International Journal of Basic & Clinical Pharmacology
Vijayakumar AR et al. Int J Basic Clin Pharmacol. 2021 Jun;10(6):748-758
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20212089

Review Article

Systemically administered central nervous system drugs induced ocular side effects: a review

Vijayakumar A. R.[1]*, Prabu Daniel Epison[2], Kabeera Begum A.[2], Abirami V. P.[2], Ajmal Hussain[2], Abdul Azeez Kader[2], Ansar Ali Abdunnasir[2]

[1]Department of Pharmacology, Faculty of Pharmacy, Sree Balaji Medical College and Hospital Campus, BIHER, Chromepet, Chennai, Tamil Nadu, India
[2]Department of Pharmacology, Mohammed Sathak A. J. College of Pharmacy, Chennai, Tamil Nadu, India

Received: 07 April 2021
Accepted: 07 May 2021

***Correspondence:**
Dr. Vijayakumar A. R.,
Email: marunthiyal2013@gmail.com

ABSTRACT

Several systemic drugs have reported ocular and visual side effects that affect patient management. It is imperative to be familiar with the associated side effects which can be mild or transient and may seriously threaten vision. This article deals briefly with the mechanisms and reasons that account for the impact that systemically administered central nervous system (CNS) drugs can exert on the visual or ocular system. The eye care practitioner can be instrumental in detecting and reporting ocular side effects, advising patients and collaborating with other members of the patient's healthcare team. One of the difficulties include becoming familiar with the countless systemic medications prescribed to patients. Another is being able to correlate a particular side effect with a suspected drug. Several of the ocular adverse effects such as glaucoma, cataract, blurred vision, color vision, optic neuritis, maculopathy, dry eye, etc., are vision threatening and often patients fail to recognize or describe the symptoms appropriately. Therefore, physicians and paramedical members like staff nurses, clinical pharmacists and other members must make adequate observations while recommending these drugs to patients.

Keywords: Systemic administration, Ocular toxicity, Central nervous system drugs, Alcohol, Epileptics, CNS stimulants

INTRODUCTION

Paracelsus, who is the father of toxicology said "What is there that is not poison? All things are poison, and nothing is without poison.[1] In this context, the drug also acts in line with the Paracelsus's statement. The medications even at their therapeutic doses carry the chances of unwanted effects or adverse drug reactions. Once the drug enters the body, it is free to move and reside anywhere unless restricted by the tissue specificity or the drug molecule itself. In this regard, the drugs that are taken systemically can enter the eye inspite of presence of safety barriers like the blood-retinal barrier (BRB) posteriorly and the blood-aqueous barrier (BAB) anteriorly and can affect the physiology adversely.[2,3]

Many common systemic medications can affect the ocular tissues and visual function. The ophthalmologist and ocular paramedical staff are in the ideal position to identify and manage such occurrences. To educate patients and to prevent and minimize serious consequences, clinicians should keep in mind the potential effects of systemic drugs.[4-6] Unwanted side effects can be incurred in patients who take medications quite frequently. In this literature of review, we summarize the systemically administered central nervous system (CNS) drugs induced ocular side effects in the standard medical search engine such as Google, Google Scholar, PubMed, PubMed Central (PMC), Scirus and IEEE.

CNS DRUGS INDUCED OCULAR ADVERSE EFFECTS

Since the drugs acting on the CNS are supposed to cross the blood-brain-barrier (BBB), it is quite natural for them to precipitate side effects on the neural system. Even though the retina originates as a direct projection of the optic stalk during early development, most of the drugs are prevented from entering into the ocular compartment by the additional presence of transporters both on the posterior and anterior side. However, prescribed central nervous system medications are reported to produce numerous diverse and unwanted ocular side effects to patients.

SEDATIVE-HYPNOTICS

Barbiturates were popularly used as hypnotics and sedatives earlier, but in the recent times they are not widely used to promote sleep or to calm patients. It generally produces dose-dependent effects like depression, sleep, anesthesia and coma. They cause systemic adverse effects like ptosis, nystagmus, mydriasis, glare, extraocular palsies, bilateral blindness, optic neuropathy, and cortical blindness.[7,8]

Table 1: Sedative-Hypnotics induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Alprazolam	Anxiety	Blurred vision, Diplopia, Burning, Tearing, Allergic conjunctivitis, Angle Closure Glaucoma (ACG), Decreased corneal reflex and accommodation
Clonazepam	Anxiety, Epilepsy	Blurred vision, Diplopia, Burning, Tearing, Allergic conjunctivitis, Retinopathy, Angle Closure Glaucoma (ACG), Decreased corneal reflex and accommodation, Loss of eyelashes or eyebrows
Chlordiazepoxide	Anxiety	Decreased depth perception
Chloral hydrate	Anxiety	Decreased convergence, Miosis, Lilliputian hallucination, Lid edema, Ocular hyperemia, Ocular chemosis[9,10]
Clorazepate	Anxiety, Acute alcohol withdrawal, Epilepsy	Decreased corneal reflex
Diazepam	Anxiety, Epilepsy	Allergic conjunctivitis, Blurred vision, Dry eye, Diplopia, Decreased accommodation, Mydriasis, Retinal hemorrhage, Pupil-block glaucoma, Visual field defects, Abnormal EOG, Brown lens opacification
Lorazepam	Anxiety, Epilepsy	Blepharospasm, Colour vision defect
Midazolam	Anxiety	Blurred vision, Diplopia, Burning, Tearing, Miosis, Allergic conjunctivitis, Angle Closure Glaucoma (ACG), Decreased corneal reflex and accommodation
Oxazepam	Anxiety	Colour vision defect, Epicanthal folds, Slant eyes
Phenobarbitone	Insomnia, Anxiety	Ptosis, Nystagmus, Mydriasis, Cycloplegia, Colour vision, Glare, Extraocular palsies, Blepharoclonus, Bilateral blindness, Optic neuropathy[7,8]
Thiopental	Anxiety	Cortical blindness, Swelling of eyelids

Benzodiazepines (BDZs) are mainly used in anxiety and acts as a replacement for barbiturate derivatives as a hypnotic and sedative. Diazepam, the prototype of anti-anxiety drugs causes different ocular side effects when administered via systemic route. Upon withdrawal of the medication, ocular symptoms are reduced. Diazepam mainly causes retinal hemorrhage, pupil-block glaucoma, visual field defects, and brown lens opacification. Continued administration of benzodiazepines produces blurred vision, diplopia, burning sensation, and allergic conjunctivitis. Lorazepam and Oxazepam cause color vision defects. Decreased convergence, miosis, hallucination, lid edema, ocular hyperemia and ocular chemosis are common in systemic administration of chloral hydrate. Alprazolam, clonazepam and midazolam produces angle closure glaucoma (Table 1).[9,10]

ETHYL AND METHYL ALCOHOL

Methanol intoxication produces toxic injury to the retina and optic nerve resulting in blindness. Toxic exposure to methanol typically leads to the development of formic

acid, metabolic acidosis, visual toxicity, coma and in extreme cases death has also been documented.[11] Visual disturbances generally develop between 18 and 48hrs after methanol ingestion and range from hazy or blurred vision to complete blindness. Both acute and chronic methanol exposure has been shown to produce retinal dysfunction and optic nerve damage clinically and in experimental animal models.[12] Local effects of alcohol eyeballing include pain, burning, blurred vision, conjunctive injection, corneal ulcers or scarring, permanent vision damage and eventually blindness. Ethanol-induced disruption of the median ventral telencephalon, a key site for the expression of ocular morphogens such as sonic hedgehog pathway was further established (Table 2).[13]

ANTIEPILEPTIC DRUGS

Epilepsy is another major class of disorders treated with a wide range of CNS medications. Diplopia, blurred vision, nystagmus, extraocular muscle palsies, disturbances in eye movement and color disturbances have frequently been reported as the side effects of anti-epileptic drugs. This association was consistently higher in patients who take carbamazepine for neuropathic pain. Loss of vestibulo-ocular reflexes are seen with acute supratentorial lesions.[21] Carbamazepine has been associated with a reduced color vision and reduced vision contrast sensitivity. Nystagmus, diplopia and extraocular muscle palsies have also been reported when carbamazepine is used in the treatment of epilepsy. In-utero exposure to carbamazepine has resulted in congenital ocular malformations in the fetus.[22]

The mechanism underlying ophthalmoplegia may be related to the ability of phenytoin to potentiate inhibitory synapses in the vestibulo-oculomotor pathway which utilize GABA. Vigabatrin is extensively used for the treatment of partial seizures.[22] Vigabatrin is known to cause visual field defects in approximately one-third of the patients treated. As a result of retinal toxicity, visual field defects have been reported with phenytoin and carbamazepine. Bilateral concentric visual field loss and color vision defects have also been reported with valproic acid.

Table 2: Ethyl and methyl alcohol induced ocular side effects.

Name of the drug	Treatment/Use	Ocular adverse effects
Ethanol	Methanol poisoning	Toxic neuropathy, toxic amblyopia, diplopia, nystagmus, mydriasis, colour vision (blue-yellow or red-green) defect, visual hallucinations, Abnormal ERG or VEP, corneal deposits, ocular teratogenic effects, cataract[14-16]
Fomepizole	Methanol poisoning	Toxic neuropathy, diplopia[17]
Methanol	Used as a solvent, Antifreeze agent	Blurred vision, optic neuropathy, blindness, visual field defects, irritation[18-20]

Table 3: Antiepileptic drugs induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Benzodiazepine (Lorazepam, Clonazepam, Clobazam and Diazepam)	Epilepsy	Blurred vision, electroretinogram (ERG) and visual evoked potential (VEP) changes, maculopathy, improved nystagmus, diplopia, burning, tearing, allergic conjunctivitis, angle-closure glaucoma, decrease corneal reflex and accommodation, impaired contrast sensitivity
Carbamazepine	Epilepsy, Trigeminal neuralgia	Allergic conjunctivitis, photosensitivity, Colour vision (blue perception decreased), blurred vision, ocular teratogenic effects, decreased accommodation and convergence, diplopia, ptosis, lateral or downbeat nystagmus
Ethosuximide Methsuximide	Epilepsy	Dyskinesia, photophobia, myopia, decreased vision, visual hallucinations, periorbital edema, hyperemia, angioedema and allergic reaction in eyelids or conjunctiva
Ethotoin	Epilepsy	Diplopia, nystagmus, photophobia
Ezogabine or Retigabine	Epilepsy	Diplopia, blurred vision, retinal pigmentation, blue pigmentation in eyelids, conjunctiva and sclera
Felbamate	Epilepsy	Diplopia, nystagmus
Gabapentin	Epilepsy	Blurred vision, nystagmus, diplopia, visual disturbances/ hallucination, conjunctivitis in eyelids or conjunctiva.

Continued.

Name of the drug	Treatment	Ocular adverse effects
Lamotrigine	Epilepsy	Blurred vision, nystagmus, diplopia, photosensitivityand conjunctivitis in eyelids or conjunctiva.
Levetiracetam	Epilepsy	Diplopia
Oxcarbazepine	Epilepsy	Diplopia, blurred vision
Phenytoin	Epilepsy	Allergic conjunctivitis, cataract, colour vision, blurred vision, secondary angle closure glaucoma, downbeat nystagmus, ocular hyperemia, macular edema, mydriasis, decreased accommodation, orbital or periorbital pain, abnormalities of ERG, ulceration and allergic reaction in eyelids or conjunctiva, ocular teratogenic effects (fetal hydantoin syndrome), glare phenomenon
Primidone	Epilepsy	Diplopia, nystagmus, decreased accommodation, dry eye, ocular teratogenic effects, photophobia[24]
Tiagabine	Epilepsy	Abnormal color perception, blurred vision, nystagmus, diplopia
Topiramate	Epilepsy, Migraine	Mydriasis, visual field defects, decreased vision, diplopia, nystagmus, increased IOP, shallow of anterior chamber, acute glaucoma, ocular hyperemia
Valproate sodium (Valproic acid)	Epilepsy	Oculomotor disturbances, abnormal colour perception, oscillopsia, altered VEPS, ocular teratogenic effect
Vigabatrin	Epilepsy	Diplopia, nystagmus, peripheral visual field loss - tunnel vision and scotoma, colour perception abnormalities, retinal abnormalities, optic nerve pallor, visual electrophysiological changes (ERG and EOG), hypo pigment spots in retina, reduced contrast sensitivity, reduced ocular blood flow
Zonisamide	Epilepsy	Decreased vision, nystagmus, diplopia, visual hallucination,

Table 4: General anaesthetics induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Ether (Diethyl ether)	Inhalational anesthesia, Analgesic	Decreased IOP, conjunctivitis, corneal opacity, blindness[25]
Methoxyflurane	Inhalational anesthesia	Flecked retinal syndrome[26]
Nitrous oxide	Inhalational anesthesia	Pupillary changes, changes in ERG, visual loss, intravitreal bubble, irreversible blindness, increase in IOP[27, 28]
Ketamine	Intravenous anaesthesia	Diplopia, visual stimulation, changes in visual perception, transient blindness, corneal edema, bilateral optic neuritis, visual hallucinations, horizontal nystagmus, abnormal eye movement, increased IOP[29-32]
Propofol	Intravenous anesthesia	Blurred vision, diplopia, nystagmus, change in IOP, Inability to open the eye, keratitis, transitory loss of ocular or periocular muscle movements[33-35]

Lamotrigine was found to produce dose-dependent oculogyric crises in patients with no pre-existing movement disorders.[23] Topiramate may have GABAergic effects on the visual field. Other adverse effects include ocular dystonia, uveal tract disorders, myopia, eye movement disorders, color abnormalities and reduced contrast discrimination. Neuro-ophthalmologic manifestations such as myokymia are rarely reported. Compression of the trochlear nerve is characterized by attacks of monocular oscillopsia and superior oblique myokymia caused by oxcarbazepine. Oculomotor disturbances, abnormal color perception, oscillopsia, altered visual evoke potentials (VEPs) and ocular teratogenic effects were documented in epilepsy treatment with sodium valproate. Primidone causes diplopia, nystagmus, decreased accommodation, dry eye, ocular teratogenic effects and photophobia (Table 3).[24]

GENERAL ANAESTHETICS

Inhalational anesthetic agents cause changes in intraocular pressure, conjunctivitis, corneal opacity, blindness, changes in electroretinogram (ERG) and intravitreal bubble. Diplopia, blurred vision, changes in intraocular pressure (IOP), visual hallucination, different types of nystagmus, corneal edema and difficulty in opening the eyes were documented as side effects when anesthetics were used intravenously (Table 4).

LOCAL ANESTHETICS

Lidocaine causes visual hallucination, color vision defect, mydriasis, decreased vision, cataract, extraocular nerve palsy, central scotomas, macular ischemia, diplopia, transient bilateral blindness, ptosis, mild increase in IOP and retinopathy (Table 5).

Table 5: Local anaesthetics induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Cocaine	Local anaesthesia	Mydriasis, visual hallucination, corneal anaesthesia, keratitis, corneal ulceration, retinal emboli, retinal venous occlusion[36]
Lidocaine	Local anesthesia	Visual hallucination, colour vision defect, mydriasis, decreased vision, toxicity to lens and corneal epithelium, cataract, extraocular nerve palsy, central scotomas, macular ischemia, diplopia, bilateral transient blindness, ptosis, slight increase in IOP, retinopathy[37-39]
Procaine	Local anesthesia	Transient loss of vision

SKELETAL MUSCLE RELAXANT

Depolarizing agent succinylcholine can cause increase in IOP within 20-30 sec, this short time elevation of IOP being less in the normal eye.[40] Administration of succinylcholine causes eyelid retraction due to direct action on the Muller's muscle, which lasts for five minutes (Table 6).[41]

Table 6: Skeletal muscle relaxant induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Succinylcholine	Relaxation of skeletal muscles	Increased IOP, Diplopia, allergic reaction in eyelids or conjunctiva, acute glaucoma

ANTIPSYCHOTIC DRUGS (NEUROLEPTICS)

Antipsychotics are known to produce several visual adverse effects such as mydriasis, ocular dystonia, angle-closure glaucoma, uveal tract disorders, eye movement disorders and abnormality in color perception.[42]

Phenothiazine-derivative drugs are one of the widely prescribed CNS drugs. They are used as pre-anesthetic medication, which is used to alleviate anxiety and provide additional sedation by synergizing the actions of co-administered sedatives or analgesics. However, eyelid and keratoconjunctivitis disorders are widely reported as side effects.[43] Phenothiazines are known to cause abnormal pigmentation of eyelids, cornea, and conjunctiva. It also results in corneal edema leading to visual impairment and retinopathy. Lenticular opacification and retinopathy are reported in chronic administration of chlorpromazine and thioridazine.

Topiramate was initially used to treat epilepsy in children later it was known to enhance GABA transmission and cure cases of bipolar disorder.[22] This drug may also have the GABAergic effect on the visual field. Angle-closure glaucoma and uveal tract problems are the most frequent adverse effects seen with many typical antipsychotics and selective serotonin reuptake inhibitors [SSRIs].[43] Dry eye, oculogyric crisis and retinal vein occlusion are well documented adverse drug effects of treatment with atypical antipsychotic drugs (Table 7).[44,45]

HALLUCINOGENS AND ANTI-MANIC INDUCED OCULAR SIDE EFFECTS

Lysergic acid diethylamide (LSD) and other related drugs cause blurring of vision, the imagery of patterns, fog, smoke which fills the visual field, image size and shape distortion, heightened colors, false perception of movement and trailing phenomenon (Table 8a).[50]

Lithium is one of the principle drugs used for the treatment of depression. This drug is associated with keratin deposits on the cornea. It affects sodium transport and causes eye irritation (Table 8b).[59]

ANTIDEPRESSANT AND ANTI ANXIETY DRUGS

Depression is one of the most common mental health disorders characterized by the absence of a positive effect, low mood and a range of associated emotional, cognitive, physical and behavioral symptoms. Antidepressant agent isocarboxazid causes photophobia, mydriasis, diplopia, strabismus, colour vision defects and red-green defects.[61]

Tricyclic antidepressants (TCAs) induce accommodation interference and blurred vision. Patients with narrow iridocorneal angles also experience glaucomatous attacks while using these drugs. Uveal tract problems, mydriasis and angle closure glaucoma are caused by the administration of TCAs and selective serotonin reuptake inhibitors (SSRIs).[43]

Antidepressants may have an impact on the course of eye dryness. Schirmer's test was performed without prior instillation of topical anesthesia to the ocular surface, and the wetting result was recorded for each eye. Bilateral acute angle closure caused by supraciliary effusions was associated with venlafaxine intake. Pendular nystagmus is also reported to venlafaxine overdose and its importance in the recognition of serotonin syndrome (Table 9).[62]

OPIOID ANALGESICS AND ANTAGONISTS

The first description of Italian cases of nystagmus related to the use of methadone during pregnancy underlines the

importance of a careful investigation of drug use in pregnancy in cases of unexplained congenital nystagmus. Impaired eye-tracking skills in 4-year old children exposed to methadone or buprenorphine and tobacco prenatally could inhibit the development of some cognitive functions in later life.[66]

Morphine stimulates the retinogeniculate cortex pathway, thalamus-cortical circuit through the opioid receptors and fentanyl stimulates the thalamus cortical circuit through the opioid receptors. It can therefore, be assumed that visual evoked potential (VEP) is a useful tool for examining the side effects of drugs, including narcotics, on the visual system.

Table 7: Antipsychotic drugs induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Aripiprazole	Schizophrenia	Oculogyric crisis, blepharospasm, myopia, mydriasis
Chlorpromazine	Schizophrenia	Abnormal pigmentation of eyelids, cornea and conjunctiva, visual impairment and retinopathy, anterior lens stellate cataract.[46]subcapsular dust-like granular deposits-whitish to yellowish brown in the pupillary area and blue-yellow color vision. Retrobulbar injections→ secondary diffuse orbital fibrosis and neurotrophic corneal ulcer[47]
Fluphenazine	Schizophrenia	Bilateral maculopathy
Thioridazine	Schizophrenia	Retinal pigment epithelial atrophy, bull's eye changes, cataract, lenticular opacification
Clozapine Loxapine	Schizophrenia	Nystagmus, ptosis, oculogyric crises, decreased vision, mydriasis,
Haloperidol	Schizophrenia	Mydriasis, decreased vision, visual hallucination, decreased IOP, subcapsular cataracts, myopia, allergic reactions in eyelids or conjunctiva, oculogyric crises[48]
Pimozide	Schizophrenia	Keratoconjunctivitis sicca, blurred vision, visual hallucination, oculogyric crises[49]
Quetiapine fumarate	Schizophrenia, Bipolar disorder	Dry eye, oculogyric crisis[44], retinal vein occlusion[45]
Tiotixene or Thiothixene	Schizophrenia	Blurred vision, mydriasis, corneal or lens deposits, photosensitivity[49]

Table 8a: Hallucinogens induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Lysergic acid diethylamide (LSD)	To alter mood and Behaviour	Diplopia, cycloplegia, mydriasis, visual hallucination, palinopsia, irreversible impairment of color vision defect, cataract, corneal opacities, macular damage, ocular teratogenic effects[51-53]
Phencyclidine	To alter mood and Behaviour	Nystagmus, decreased corneal reflux, visual hallucinations, visual defects, miosis, ptosis[54]
Ecstasy (3, 4 Methylenedioxymethamphetamine (MDMA))	To alter mood and Behaviour	Acute bilateral angle closure, transient myopia, bilateral ciliochoroidal effusions[55]
^{9}ΔTetrahydrocannabinol (^{9}Δ THC) (Marijuana)	To alter mood and Behaviour	Bright spots flickering effect, Intermittent light phenomena, strobe-like effects, irreversible disruption of a classic eye blink, visual hallucination, photosensitivity, nystagmus, decrease in IOP visual acuity[56-58]

Table 8b: Anti-manic drug-induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Lithium carbonate	Acute Mania	Contact lens intolerance, downbeat jerk nystagmus, decreased accommodation, cycloplegia, blurred vision, papilledema, abnormal EOG or VEP, decreased dark adaptation, visual hallucination, exophthalmos, vertical or lateral far-gaze diplopia, epiphora[60]

Table 9: Antidepressant and anti-anxiety drugs induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Amitriptyline, clomipramine, doxepin, imipramine, trimipramine	Depression, Psychoneurotic anxiety	Cycloplegia, dry eye, diplopia, mydriasis, increased IOP, toxic amblyopia, pupil-block glaucoma, visual hallucination, nystagmus, retinal pigments abnormalities, retinal damage
Amoxapine, desipramine, nortriptyline,	Depression	Blurred vision, photophobia, visual hallucinations, mydriasis, floppy iris syndrome
Citalopram, fluoxetine, fluvoxamine, paroxetine sertraline (SSRIs)	Depression	Blurred vision, photophobia, abnormal ocular sensations, increased eye movements during sleep, anisocoria, diplopia, dry eye, angle-closure glaucoma, maculopathy, mydriasis, oculogyric crisis
Isocarboxazid	Depression	Photophobia, blurred vision, mydriasis, colour vision defects (red-green defects)
Pheniprazine	Depression, Angina pectoris Schizophrenia	Amblyopia, optic neuritis, colour vision (red-green discrimination)
Trazodone	Depression	Visual hallucinations, decreased vision, diplopia, palinopsia[63], keratoconjunctivitis sicca, angle closure glaucoma[64,65]
Venlafaxine	Depression	Blurred vision, bilateral acute angle closure, pendular nystagmus

Table 10: Opioid analgesics and antagonists induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Codeine	A cough	Miosis, decreased vision, transient myopia, lid dermatitis, iritis, ophthalmoplegia, angioedema in eyelids or conjunctiva[68-69]
Hydromorphone, Oxymorphone	Moderate to Severe pain	Miosis, allergic reaction, decreased vision, visual hallucination[70-71]
Heroin	Cancer pain	Miosis, ocular irritation, changes in the conjunctiva, exotropia, talc retinopathy[72-74]
Morphine	Cancer pain	Miosis, pinpoint pupils, iritis, colour vision, visual field changes, visual hallucination, vertical nystagmus, eyelid pruritus[69,74-77]
Methadone	A cough	Miosis, pinpoint pupils, talc retinopathy, cortical blindness, strabismus, decreased vision[72, 74, 78-80]
Naloxone	Narcotic antagonist	Miosis, vivid visual hallucinations, pupillary changes, erythema multiforme, ophthalmoplegia, photosensitivity[69, 81]
Opium	Cancer pain	Miosis, iritis
Pentazocine	Adjuvants, Narcotic antagonist	Miosis, vivid visual hallucination, diplopia[82]
Pethidine	Analgesics, Preanesthetic medication	Miosis, decrease in IOP, blepharitis, conjunctivitis, visual hallucination[83]

These results suggest that biochemical mechanisms related to nitric oxide release are involved, at least in part, in morphine effects on the eye. It may be possible that μ-opioid receptors are involved in morphine-induced miosis and reduction in IOP (Table 10).[67]

CNS STIMULANTS AND COGNITION ENHANCERS

Intravenous injection of caffeine was found to increase intraocular pressure (IOP). Caffeine was found to have a positive association between their intake and elevation in intraocular pressure in patients with open-angle glaucoma. Cocaine causes talc retinopathy and epithelial defects.[61]

Methylphenidate hydrochloride is the drug of choice for treatment of attention deficit hyperactivity disorder (ADHD). However, an association of methylphenidate with glaucoma has been reported (Table 11).

Table 11: CNS stimulants and cognition enhancers induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Caffeine	CNS stimulant, Migraine, Apnoea in premature infant	Increase in IOP
Cocaine	CNS stimulant	Mydriasis, retinal emboli, keratitis, retinal venous occlusion, orbital disease, visual hallucination, decreased vision, myopia
Dexmethylphenidate	Attention deficit hyperactivity disorder (ADHD)	Blurred vision, visual changes
Methylphenidate	Concentration & Attention defects	Mydriasis, urticaria in eyelids or conjunctiva, decrease accommodation, blurred vision, visual hallucination, diplopia, mydriasis, talc retinopathy
Methamphetamines	CNS stimulant	Mydriasis, retinal venous occlusion, keratitis, corneal ulceration, intra-retinal hemorrhage, talc retinopathy, visual hallucination
Memantine	Cognition enhancer	Worsening or de novo visual hallucination[84]
Rivastigmine	Cognition enhancer	Subconjunctival hemorrhage[85]
Tacrine	Cognition enhancer	Diplopia

ANTI-PARKINSONIAN DRUGS

Blurred vision, increased eye blinking or twitching symptoms were observed in parkinsonian patient's administration with a combination of levodopa and carbidopa (Table 12).

Table 12: Anti-parkinsonian drugs induced ocular side effects.

Name of the drug	Treatment	Ocular adverse effects
Levodopa+ Carbidopa	Parkinson symptoms	Blurred vision, greatly increased eye blinking/ twitching

CONCLUSION

Ocular adverse events are newly identified in this decade and mostly come from systemic drugs some of which are existent in the market for several years. These systemically administered drugs reach CNS area and cause several certain, probable and possible ocular side effects or symptoms such as blurred vision, diplopia, cataract, glaucoma, optic retinopathy, colour vision defect, visual hallucination, abnormality of the electroencephalogram (EEG) and electroretinogram (ERG), altering intraocular pressure and pupil sizes. On discontinuing the medication further damage or toxicity to the eyes can be avoided, but some cases may take time to reverse to normality even after drug discontinuation.[86] Ophthalmologists and paramedical members should be aware of the ophthalmic medication induced side effects/ adverse effects and examine the entire eye tissues effectively and periodically and should discuss with the patients regarding drug induced ocular sideeffects or symptoms before initiating the therapy. This could possibly prevent their progression which can end up in visual impairment. Therefore, there is a need for an early warning system where prescribers can share their experiences of potential ocular reactions. The first stage should involve setting up of a registry for reporting of drug induced ocular side effects.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Deichmann WB, Henschler D, Holmstedt B, Keil G. What is there that is not poison? A study of the third defense by Paracelsus. Archives of Toxicology. 1986;58:207-13.
2. Jaanus SD, Bartlett JD, Hiett, JA. Ocular effects of systemic drugs. In: Bartlett JD and Jaanus SD, eds. Clinical Ocular Pharmacology, 3rd ed. Boston: Butterworth-Heinemann. 1995;957-1006.
3. Koneru PB, Lien EJ, Koda RT. Review: Oculotoxicities of systemically administered drugs. J Ocular Pharm. 1886;2(4):385-99.
4. Mycek MJ, Harvey RA, Champe PC. Lippincott's Illustrated Reviews: Pharmacology, 2nd ed. Philadelphia: Lippincott-Raven. 1997.
5. Muchnick BG. The ocular manifestations of systemic drugs. Optom Today. 1998;44-52.

6. Bartlett JD. Ophthalmic toxicity by systemic drugs. In: GCY Chiou, ed. Ophthalmic Toxicology, 2nd ed. Michigan: Taylor and Francis. 1999;225-83.
7. Hamburger E: Identification and treatment of barbiturate abusers, JAMA. 1965;193:143-4.
8. Homma K, Wakakura M, Ishikawa S. A case of phenobarbital-induced optic neuropathy, Neuro-Ophthalmol. 1989;9(6):357-9.
9. Levy DL, Lipton RB, Holzman PS. Smooth pursuit eye movements: effects of alcohol and chloral hydrate, J Psychiatr Res. 1981;16:1-11.
10. Mowry JB, Wilson GA. Effect of exchange transfusion in chloral hydrate overdose, Vet Human Toxicol. 1983;25(Suppl 1):15.
11. Kavet R, Nauss KM. The toxicity of inhaled methanol vapors. Critical reviews in toxicology. 1990;21:21-50.
12. Sharpe JA, Hostovsky M, Bilbao JM, Rewcastle NB. Methanol optic neuropathy: a histopathological study. Neurology. 1982;32:1093-100.
13. Lantz CL, Sipe GO, Wong EL, Majewska AK, Medina AE. Effects of Developmental Alcohol Exposure on Potentiation and Depression of Visual Cortex Responses. Alcohol ClinExp Res. 2015;39:1434-42.
14. Wang S, Wang JJ, Wong TY. Alcohol and eye disease, SurvOphthalmol. 2008;53(5):512-25.
15. Kanthan GL, Mitchell P, Burlutsky G. Alcohol consumption and the long-term incidence of cataract and cataract surgery: the blue mountain eye study, Am J Ophthalmol. 2010;150(3):434-40.
16. Knudtson MD, Klein R, Klein BE. Alcohol consumption and the 15-year cumulative incidence of age-related macular degeneration. Am J Ophthalmol. 2007;143(6):1026-9.
17. Brent J, Mc Martin K, Phillips S. Fomepizole for the treatment of methanol poisoning, N Engl J Med. 2001;344(6):424-9.
18. Dethlefs R, Naragi S. Ocular manifestations and complications of acutemethyl alcohol intoxication, Med J Aust. 1978;4(10):483-5.
19. Barceloux DG, Bond GR, Krenzelok EP. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning, J Toxicol Clin Toxicol. 2002;40(4):415-6.
20. Desai T, Sudhalkar A, Vyas U. Methanol poisoning: predictors ofvisual outcomes, JAMA Ophthalmol. 2013;131(3):358-64.
21. Horiguchi J, Inami Y. Effect of clonazepam on neuroleptic-induced oculogyric crisis. ActaPsychiatr Scand. 1989;80:521-3.
22. Hilton EJ, Hosking SL, Betts T. The effect of antiepileptic drugs on visual performance. Seizure, 2004;13:113-28.
23. Veerapandiyan A, Gallentine WB, Winchester SA, Baker J, Kansagra SM, Mikati MA. Oculogyric crises secondary to lamotrigineoverdosage. Epilepsia. 2011;52:4-6.
24. Marino D, Malandrini A, Rocchi R. Transient "sicca syndrome" during phenobarbital treatment, NeurolSci. 2011;300(1–2):164.
25. Tripathi RC, Tripathi BC. The Eye. In Riddell RH, editor: Pathology of Drug-Induced and Toxic Diseases, New York, 1982, Churchill Livingstone. 1982;377-450.
26. Bullock JD, Albert DM. Flecked retina. Arch Ophthalmol. 1975;93:26-31.
27. Lockwood AJ, Yang YF. Nitrous oxide inhalation anaesthesia in the presence of intraocular gas can cause irreversible blindness. Br Dent J. 2008;204(5):247-8.
28. Fenwick PB, Stone SA, Bushman J. Changes in the pattern reversalvisual evoked potential as a function of inspired nitrous oxideconcentration, Electroen-cephalogr Clin Neurophysiol. 1984;57:178-83.
29. Starte JM, Fung AT, Kerdraon YA. Ketamine-associated corneal edema. Cornea. 2012;31(5):572-4.
30. Fine J, Weissman J, Finestone SC. Side effects after ketamine anesthesia: transient blindness, AnesthAnalg. 1974;53:72-4.
31. Drayna PC, Estrada C, Wang W. Ketamine sedation is not associated with clinically meaningful elevation of intraocularpressure, Am J Emerg Med. 2012;30(7):1215-8.
32. Fantinati S, Casarotto R. Bilateral retrobulbar neuritis after general anesthesia, Ann Ophthalmol. 1988;114:649.
33. Ameen H. Can propofol cause keratitis? Anaesthesia. 2001;56:1017-8.
34. Neel S, Deitch R, Moorthy SS. Changes in intraocular pressure during low dose intravenous sedation with propofol before cataract surgery. Br J Ophthalmol. 1995;79:1093-7.
35. Reddy MB. Can propofol cause keratitis? Anesthesia. 2002;57:183-208.
36. Ghosheh FR, Ehlers JP, Ayres BD. Corneal ulcers associated with aerosolized crack cocaine use. Cornea. 2007;26:966-9.
37. Lemagne JM, Michiels X, Van Causenbroeck S. Purtscher-like retinopathy after retrobulbar anesthesia, Ophthalmol. 1990;97(7):859-61.
38. Sawyer RJ, von Schroeder H. Temporary bilateral blindness after acute lidocaine toxicity, AnesthAnalg. 2002;95:224-6.
39. Han SK, Kim JH, Hwang J-M. Persistent diplopia after retrobulbar anesthesia, J Cataract Refract Surg. 2004;30:1248-53.
40. Robinson R, White M, McCann P. Effect of anesthesia on intraocular blood flow. Br J Ophthalmol. 1993;75:92-3.
41. Eldor J, Admoni M. Acute glaucoma following nonophthalmic surgery, Isr J Med Sci. 1989;25:293-4.
42. Jaanus SD. Ocular side effects of selected systemic drugs. OptomClin. 1992;2:73-96.
43. Richa S, Yazbek JC. Ocular adverse effects of common psychotropic agents: a review. CNS drugs. 2010;24:501-26.
44. Ghosh S, Bhutan D. Oculogyric crisis with quetiapine: a case report. 14th World Congress of Psychiatry 894 abstr. 2008;1-168.

45. Yong KC, Kah TA, Ghee YT. Branch retinal vein occlusion associated with quetiapine fumarate. BMC Ophthalmol. 2011;11(1):24.
46. Kanaski JJ. Clinical diagnosis in ophthal. Elsevier. 2006.
47. Cotliar JM, Shields CL, Meyer DR. Chronic orbital inflammation and fibrosis after retrobulbar alcohol and chlorpromazine injections in a patient with choroidal melanoma, Ophthal Plast Reconstr Surg. 2008;24(5):410-1.
48. Isaac NE, Walker AM, Jick H. Exposure to phenothiazine drugs and risk of cataract, Arch Ophthalmol. 1991;109:256-60.
49. Physician's Desk Reference, ed 60, Montvale NJ. Thomson PDR. 2006;2124-5.
50. Firht AY. Ocular sequelae from the illicit use of class A drugs. Br I Orthop J. 2004;1:10-8.
51. Abraham HD: A chronic impairment of colour vision in users of LSD, Br J Psychiatry. 1982;140:518-20.
52. Kawasaki A, Purvin V. Persistent palinopsia following ingestion of lysergic acid diethylamide (LSD), Arch Ophthalmol. 1996;114:47-50.
53. Halpern JH, Pope HG. Hallucinogen persisting perception disorder: what do we know after 50 years?, Drug Alcohol Depend. 2003;69:109-19.
54. Cox D, Jufer Phipps RA, Levine B. Distribution of phencyclidine into vitreous humor, J Anal Toxicol. 2007;31(8):537-9.
55. Kumar RS, Grigg John, Farinelli AC. Ecstasy induced acute bilateral angle closure and transient myopia. Br J Ophthalmol. 2007;91:693-5.
56. Huestegge L, Kunert HJ, Radach R. Long-term effects of cannabis on eyemovement control reading, Psychopharmacol. 2010;209(1):77-84.
57. Levi L, Miller NR. Visual illusions associated with previous drug abuse,FClin Neuro-ophthalmol. 1990;10:103-10.
58. Semple DM, Ramsden F, McIntosh AM. Reduced binocular depthinversion in regular cannabis users, PharmacolBiochemBehav. 2003;25:789-93.
59. Hiroz CA, Assimacopoulos T, Cuendet JF, Calanca A, Carron R. [Ophthalmological side effects of lithium (author's transl)]. L'Encephale. 1981;7:123-8.
60. Fraunfelder FT, Fraunfelder FW, Jefferson JW. Monograph: the effects oflithium on the human visual system, J Toxicol Cut Ocular Toxicol. 1992;11:97-169.
61. Fraunfelder FT, Fraunfelder FW, Chambers WA. Clinical Ocular Toxicology: Drug-Induced Ocular Side Effects. Philadelphia, USA: Elsevier Health Sciences. 2008.
62. Varatharaj A, Moran J. Pendularnystagmus associated with venlafaxine overdose: a formefruste of the serotonin syndrome?. BMJ Case Rep. 2014;1-2.
63. Hughes MS, Lessell S. Trazodone-induced palinopsia, Arch Ophthalmol. 1990;108:399-400.
64. Chi-un P, Chang-uk L, Soo-Jung L. Association of low dose trazodone treatment with aggravated angle-closure glaucoma, Psychiatry ClinNeurosci. 2003;57:127-9.
65. Pae C-U, Lee C-U, See S-J. Association of low dose trazodone treatment with aggravated angle-closure glaucoma, Psych Clin Neuros. 2003;57:127-8.
66. Melinder A, Konijnenberg C, Sarfi M. Deviant smooth pursuit in preschool children exposed prenatally to methadone or buprenorphine and tobacco affects integrative visuomotor capabilities. Addiction. 2013;108:2175-82.
67. Bonfiglio V, Bucolo C, Camillieri G, Drago F. Possible involvement of nitric oxide in morphine-induced miosis and reduction of intraocular pressure in rabbits. Eur J Pharmacol. 2006;534:227-32.
68. El-Mallakh RS. Internuclear ophthalmoplegia with narcotic overdosage, Ann Neurol. 1986;20:107.
69. Nomof N, Elliott HW, Parker KD. The local effect of morphine, nalorphine, and codeine on the diameter of the pupil of the eye, ClinPharmacolTher. 1968;9:358-64.
70. De Cuyper C, Goeteyn M. Systemic contact dermatitis from subcutaneous hydromorphone, Contact Dermatitis. 1992;27(4):220-3.
71. Gilman AG, Goodman LS, Gilman A, editors. The Pharmacological Basis of Therapeutics, ed 6, New York, 1980, Macmillan. 1980;495-511.
72. Firth AY. Heroin and diplopia. Addiction. 2005;100:46-50.
73. Rizzo M, Corbett J. Bilateral internuclear ophthalmoplegia reversed by naloxone, Arch Neurol. 1983;40:242-3.
74. Firth AY. Heroin and diplopia. Addiction 200;100:46-50.
75. Fish DJ, Rosen SM. Epidural opioids as a cause of vertical nystagmus. Anesthesiology. 1990;73:785-6.
76. Henderson RD, Wijdicks EF. Downbeat nystagmus associated with intravenous patient-controlled administration of morphine. AnesthAnalg. 2000;91:691-2.
77. Castano G, Lyons CJ. Eyelid pruritus with intravenous morphine, J AmAssocPediatrOphthalmol Strabismus. 1999;3(1):60.
78. Gupta M, Mulvihill AO, Lascaratos G. Nystagmus and reducedvisual acuity secondary to drug exposure in utero: long-term followup. J Ped Ophthalmol Strab. 2012;49(1):58-63.
79. Hamilton R, McGlone L, MacKinnon JR. Ophthalmic, clinical andvisual electrophysiological findings in children born to motherspresscribed substitute methadone in pregnancy, Br J Ophthalmol. 2010;94:696-700.
80. Nelson LB, Ehrlich S, Calhoun JH. Occurrence of strabismus in infants born to drug-dependent women, Am J Dis Child. 1987;141:175-8.
81. Rizzo M, Corbett J. Bilateral internuclear ophthalmoplegia reversed by naloxone. Arch Neurol. 1983;40:242-3.
82. Burstein AH, Fullerton T. Oculogyric crisis possibly related to pentazocine. Ann Pharm. 1983;27(7–8):874-6.
83. Waisbren BA, Smith MB. Hypersensitivity to meperidine. JAMA. 1978;239:1395.

84. Monastero R, Camarda C, Pipia C, Camarda R. Visual hallucinations and agitation in alzheimer's disease due to Memantine: report of three cases. J Neurology Neurosurgery and Psychiatry. 2006;78: 546.
85. Anwar A, Gutting P. Potentiation of warfarin's anticoagulant effect and subconjunctival haemorrhage with rivastigmine transdermal patch. BMJ Case reports. 2010;10:1136.
86. Vijayakumar AR, Velpandian T, Saxena R. Ocular adverse effects of systemically administered drugs. In: Renu Agarwal, Puneet Agarwal, editors. Essential of Ocular Pharmacology, 1stedn. Malaysia: University Publication Centre (UPENA). 2011;343-64.

Cite this article as: Vijayakumar AR, Epison PD, Kabeera BA, Abirami VP, Hussain A, Kader AA, et al. Systemically administered central nervous system drugs induced ocular side effects: a review. Int J Basic Clin Pharmacol 2021;10:748-58.