of the eye drop which made him feel “high” and described tolerance and dose escalation on repeated use. Withdrawal symptomatology on attempts to cease use included nausea and sweating. Abuse of cyclopentolate eye drops and alcohol was reported by Akkaya (2008) who described a 39-year-old male case with Behcet’s disease and correlated vision disorder. This patient abused cyclopentolate eye drops and alcohol for 15 years and increased the dose to 100 drops per day. He reported blurred vision, impaired concentration, loss of interest, and increased anxiety when attempting to decrease or abstain from the dose. Treatment for dependency was successful for alcohol but not for eye drops, and the patient continued with the use of 100 drops per day. Sato et al. (1992) reported on two female cases of

cyclopentolate abuse, both administering between 100 and 400 drops per day, and with typical withdrawal symptoms of tremors, weakness, nausea, and vomiting. The first case aged 18 years had a conjunctival infection and corneal epithelial keratitis and within four months of abuse underwent psychiatric intervention. The second case aged 30 years had pan uveitis and multifocal choroiditis with a co-dependency on alcohol. Lately, Görgülü et al. (2015) reported a case for a 28-year-old male patient with a history of bipolar disease, depression, and manic disorders since he was 20. Cyclopentolate eye drops were suggested by his friend to improve his symptoms of depression. In contrast to previous case presentation, intranasal administration was used with up to 100 drops each day. Cravings, manic episodes, and mood elevation were the driving forces to continue this use.

Several cases of tropicamide abuse through intra-venous (IV) injection have been reported online (Bersani et al. 2013) and in Turkey (Bozkurt et al. 2014), Italy (Spagnolo et al. 2013), France (Ponté et al. 2017), Tajikistan (Otiashvili et al. 2016), and Kazakhstan (Prilutskaya and Kuliev 2015). Abuse is associated with blurred vision, dissociation, loss of concentration, weight loss, slurred speech, hallucinations, suicidal feelings, and forgetfulness (Bersini et al. 2015). Descriptions of user experiences ranged from pleasurable to fear inducing, and the primary reported motives for IV abuse were for intensifying the pleasurable effect of heroin, marijuana, and alcohol and delaying or minimizing heroin withdrawal symptoms (Bersani et al. 2013; Bersani et al. 2015).

Prilutskaya and Kuliev (2015) in their observational study described clinical characteristics of patients (n=118) with poly-drug dependence, which included tropicamide. Otiashvili et al. (2016) conducted 12 focus groups with 100 male participants at needle exchanges in Khorog and Kulob, where one participant reported using tropicamide to relieve opiate withdrawals. The first

patient case of IV injection was reported in Italy (Spagnolo et al. 2013), where a heroin dependent 22-year-old female entered a methadone substitution programme and was admitted with palpitations and visual and auditory hallucinations. She reported injecting 1% tropicamide-containing eye drops for two years in order to self-manage opiate and methadone withdrawals and experience the euphoric effect. During this timeframe the dose was increased from 50 ml to 150 ml per day. Visual and auditory hallucinations were described on injection of higher doses. The patient later underwent a successful detoxification (Spagnolo et al. 2013). Two cases of IV use of tropicamide were reported in Turkey by Bozkurt et al. (2015). The first case was an unemployed 37-year-old male, long term poly-drug user (heroin, clonazepam, ecstasy, cocaine, biperiden) who reported mixing 0.25 mg heroin with 1 ml tropicamide three to five times daily. He claimed that a tropicamide injection enhanced the heroin effect, increased sedation, and decreased heroin related cravings. The second was a 38-year-old male, long term poly-drug user (heroin, codeine, alprazolam, ecstasy, cocaine) who also mixed heroin with up to five bottles of 1% tropicamide each day. Similar to the first case, he reported the enhanced and prolonged euphoric effect of heroin when mixed with tropicamide and reduced heroin related cravings. Both cases reported hallucinations, blurred vision, dizziness, decreased appetite, cognitive impairment, short term memory loss, and weight loss (Bozkurt et al. 2015). Prilutskaya and Kuliev (2015) commented on tropicamide dependence implicated clinical outcomes such as psychological dependence, intoxication-related psychosis, cardiovascular toxicity, and post-injection purulent soft tissue complications.

Misuse and Abuse of Topical Ophthalmic Anaesthetics

Misuse of topical ophthalmic anaesthetics was reported in case series, case reports, and reviews and primarily focused on toxicity and related complications. A review by Patel and Fraunfelder (2013) illustrated the history of topical ocular anaesthetics, the emergent abuse of topical anaesthetic drops, mechanisms of toxicity, and comparison of toxicity of topical anaesthetics including the topical anaesthetic gels.

Webber Frcophth et al. (1999) have reported on how topical anesthetic abuse is accepted as a differential diagnosis of ring keratitis. Frequent and continuous application can contribute to anesthetic induced keratitis (Henkes and Waubke 1978), ring keratitis (Kurna et al. 2012) and herpetic keratitis (Solomon et al. 1996). Bilateral corneal ring infiltrates were also described by Hou et al. (2009) and Chen et al. (2004) in their reported cases where toxic keratopathy could occur as a result of the abuse of topical anesthetics even at very low concentrations of 0.05%. Dayanır et al. (2013) described the topical anesthetic abuse keratopathy and clinical progression in six eyes of three patients. Chern et al. (1996) reported on four cases of patients (three females and one male aged between 21 and 35 years) with topical anaesthetic abuse of the cornea and development of candida keratitis, causing severe ocular morbidity. Sugar (1998) reported on self-medication of topical anesthetics by a female patient with corneal epithelial defects and stromal infiltration. Varga et al. (1997) reported on four cases of topical anaesthetic abuse keratopathy. Rao et al. (2007) in Hong Kong reported on a 42-year-old female patient with keratopathy after progressive misuse of high dosages of oxybuprocaine eye drops, initially prescribed for post LASEK surgery pain. Kintner et al. (1990) reported on two cases of infectious crystalline keratopathy associated with topical anesthetic abuse. Risco (1992) also reported on topical anesthetic keratopathy with the abuse of oxybuprocaine causing irreversible damage to the corneal endothelial cells.

Some reported studies described the treatment options for keratitis associated with topical anesthetic abuse. Altinok et al. (2010) suggested non-preserved amniotic membrane transplantation for relieving the pain and improving the corneal surface in patients with bilateral toxic keratopathy related to topical anaesthetic abuse. Georgakopoulos et al. (2011) discussed the bevacizumab role in the treatment of corneal neovascularization associated with topical anesthetic abuse. A case series by Burcu et al. (2013) assessed the role of early amniotic membrane transplantation in patients with toxic keratopathy due to topical anesthetic abuse.

Other studies reported on initial legitimate use which progressed over time. Goldich et al. (2011) reported on a 47-year-old male with varied eye complications and with a history of abuse of oxybuprocaine resulting in keratitis. Matti and Saha (2012) reported on a 26-year-old woman who wore contact lens daily, usually slept without removing them, and complained of blurred vision, irritation, and redness in her right eye. Proxymetacaine 0.5% eye drops were applied to remove lenses without discomfort (Matti and Saha 2012). A case presented by Wu et al. (2016) sheds light on a severe case of keratopathy reported as a Mooren-like ulcer related to the abuse of topical anaesthetics and dexamethasone by a 38-year-old male physician who self-treated with tetracaine, dexamethasone (DEX), and lidocaine eye drops. Daily use was reported every hour for the previous six months to manage severe pain. At presentation his left cornea was melted and exhibited iris prolapse, where the right cornea exhibited circular melting with full-thickness stromal permeation. Keratoplasty was done to the patient, resulting in retained proper vision (Wu et al. 2016). A case report by Kim et al. (1997) described a 29-year-old male patient with stromal ring infiltrates and delayed epithelial healing for a 29-year-old male who had Excimer laser photorefractive keratectomy (PRK) on both eyes. The patient admitted abuse of proparacaine 0.5% eye drops after PRK surgery.

Some records underscored the presence of co-morbid conditions in patients. Case series by Rosenwasser et al. (1990) reported on two male and four female patients, all characterized with ring infiltrates and some with serious intraocular inflammation. Abuse of topical ocular anaesthetic was the common feature in all cases, with five out of six patients diagnosed with personality disorder, chemical dependency, and/or depression. This case report revealed that abusers obtained eye drops from ophthalmologists and pharmacies, along with thefts from clinics. Katsimpris et al. (2007) described five male cases admitted to the emergency unit complaining from corneal epithelial defects combined with a ring infiltrate in the corneal stroma as a result of topical anaesthetic abuse keratitis with no history of ophthalmic disease. All patients obtained the drugs from pharmacies without a prescription. Four patients had used proparacaine, while tetracaine was used by the fifth. All patients underwent a psychiatric consultation and different disorders were noted including depression, bipolar psychosis, substance abuse, and suicidal tendency (Katsimpris et al. 2007). Yeniad et al. (2010) reported on psychiatric co-morbidity in their eight cases, with four patients diagnosed with anxiety disorder and one with bi-polar. Toc et al. (2015) described that five patients (out of ten cases) were diagnosed with personality disorder, depression, and smoking addiction. Psychiatric disorder was associated with seven patients out of 19 cases of topical anaesthetic abuse (Yagci et al. 2011). Erdem et al. (2013) reported on eight cases with psychomotor agitation and insomnia associated with severe ocular pain and anxiety and half diagnosed with psychiatric conditions such as anxiety, affective disorder, and drug abuse. Ansari et al. (2006) discussed two female cases with a history of major depression who presented with ring shaped stromal opacities and large bilateral corneal epithelial defects. Both reported unsuccessfully self-treating with topical antibiotic to manage their topical anaesthetic associated keratitis. Authors reported that topical anaesthetic abuse keratopathy is usually a phenomenon of

underlying psychiatric disorder, and psychiatric consultation is a very critical part of treatment (Ansari et al. 2006).

Occupational hazards, pharmacists' recommendations, and availability OTC appeared central to some patient cohorts. The over prescription of topical anaesthetic drugs by pharmacists was described by Moreira et al. (1991) in Brazil. High prevalence of self-medication and abuse of topical anaesthetics (commonly tetracaine) among welders in Iran was reported by Sharifi et al. (2013), with 97.4% reporting direct sourcing from pharmacies without prescription and with low awareness around potential complications. Yagci et al. (2011) in their retrospective case analysis of topical anesthetic abuse keratopathy underscored the need for awareness and vigilance of ophthalmologists. Awareness was particularly needed in young male labourers employed in the welding and foundry sectors and presenting with ring shaped keratitis, severe ocular pain, and persistent epithelial defects. Shirzadeh et al. (2016) reported on topical anaesthetic misuse in patients admitted to an eye clinic in Iran and observed a trend of misuse among welders who sourced via pharmacies without prescriptions. Eight cases of toxic keratopathy (including ring infiltrates) resulting from the abuse of topical anesthetic drugs were reported by Yenziad et al. (2010) with sourcing primarily via pharmacy dispensing without prescription. Five out of the eight had a corneal foreign body history, with the remainder reporting a chemical burn, ultraviolet radiation exposure, and a basal membrane dystrophy. On cessation of use, all clinical signs improved (Yenziad et al. 2010). Toc et al. (2015) described the abuse of topical anaesthetics in ten males who applied 0.5% proparacaine hydrochloride to manage pain resulting from foreign bodies, car battery explosions, and welding flash burns experienced as occupational hazards. The majority sourced via community pharmacies without prescription. All presented with ring ulcer, epithelial defect, corneal edema, and stromal infiltration and complained from lacrimation, severe pain, and

photophobia. All patients underwent amniotic membrane transplantation (AMT) and achieved pain relief after one week (Tok et al. 2015). Similar findings in terms of occupational reasons contributing to misuse and abuse patterns were reported by Yagci et al. (2011), who recorded 19 cases of topical anaesthetic abuse relating to welding flash in eight patients, metallic foreign body exposure in eight patients, and chemical injury in three patients. Conjunctival injection and oval corneal epithelial defect were reported in all 19 cases, 57.7% reported with ring-shaped keratitis, 46.2% reported with stromal infiltrate, and 42.3% reported a hypopyon (Yagci et al. 2011). Lastly, Erdem et al. (2013) described eight cases, five males and three females, admitted to the cornea unit with keratopathy because of abusing topical anaesthetic drugs. Sourcing was described as via a prescription from a primary care practitioner (one) with the remainder sourcing via community pharmacies without prescription. Motives and reasons for use centred on traumatic corneal abrasion, exposure to welding flash, exposure to silica dust, and lagophthalmos-related keratopathy. Two had lagophthalmos associated exposure keratopathy.

Misuse of Topical Ophthalmic Vasoconstrictive and Topically Applied Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Adefule-Ositelu (1989) reported the misuse of ophthalmic agents in Nigeria, where vasoconstrictive eye drops are a major constituent of drugs contributing to ocular morbidity (Adefule-Ositelu 1989). Soparkar et al. (1997) reported on a case series of patients with conjunctival inflammation caused by excessive use of eye drops containing the vasoconstrictors phenylephrine, tetrahydrozoline, or naphazoline. In their study, 137 eyes for 70 patients were analysed. On presentation ocular symptoms were redness, itching, eyelid swelling, irritation, burning, pain, or foreign body sensation. Daily use patterns ranged from 1 to 12 times per day and from the previous 8 hours to 20 years. The most frequent pattern of conjunctivitis was conjunctival

hyperemia which was present in the majority of cases as an induced rebound phenomena (Soparkar et al. 1997). Tappeiner et al. (2009) reported on a case of a 45-year-old man who had applied phenylephrine eye drops hourly for years. The phenylephrine eye drops were first prescribed by a resident ophthalmologist, and then sourced via pharmacies without prescription. The case presented with fornix shortening, eye redness, and scarring of lacrimal puncta. Ocular pemphigoid was excluded due to negative immunofluorescence, but neovascularization in the conjunctiva and signs of chronic inflammation were observed. On cessation within seven weeks complete healing was achieved. A second report by Flach (2001) reported on a case series of five males and six females with corneal melting associated with misuse and abuse of topical NSAIDs. Flach also reported in 2006 on three cases of corneal melting following topical use of NSAIDs (on this occasion bromfenac).

Public and Pharmacist Views on Ophthalmic Drug Abuse/Misuse

This review has highlighted the scarcity of available literature on the misuse and abuse of ophthalmic products in the public and community pharmacy settings. In 2005, a study was conducted in Bangkok to measure general population attitudes towards OTC ophthalmic remedies. A questionnaire was filled out by 200 members of the public. Only 93/200 (46.5%) noticed that the maximum allowable duration to use these preparations was only one month after opening and 88/200 (44%) did not read the directions before use. The authors concluded that greater awareness is warranted in order to achieve safe public use of OTC ophthalmic preparations (Tayanithi and Aramwit 2005). In 2011, an interview based study was conducted in India to measure how OTC ophthalmic drops could be misused by customers and to gain a better understanding of their attitudes, knowledge, and triggers for misuse of such medications (Kadri et al. 2011). Data also

included type of OTC ophthalmic drops, duration and indication for use, pharmacist role in counselling and the status of their condition as improved or declined. Findings illustrated a lack of customer awareness, with the majority of patients indicating no knowledge about the choice of OTC and prescription ophthalmic products. Misuse and abuse was reported mainly due to inadequate knowledge of dangerous side effects occurring from excessive use (Kadri et al. 2011).

In terms of pharmacist attitudes, a study conducted in India investigated perceptions around how OTC ophthalmic drops were misused (Kadri et al. 2010). There were 89 pharmacists that completed a semi-structured questionnaire, and the results were that the average number of patients attending community pharmacies complaining from ophthalmic problems was seven per day, with the main complaint being redness and itching of the eye. The most common eye drops dispensed were antibiotics (96.6%), steroids (55.1%), decongestants (54.1%), steroid-antibiotic combinations (29.2%), and lubricants (16.8%). Knowledge of steroid side effects was observed only in 40.6% pharmacists, and 6.7% pharmacists had noticed some of the side effects resulted from eye drop preparation when misused or abused by their patients. The study highlighted that educating the public and pharmacists about these remedies may reduce the ocular complications and improve safety of use (Kadri et al. 2010). A recent survey in Jordan has revealed that ophthalmic drug abuse sourced from community pharmacies is on the rise (Wazaify et al. 2016). In 2016, a study was conducted which investigated the knowledge, attitudes, and experience of community pharmacists regarding misuse and abuse of ophthalmic drops. A structured questionnaire was completed by 220 pharmacists. The majority of ophthalmic drugs were reported to be dispensed without a prescription (61.85%). Five OTC drops and two prescription-only products were reported by pharmacists to be liable for abuse. With regard to management of the

problem, 69.5% of pharmacists refused to sell the product and claimed that the drug was unavailable (Wazaify et al. 2017).

Discussion

This paper is the first known attempt to scope and map the extant literature on the topic of misuse and abuse of ophthalmic drugs. The abuse of ophthalmic anticholinergic drugs is related to their effect in causing euphoria, relaxation, hallucination, and reduction of depression symptoms (Darcin et al. 2011; Bersani et al. 2013; Bersani et al. 2015). A range of health harms are observed in the literature. Studies on the abuse of ophthalmic drugs report associated outcomes of ocular toxicity, impaired vision, uveitis, and blindness (Darcin et al. 2011; Kadri et al. 2010). Different ocular disorders have been associated with the abuse of these drugs, including keratopathy, stromal infiltrates, persistent epithelial defects, and secondary infectious keratitis and may lead to corneal melting, permanent visual loss, and perforation (Rosenwasser et al. 1990; Chern et al. 1996; Flach 2001; Yeniad et al. 2010; Hendershot et al. 2011; Erdem et al. 2013; Sharifi et al. 2013; Tok et al. 2015). Misuse of topical ophthalmic anaesthetics causes anesthetic induced keratitis (Henkes and Waubke 1978; Webber Frcophth et al. 1999; Goldich et al. 2011; Kurna et al. 2012; Matti and Saha 2012; Wu et al. 2016), bilateral corneal ring infiltrates (Rapuano 1990; Katsimpris et al. 2007), toxic keratopathy (Risco 1993; Varga et al. 1997; Chen et al. 2004; Rao et al. 2007; Kirikkaya et al. 2013), candida keratitis (Chern et al. 1996), stromal infiltration (Sugar 1998; Kim et al. 1997), and infectious crystalline keratopathy (Kintner 1990). Acute and chronic conjunctivitis generally occur as a result of the excessive use of ophthalmic decongestants (Soparkar et al. 1997; Tappeiner et al. 2009; Kadri et al. 2010). Conjunctivitis rebound phenomena and chronic inflammation have been reported in patients misusing eye drops containing the

vasoconstrictors phenylephrine, tetrahydrozoline, or naphazoline (Soparkar et al. 1997; Tappeiner et al. 2009).

Systemic absorption of these drugs can also happen and lead to psychosis and/or hallucinations if used in high doses and for prolonged periods of time (Balbani et al. 2000). Additional patient vulnerability to co-morbid conditions such as personality disorder, bi-polar disorder, anxiety disorder, chemical dependence, depression, and suicidal ideation are evident (Rosenwasser 1990; Ansari et al. 2005; Katsimpris et al 2007; Yeniad et al. 2010; Yagci et al. 2011; Erdem et al. 2013; Toc et al. 2015). Therefore, psychiatric diagnosis is a vital component of the clinical care pathway (Ansari et al. 2005). Drug induced toxicity in the case of abuse of cycloplegic and mydriatic ophthalmic drugs contribute to keratitis with some reports around withdrawal symptomatology and difficulties in the treatment of dependence (Ostler 1975; Sato et al. 1992; Akkaya 2008; Darcin et al. 2011). Cyclopentolate systemic side effects reported in the literature range from inappropriate behaviour, visual and auditory hallucinations, changes in emotional attitude, and generalized seizures to a lesser extent (Rajeev et al. 2010; Bhatia et al. 2000). Cognitive impairment and weight loss are common (Bersini et al. 2015). IV injections of tropicamide were reported in heroin users to intensify the effect and when self-medicating to delay withdrawals (Spagnolo et al. 2013; Bersani et al. 2013; Bozkurt et al. 2014; Prilutskaya and Kuliev 2014, 2015; Bersani et al. 2015; Otiashvili et al. 2016; Ponté et al. 2017). These injections are concerning, particularly given the clinical outcomes such as psychosis, dependence, injecting harms, and cardiovascular toxicity (Prilutskaya and Kuliev 2014, 2015). Particularly among IV injectors of tropicamide, poly-drug use is common and associated with psychiatric co-morbidities (Bersani et al. 2015).

Occupational hazards and the availability of OTC drugs appeared central to some patient cohorts such as welders and labourers (Yeniad et al. 2010; Yagci et al. 2011; Sharifi et al. 2013; Erdem et al. 2013; Toc et al. 2015; Shirzadeh et al. 2016). Sourcing of topical anaesthetics via the ophthalmologist and pharmacy, along with diversion via theft were described (Rosenwasser et al. 1990; Katsimpris et al. 2007; Yeniad et al. 2010; Yagci et al. 2011; Erdem et al. 2013; Toc et al. 2015; Shirzadeh et al. 2016).

Generally, public and pharmacy awareness of the issue of misuse and abuse of ophthalmic drugs remains low and warrants targeted efforts to inform both parties regarding ocular complications, safe use, and consequences of misuse (Tayanithi and Aramwit 2005; Kadri et al. 2010; Kadri et al. 2011; Wazaify et al. 2017). The studies where available have highlighted the need for ophthalmologist and community pharmacist awareness and training for recognising and intervening where potential misuse and abuse of ophthalmic products is suspected. (Rapuano 1990; Sugar 1997; Bozkurt et al. 2015).

Conclusion

This review underscores the complexities around motives for misuse and abuse of a range of ophthalmic drugs, availability of OTC ophthalmic products, self-medication practices, presence of co-morbidities, and low public awareness around harms highlighting the important role of health professionals regarding suspected misuse of these common products. Further research is warranted to investigate abuse limit of these ophthalmic drugs and potential regulatory efforts to address the issue.

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