

Review Article

Bimatoprost Ophthalmic Solution (BOS) 0.3 mg w/v for 1 Open Trial of Long-term Preventive Therapy of Migraine in 3 patients with Pathophysiologic Shift from Brain to Eye

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Abstract

Known since antiquity, migraine is a complex primary disorder, an episodic painful Autonomic Nervous System (ANS) storm, generally following the stress/post-stress phase. Despite exhaustive study of neuropeptides, neurochemicals, molecules, neurogenetics, neuroimaging along with animal and human experiments over the last 50 years, the scientific basis of migraine remains unknown. Straddling eight decades from Cortical Spreading Depression (CSD) to Calcitonin-Gene Related Peptide (CGRP) and its antagonists, exponentially increasing data have failed to create a gestalt synthesis. This article lays cohesive and robust fundamental principles for the comprehension and management of migraine. The continuum between migraine and non-congestive Primary Open-Angle Glaucoma (POAG), Normal Tension Glaucoma (NTG), or Low-Tension Glaucoma (LTG) is advancing. The case of sustained remission of migraine attacks (> 75%) over 3 years - 5 years with ocular hypotensive topical Bimatoprost Ophthalmic Solution (BOS) 0.3% in an N-of-1 trial in 3 patients with refractory migraine is presented. A cause-effect-adaptive process underlies the ANS-stress/post-stress-linked biology of migraine. Vasopressin-serotonin-norepinephrine 'homeostatic-adaptive system' Lowers Intraocular Pressure (IOP), while enhancing anti-stress, antinociception, vasomotor, and behaviour control functions, thereby selectively decreasing algogenic neural traffic in the ophthalmic division of trigeminal nerve (V1), and, raising the threshold to develop migraine. Striking migraine headache-aborting feature of vomiting is also likely linked to a several hundred-fold increase in arginine-vasopressin secretion. Eye-cover tests and self-ocular digital displacement are essential to studying the visual aura. Real-time physical displacement of Scintillating Scotoma (SS) and floating 'stars' is reported. The basis of spontaneous onset and offset, self-limited duration of migraine attacks, as well as female preponderance, and age/menopause decline in prevalence, are elucidated. Intraocular implants with long-term ocular hypotensive effects, including bimatoprost, are the future of migraine management. Controlled trials are required to establish the migraine-preventive effect of topical bimatoprost, a revolutionary advance in neuroscience.

Abbreviations

AH: Aqueous Humor; AMT: Amitriptyline; AN: Anxiety Neurosis; AVP: Arginine Vasopressin; BBB: Blood-Brain Barrier; CM: Chronic Migraine; CSD: Cortical Spreading Depression; NTG: Normal Tension Glaucoma; EA: Ebstein Anomaly; EM: Episodic Migraine; NTG: Nitroglycerine; LTG: Low-Tension Glaucoma; MWA: Migraine with Aura; MwoA: Migraine Without Aura; MO: Morbid Obesity; OAG: Open-Angle Glaucoma; ONH: Optic Nerve Head; POAG: Primary

Open-Angle Glaucoma; RCCT: Randomized Controlled Clinical Trials; RNFL: Retinal Nerve Fibre Layer; m-GCIPL: Macular Ganglion Cell Inner Plexiform Layer; m-RNFL: Macular Retinal Nerve Fibre Layer; p-RNFL: paramacular Retinal Nerve Fibre Layer; RSD: Retinal Spreading Depression; SBP: Systemic Blood Pressure; SD: Spreading Depression; SD-OCT: Spectral Domain Optical Coherence Tomography; V1: Ophthalmic Division of the Trigeminal Nerve; VM: Valsalva Maneuver

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Submitted: September 26, 2023

Approved: November 08, 2023

Published: November 09, 2023


How to cite this article: Gupta VK. Bimatoprost Ophthalmic Solution (BOS) 0.3 mg w/v for 1 Open Trial of Long-term Preventive Therapy of Migraine in 3 patients with Pathophysiologic Shift from Brain to Eye. J Neurosci Neurol Disord. 2023; 7: 134-154.

DOI: 10.29328/journal.jnnd.1001087

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Keywords: Migraine; Psychosocial stress; ANS-dysfunction; Choroido-retinal arterial circulation; Intraocular pressure; Ocular globe; Corneoscleral envelope; Corneoscleral distention; Pan-trigeminal; Ophthalmic division of trigeminal nerve (V1); Mechanical pronociceptive neural traffic; Ocular rigidity; Tamponade; Elasticity; Spontaneous onset; Spontaneous offset; Ebstein anomaly; Congenital heart disease; Morbid obesity; Female preponderance; Age-linked prevalence

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Introduction

Migraine is a common poorly understood typically-protean primary painful disorder characterized by episodic, moderate-to-severe, often pulsating, and more frequently-than-not lateralizing headache (unilateral, bilateral, side-shifting, or side-fixed) associated with photophobia, phonophobia, nausea/vomiting, and sometimes auras (visual or non-visual or both [1-4]. Consistently ranked as one of the most disabling neurological conditions affecting ~20% of the general population, migraines often substantially impairs daily activities (personal, family, social, and professional) as well as quality of life and carries a high economic burden of direct and indirect healthcare costs (emergency care, abortive and preventive therapies, and absenteeism or presenteeism) [1,5,6]. Migraine is currently regarded as a social stigma [7-9]. Migraine has been split into Episodic Migraine (EM) and Chronic Migraine (CM) by the criterion of 15 headache days in a month [10,11]. Such nosologic splitting of migraine is based entirely on symptomatic phenotypic expansion, and is a commonsense-challenging subdivision resulting in exponential accumulation of data without any pathophysiologic insight or matrix/blueprint [11]. Neuronal dysmodulation, central neural plasticity and sensitization are believed to underlie the progression from EM to CM [10-14]. Cross-species circumstantial or indirect evidence, largely from animal experiments (mainly, rodents) with direct extrapolation to humans, form the speculative basis of the currently-favored belief-stimulated pathogenesis of both subtypes of migraine -- EM and CM [11,15,16].

Etiology of migraine, both EM and CM subtypes, however, continues to be elusive and its mechanistic basis remains speculative, with multiple discrete and rather diverse physiologic disease mechanisms being proposed and supported over the last 2 decades – usually as per the *presumed* basis of a few common phenotypic symptoms [1,17-20]. All key elements of migraine have never been incorporated into a single biologically-plausible, robust, generalizable, and overarching gestalt synthesis [11]. Fundamental pathophysiologic difference(s) between Migraine with Aura (MwA) and migraine without aura (MwoA) are also maintained through speculative interpretation of the basis of phenotype, underscoring a prominent dichotomy running between migraine pathophysiology and migraine neuro-pharmacology. No clinically substantial or statistically significant and replicable difference between MwA and MwoA subtypes has been found in their responses to pharmacotherapeutic or non-pharmacotherapeutic strategies. First- and second-line migraine preventive pharmacotherapeutic drugs show comparable efficacy in MwA patients and MwoA patients, thereby not supporting the widely-supported ‘two entity’ research presumption. An extraordinary amount of scientific effort and literature has been devoted to creating, maintaining, and studying the two ‘imaginary’ nosologic subdivisions of migraine, both EM and CM as well as MwA and MwoA. Not surprisingly, statistically significant therapeutic differences between these nosologic subdivisions have been underscored [1-3,10,14,18-29]. These therapeutic assertions of any statistical difference between subdivisions of migraine (EM v/s CM; MwA v/s MwoA) are not clinically valuable or practically useful, and the scientific foundation of the supporting data itself not being are theoretically-robust [11,15,16,30-34]. All therapies in migraine are empirical, including those supported by Randomized Controlled Clinical Trials (RCCTs) [15,16,30,31,35,36]. By a canonical but belief-based general consensus among primary headache researchers over

the last fifty years, migraine is currently believed to originate in a vague dysfunction of the brain that lends no insight into spontaneous onset and offset of protean, periodic onset (cyclic menstrual or non-cyclic non-menstrual), and self-limited duration (4 hours - 72 hours) of headache. Similarly, the scintillating Scotoma (SS) of MwA appears and disappears spontaneously in an equally bizarre and mysterious manner, the time period being foreshortened to 30-60 minutes. The Blood-Brain Barrier (BBB) is not disrupted during migraine attacks [37,38]. Many researchers favour a meningitic basis as the source of migraine headaches; the nature of the meningitic process and its ability to produce unpredictable lateralizing self-limited headaches for decades or a lifetime raises reservations. To the best of my knowledge, the role of the presumed ‘meningitic’ process in the genesis of SS of migraine finds no mention in the literature. Neuronal, vascular, and neurovascular theories have variably prevailed over the last 50 years without any definitive headway [11,15,16] [Gupta 2006]. The chicken-egg controversy has never been solved in migraine: how does cranially-lateralizing headache or SS just appear de-novo, and then spontaneously disappear or resolve by itself?

Seven decades after the chance discovery of Cortical Spreading Depression (CSD) in rodents, key issues remain unsettled. [11,15,16,39] Spreading Depression (SD) has been recently recorded during multimodal neuromonitoring in neurocritical care and is believed to represent a universal principle of cortical lesion development from asphyxia/anoxia to traumatic brain injury; not unexpectedly. therapeutic suppression of SD has been suggested [40,41] There is no link between the pain of migraine headache – the most bothersome symptom – and CSD/SD, as reviewed [11,15,16,35].

Conversely, CSD has well-defined adaptive/homeostatic neuronal protective and vascular preconditioning role in lower mammals, locusts, and *Drosophila* [Box 1].

Migraine, as a co-morbidity, confounds contemporary clinical glaucoma evaluation and management. Migraine has been reported more commonly in Primary Open-Angle Glaucoma (POAG); after adjusting patients’ age and vascular comorbidities, migraineurs were found to have a 1.68 - fold (95% confidence interval, 1.20 - 2.36) greater risk of developing OAG than the comparison cohort [70]. The migraine-POAG link was found in case-control design studies but not in cohort design studies [71]. Association was also noted between migraine and Low-Tension Glaucoma (LTG) [72,73]. Across studies of the migraine-glaucoma continuum, without assessment of visual function dysfunction, a clinically subtle heterogeneity confounds the association, both with POAG and Primary Angle-Closure Glaucoma (PACC), particularly with cross-sectional population-based studies or retrospective analyses of insurance-related databases [74,75]. In an epidemiologic survey with key diagnostic glaucomatous features established by ophthalmologists, including IOP, glaucomatous optic disc cupping, nerve bundle visual field defect, open anterior chamber angles, atrophy of ONH, and no discernible cause of outflow obstruction, migraine prevalence did not significantly differ between high IOP-glaucoma (IOP > 21 mm Hg) and LTG (IOP < 21 mm Hg) patients (22.8% and 32%, respectively) [72].

Migraine attacks are associated with a wide range of visual sensory symptoms [76,77]. In prospective studies, visual performance tests allow a clearer clinical correlation between glaucoma and migraine than cross-sectional epidemiologic or retrospective studies. Growing



Box 1: Adaptive / Homeostatic Effects of Cortical Spreading Depression / Spreading Depression in brain neuronal and vascular function.

1. CSD stimulates hippocampal cell proliferation increasing the number of newborn dentate granule neurons and consistently enhance exploratory behavior and object location memory thereby likely influencing positively hippocampus-dependent cognition and emotion in associated brain pathology [42].
2. SD in insects is associated with environmental stress-induced neural shutdown. Cellular mechanisms of SD in *Locusta migratoria* and *Drosophila melanogaster* have all hallmarks of mammalian SD, and appear to be evolutionarily conserved [43-45].
3. SD-activity induces brain tissue maintenance functional remodeling with a shift of cell fate of NG2-containing progenitor cells (NG2 cells) from oligodendrocytes to astrocytes [46] and cell division of astrocytes in the subpial zone, generating neural precursor-like cells and new immature neurons in the adult cerebral cortex [47].
4. SD is associated with persistent neurogenesis in neurons in caudate putamen and cortex neurons [48].
5. CSD offers vascular-preconditioning / long-lasting brain protection against infarcted lesion development possibly involving excitatory neurotransmission and metabolism, nitric oxide, genomic reprogramming, inflammation, cellular stress response, and neurotropic factors [49-53]. Relative to the striatum and hippocampus, cerebral cortical neurons are particularly protected by CSD-induced tolerance to ischemia with early dose-dependent regional expression of putative neuroprotective proteins, c-fos mRNA, BDNF mRNA, and 72-kDa heat shock protein with increasing number of KCL-induced CSD stimulations [54,55].
6. Glutamate (and potassium) efflux contributes to CSD [56]. Implicated in the pathogenesis of migraine, [57] the role of glutamate in synaptic homeostasis and in migraine-related stress/post-stress neurobiology continues to evolve [58,59].
7. SD not associated with neuronal injury in normal rat brain [60].
8. CSD can occur during elective neurosurgery surgery in a well-regulated physiologic environment in brain regions distant from the immediate operative site, i.e., surgical trauma in the ICU, without any known underlying brain injury or predisposition [61].
9. CSD typically induces prolonged hypesthesia; CSD is not algogenic or aversive, but promotes eating, drinking, exploratory, motivated behavior, and blocks naloxone-induced escape / acute abstinence syndrome to opioids [62-66].
10. CSD suppresses seizure discharge, an intrinsically homeostatic function [67].
11. CSD is unaffected by CGRP-antagonist (fremanezumab or its isotype) which only slows CSD propagation and shortens the cortical recovery period [68]. CGRP, a potent vasodilator, dilates dural arteries, which is effectively blocked by fremanezumab, but CGRP does not dilate pial arteries, pial veins, or dural veins or induce plasma protein extravasation [69]. CSD- induction and systemic CGRP infusion are divergent models for migraine and conclusions drawn from one model may not be true or relevant to the other [69].

Other favoured pathophysiological hypotheses from over a100 years previously will be discussed later in this article under discussion in an organized manner with absolute principles/laws.

evidence suggests inter-ictal visual function impairment in migraine with standard tests of visual function necessary for the diagnosis and monitoring of glaucoma (visual fields, electrophysiology, ocular imaging). These abnormalities are measurable in between migraine events, despite patients being asymptomatic and otherwise healthy [78]. Habituation of Visually Evoked Potentials (VEP) also significantly differ in subgroups in the migraine cohort, influenced by the presence or absence of perceived stress or family history of migraine or hyperventilation or disease heterogeneity as markers of arousal [79-81]. Interictal habituation studies do not report uniform results [82]. Ocular (scleral/choroidal/retinal) activation, functional or structural, will invariably also affect the brain's cortical and subcortical regions, and visual impairment in migraine is apparently of retinal origin, a distinction made over three decades previously [83,84].

Structural changes in the papillary retina and ONH are shared between migraine and *glaucoma*. Reduction of mean peripapillary retinal nerve fibre layer thickness (pRNFL), mean macular ganglion cell-inner plexiform layer (mGC IPL) and macular retinal nerve fibre layer (mRNFL) detected with spectral domain optical coherence tomography (SD-OCT) is a sensitive feature of diagnostic value in glaucoma; statistically significant sectoral thinning of inferior and temporal functional subzones best differentiate changes between controls and glaucoma patients [85,86] Similarly, in migraineurs, meta-analysis with large datasets strengthens the clinical evidence of RNFL thinning via SD-OCT as well as significantly larger optic disc rim area and foveal avascular zone optical coherence tomography angiography [87-89].

Mean choroidal thickness and subfoveal choroidal thickness are also significantly thinner in migraine, both in MwA and MwoA patients than healthy controls, as well as both in-between attacks (inter-ictal phase) and during headache attacks (ictal phase) [90-94]. Non- homonymous visual field loss is reported during headache attacks in migraine patients, decreasing but persisting as long as

75 days in a cohort of MwoA patients [76,95-97]. In asymptomatic interictal periods, visual surround suppression for drifting stimuli is greater in migraine patients than in controls [98]. This behaviourally measurable imbalance in inhibitory and excitatory visual processes in migraine is not compatible with a simple model of reduced cortical inhibitory function within the visual system.

The amount of CGRP-monoclonal antibodies (CGRP-mAbs) that enter the brain, if at all, is too small to be even physiologically meaningful; certainly, there is no evidence to suggest that a critical pharmacotherapeutic modulation of central brain neuronal function underlies the migraine preventive action of these agents [6,11,32,99-102]. Decreased activation of hypothalamic nuclei or spinal tract of trigeminal nerve or both by monoclonal antibodies to CGRP in human migraine patients [103] does not exclude effects of secondary modulation of cranial sensory traffic by CGRP from outside the brain neurovascular system [11,15,16].

The largest number of known migraine-modulating clinical, experimental, and pharmacological factors – both increasing susceptibility or decreasing susceptibility to induce migraine attacks – are linked to the ocular choroid-IOP-corneoscleral system [11,15,16,30,31,38,81,84,104,105].

In placebo-controlled Randomized Clinical Trials (RCCTs) to abort migraine attacks, ocular hypotensive therapy with timolol maleate ophthalmic solution has not been found consistently useful [106-110] In a double-blind placebo-controlled crossover trial, propranolol in oral doses up to 120 mg/day was ineffective in controlling acute attacks of migraine aura or headache or both [111]. The failure of propranolol (40 mg) to abort migraine headache was also observed in a previous study [112]. Conversely, positive results with propranolol in the therapy of acute migraine attacks were reported earlier [113,114]. The ocular pathophysiology of the acute headache phase of migraine with self-cycling and self-limited choroido-retinal congestion and algogenic V1 nerve traffic is completely different from that of the pre-headache / pre-clinical

phase of migraine without choroido-retinal congestion and algogenic neural traffic in V1, as discussed below [Figure 1].

In a previous study, nocturnal topical (eye instillation) of a single drop of timolol maleate long-acting ophthalmic preparation (0.5% w/v) before going to sleep once-weekly (pre-weekend, Saturday night) in the eye ipsilateral to the weekend-migraine headache in 2 patients were shown to prevent migraines consistently over an extended period of time (≥ 3 years) [30]. Clinical evidence is now presented for the first time for a sustained (3 years - 5 years) migraine attack-preventive role for Bimatoprost Ophthalmic Solution (BOS) 0.3% in 10 patients with refractory migraine attacks. The biologically defensible mechanistic continuum between migraine, ANS hypofunction, choroidal circulation, IOP, and glaucoma is further advanced in this article.

BOS is an established prostaglandin analogue for reducing elevated IOP by promoting AH outflow in patients with POAG and OH. In the absence of existing ethical guidelines, the Food and Drug Administration of the United States of America (FDA, U.S.A.) has a long-standing ethical policy to permit the trial of an already established pharmacotherapeutic agent for a new clinical indication – a policy consistent with reason and logic (see later).

The key systems focus in this article is on the absolute and exclusive role of the eye in spontaneous genesis (onset) and cessation (offset) of the non-homonymous nasal visual field- sparing SS (15 minutes - 60 minutes (and other less well-defined forms of positive visual aura) as well as self-limited lateralizing headache (4 hours - 72 hours) through predominantly stress / post-stress and ANS hypofunction-primed ocular choroidoretinal congestion-



Figure 1: Flow-chart of proposed Rapid Time-Frame Linked Pathogenetic Algorithm for recurrent spontaneous EM and CM.

Legend: AVP-5HT-NA: Arginine Vasopressin-Serotonin-Noradrenaline; IOP; Intraocular Pressure; RNFL: Retinal Nerve Fibre Layer; mRNFL: macular; mGCIPL: Macular Ganglion Cell-Inner Plexiform Layer; pRNFL: peripapillary Retinal Nerve Fibre Layer; SS: Scintillating Scotoma; V1: Ophthalmic Division of Trigeminal Nerve; EDS-EM: Episodic Migraine; CM: Chronic Migrain



linked corneoscleral envelope distention with the generation of self-limited V1 orthodromic and antidromic algogenic neural impulses in migraine. Three principles or laws of migraine pathophysiology have been evolved; these laws robustly rationalize the entire phenomenology of migraine, and, are discussed in this article.

Case report of N-of-1 pilot study with BOS 0.3%

Therapeutic use of topical BOS 0.3 mg/ml for *prevention* of migraine attacks in 10 migraine patients (8 with Episodic Migraine [EM] and 2 with Chronic Migraine [CM]) were studied between 2015 - 2020. Ethical use of a therapeutic agent already in the market, such as bimatoprost, for a new and unconnected or unconnected indication is permitted to advance science by the FDA, U.S.A.

Diagnosis of migraine (episodic or chronic) was made according to the criteria of the International Classification of Headache Disorders-3 [4]. Inclusion criteria for this study were as follows: (i) migraine headache recurrences and suffering for over 10 years (> or = 100 episodic attacks or > or = 300 headache days), with or without aura symptoms; (ii) 8-weeks basal observation after the first consultation; (iii) migraine headache severity at least 5/10 on a Visual Analog Scale (VAS), with at least 4 attacks or > 30 days of headache in the basal period of 8-weeks basal observation; (iv) exposure to 4 (or more) different migraine preventive drugs under the care of other hospital-based physician/neurologist/ophthalmologist/psychiatrist/pain specialist/headache specialist/physiotherapist, with each regimen having been followed for at least 4 weeks; (iv) graduate education; and (v) willingness to maintain a Smartphone-based daily record of headache, lateralization of headache, occurrence of nausea/vomiting, fatigue, insomnia, side effects of therapy, or any other associated symptom(s) for ≥ 8-weeks after first consultation. For every migraine headache attack/day, the severity of pain in the first 24 hours as well as duration were to be noted. Exclusion criteria were explicit: Patients with dry eyes, eye discharge, eye pain, allergic conjunctivitis, periorbital or eyelid edema, foreign body sensation in the eye, epiphora, visual blurring, or photophobia in the inter-ictal period, using dark shades indoors or blue-light suppressing glasses, depression, insomnia, moderate-to-severe hypertension, diabetes type 1 or 2, biochemical evidence of hematologic or liver, renal or thyroid disorders, alcohol (mis) use, pregnancy, complex medical history requiring the use of corticosteroids or other immunosuppressives or NSAIDs, or naïve or unable to understand the need for extended preventive management strategy over years/decades did not take part in the study.

Psychosocial stress aggravation (graded from + to +++) and straining at stools with eyes/open or closed position were required to be noted on a daily basis. No patient with thunderclap headache or 'worst possible' headache was included. Neck pain in 1 patient was regarded as bilateral migraine.

Potential for increased brown pigmentation of the iris, for hair growth on skin contact, was advised, and running of BOS 0.3% onto the cheek was strictly prohibited. The occurrence of asymptomatic conjunctival hyperemia for a few hours following BOS instillation was recommended to be ignored.

Written informed consent was obtained on the lines of the ethical principles published by the World Medical Association, adopted as the Declaration of Helsinki, 1964, with later modifications. Current

peer comprehension of migraine pathophysiology and all available medical/surgical/interventional therapies were discussed at length without any hesitation or bar with all selected patients, with participants allowed to raise questions and issues through Google Search / Google Scholar. Given the unknown pathophysiology of migraine, the protection of the human participants in this study as well as their long-term overall interests was kept primary at all levels. Withdrawal from the study was always presented as an option. The theoretical basis for this study has evolved over 3 decades and published extensively. Interpretation of all ethical principles involved in this study was not prescriptive. The most important components of the study were the definitive explanation of self-limited visual events and self-limited headaches associated with migraines with spontaneous onset and offset for both key phenomena.

As part of the methodology, the eye-cover test and digital finger displacement tests to evaluate the source of retinal positive-negative crescents or other visual phenomena that have never been explained properly to any migraine patient cohort. Photographs of SS and its breakdown or other variants available from texts in medical periodicals were shown and explained to the 10 participants in this study. The nasal and visual halves of the visual field of each eye were explained to the participants in detail. Monocular and binocular visualization of visual objects was clarified. Personal experience of displacement of the physiologic positive-negative retinal scintillating crescents/arcs following gentle digital-finger self-compression of eyes (right and left, alternatively) with their own index finger was taught to patients to let them know what was critically expected of them.

From the 9th week onwards, patients were instructed to instil 1 drop of BOS 0.3 mg/ml in the eye(s) corresponding to the dominant side of headache, unilaterally or bilaterally, before going to sleep once daily. Patients were also instructed to keep their eye/eyes closed for at least 2 minutes after the instillation of BOS 0.3% and to maintain light pressure on the inner canthus of one or both eyes to diminish the amount of drug reaching systemic circulation, and to remove excess solution with absorbent tissue. Self-instillation of BOS was encouraged; otherwise, assisted instillation from another person was also permitted. The use of analgesics/triptans to manage the pain of migraine headaches was not discontinued. Use of opiate-like tramadol as an analgesic was not permitted.

Headache was bilateral in 3 patients, predominantly right-sided in 5 patients, and left-sided in 2 patients. The age range was 14 years - 62 years, with 7 females and 3 males. Menstrual migraine was reported by 2 females. For the purpose of analysis, headache-pain severity of VAS ≥ 5/10 only was considered. 2 patients reported habitual daily straining at stools. General physical examination of migraine patients was unremarkable. An ophthalmoscopic examination was performed for optic disc and macular retinal evaluation. 7 of 10 patients (70%) reported ≥ 75% reduction in frequency of migraine attacks/days with over 3 years - 5 years. 3 of these 7 patients (42.9%) required 2 instillations of BOS 0.3% (12 hours apart, daily). In the remaining 3 of 10 patients (30%), with ≥ 60% control of migraine attacks/days, high-level anxiety (grade +++/++++ was noted and confirmed with Spielberger's State-Trait Anxiety Inventory (SSTAI) against the most highly correlated 3 anxiety-present items -- tension, upset, and worried and the most highly correlated 3 *anxiety-absent* items – calm, relaxed, and content [115]. These 3 patients with moderate-to-severe



Anxiety Neurosis (AN) could not by themselves instil BOS 0.3%. Care-takers instilling BOS 0.3% in these 3 anxious migraine patients reported a particularly exaggerated apprehension to the instillation with resistive eye closure required to be overcome forcefully. Of these 2 migraine patients with *photophobia-unrelated* fear-induced blepharospasm, one patient with pronounced AN (+++++) revealed a new clinical phenomenon of anticipatory fear-related repetitive high-frequency tremor-or flutter-like blepharoclonus just before the instillation of BOS 0.3%. The resistance to opening her eyes while supine, her fearful inability to look up to permit conjunctival sac(s) instillation of BOS 0.3%, and the high-frequency *non-photophobic* blepharoclonus were reconfirmed.

Exacerbation of domestic / workplace psychosocial stress or the post-stress phase was the major trigger for migraine attacks in 8/10 (80%) patients in this study; 6 (60%) patients reported insomnia, and 4 (40%) reported alcohol imbibition, particularly on weekends. 4 patients noted eyes-open straining-at-stools as a migraine trigger, with 2 patients immediately developing 'stars' (~50 in number) floating away (to disappear) into the superior temporal edge of the visual field in the right eye followed almost simultaneously with right-sided migraine headache (severity 5/10 on VAS). A single female patient, age 35 years, reported a well-developed non-homonymous nasal-field sparing SS in the temporal visual field of the right eye minutes during 10-15 minutes of 5 migraine attacks. All 3 patients with migraine-related visual phenomena, performed an eye-cover test to find that the rippled SS (1 patient) and the floating 'stars' (2 patients) were confined to the right eye (monocular), corresponding to the side of the headache. The SS as well as the floating 'stars' were found to be digitally displaceable by gentle self-finger pressure. During straining-at-stools, 4 migraine patients (40%) (3 males and 1 female) noted a tendency to keep both eyes open. Enlarged cupping of the optic disc was detected in 1 migraine patient. Retinal arterial tortuosity in the form 'v' or 'u' patterns was seen in 3 migraine patients.

Hypersensitivity to BOS 0.3% (bimatoprost or excipients) or increased pigmentation of periorbital tissue (eyelids), eyelashes, and iris were neither reported nor noticed 6 of 10 (50%) patients reported conjunctival hyperemia; the hyperemia lasted 10 hours - 12 hours and was seen only in the palpebral conjunctiva, with the bulbar conjunctiva being spared. Although BOS-induced conjunctival hyperemia is the most frequent treatment-related adverse effect in up to one-third of patients, as per the manufacturer, the restriction of hyperemia to the palpebral aperture has never been previously reported and helps to differentiate from the red-eye of inflammatory/ infective conjunctivitis. No other local or systemic side-effect listed by the manufacturer (Allergan, Waco, Texas, 76712, U.S.A.) was reported in this study.

Discussion

This is the first clinical report of a prospective pharmacologically specific and biologically-defensive sustained N-of-1 study of the preventive effect of topical BOS 0.3%, Aqueous Humor (AH) outflow-promoting IOP-lowering prostaglandin analogue, in 10 patients

with long-standing (> 10 years) uncomplicated migraine, either Episodic Migraine (EM) or Chronic Migraine (CM). The preventive ocular hypotensive therapeutic effect of BOS 0.3% was observed consistently in this study in migraine for 3 years - 5 years with $\geq 75\%$ reduction in headache attacks (EM) as well as in headache days (CM), and this is the preliminary report of an ongoing study started in 2015. Every month, all participants in the study were given the option of withdrawing from the study. To date, no patients have withdrawn from the study. In a previous N-of-1 study, the preventive role of long-acting timolol maleate ophthalmic solution 0.5% w/v administered once weekly on Saturday night in the headache-ipsilateral eye, to prevent migraine attack following oversleeping the next morning, i.e., Sunday morning was demonstrated in weekend migraine without any systemic beta-blockade cardiovascular influence for the first time in primary headache literature [30]. Immediate migraine headache-aborting influence of self-applied ocular tamponade has been also reported in another long-term ongoing study [31].

Intriguingly, due to the nature of its neuroanatomy, including high choroido-retinal vascularity as well as the self-limiting tamponade effect of ocular hydrodynamics/haemodynamics, the eye is the only ANS-stress-linked organ in the head-and-neck region that can periodically or cyclically generate: (i) self-limited non-homonymous SS (15 minutes - 60 minutes) likely due to choroido-retinal overperfusion / congestion and mechanical stimulation; and (ii) self-limited (4 hours - 72 hours) lateralizing headache linked to choroidal over-perfusion, the rise of IOP, and ocular anterior segment related-congestion induced corneoscleral distention-stretch-related algogenic neural traffic in V1 distribution [11,15,16,30,31,38]. While stress / post-stress phasic ANS-hypofunction in conjunction with high choroidal vascularity can transiently generate a relatively high IOP in migraine patients, the naturally-available tamponade-limiting force of IOP itself on ocular choroidal blood vessels (higher than elsewhere in the body) combined with the relative elasto-rigidity of corneoscleral tissues that, in turn, contribute to ocular tissue properties offering a second source of tamponade that limits both the rise of IOP as well as corneoscleral distensibility-related nociceptive neural impulses in V1 with self-limitation of the duration of headache or migraine. The tamponade effect of the eye, overall, affects IOP, ocular choroidal vascularity, and corneoscleral distensibility [105,116-118]. This change in mechanical stretch-related V1 nociceptive traffic-generating IOP is relative and transient and might be evident only with direct continuous non-invasive recording of IOP with pressure-measuring contact lens sensors (with the capacity to measure the concentration of other tear-fluid-based parameters such glucose, urea, proteins, nitrite, chloride ions, corneal temperature, pH, as well as biomechanical stiffening of the corneoscleral or trabecular meshwork, peripapillary scleral structural changes, and optic nerve head remodelling [119-122].

Migraine (and other primary headaches), ultimately, relate to ocular rigidity linked to self-limited biomechanical changes in retinal (ocular blood-flow-related) and corneoscleral (V1 nociceptive neural traffic) ocular tissues with a spontaneous tamponade effect derived from components of ocular rigidity [11,15,16,30,31,38]. The self-limiting nature of IOP- elevation as part of dynamic and very rapid autoregulation of ocular blood flow-choroidal circulatory-corneoscleral elasto-rigidity nexus in the face of cranio-ocular ANS hypofunction is the single most important physiological event contributing to the highly characteristic self-limited aura- and non-



aura (SS or headache or both) phenomenology or phenotype of migraine and other primary headaches.

The link between migraine, ANS dysfunction/hypofunction, IOP, and glaucoma continues to evolve. A very large number of migraine-modulating influences, including critical links with stress/post-stress phase, that can trigger or remit attacks are known to be linked to the increase or decrease in IOP, respectively, a full discussion of which is beyond the scope of this article [11,15,16,30,31,38,104,105,123]. Key migraine modulating psychosocial stress/post-stress and cranio-ocular physiologic changes include: (i) bioavailability / efficacy of the adaptive/ homeostatic arginine vasopressin-serotonin-noradrenalin nexus; (ii) cardiac output; (iii) common carotid/external carotid arterial perfusion; (iv) cranio-ocular ANS hypofunction; (v) ocular choroido-retinal arterial overperfusion; (vi) cranio-ocular choroidal venous congestion, particularly in congenital heart disease including Ebstein anomaly and moderate-to-morbid obesity; (vii) hydrostatic increase in AH secretion with a flow-related rise in IOP; (viii) increase in global volume/distention; (ix) rheological or mechanical segmental-sectoral nasal-sparing temporal retinal spreading depression (RSD) or RSD-like activation of retinal tissue leading to self-limited SS and/or other positive-negative scotoma; and, (x) mechanical corneoscleral distention leading to V1 algogenic neural traffic (orthodromic or antidromic or both) generating lateralizing headaches. [Figure 1, see text below] First-and second-line migraine preventive pharmacologic agents some of which are established by RCCT such as the prototypic beta-blockers (propranolol, atenolol, or nadolol) and amitriptyline, melatonin, flunarizine, (Angiotensin-Converting Enzyme-Inhibitors (ACE-Is), Angiotensin Receptor Blockers (ARBs) and others clearly lower IOP – a pathophysiologic and pharmacologic absolute [11,15, 16,30,31,38,83,84,104,105] The tissue components of corneoscleral distensibility are part of an elaborate connective tissue disorder wherein genetic (trait) factors will complement the state (acquired factors). The placebo factor will also confound clinical/investigative pathophysiologic issues and interpretations. A fuller discussion of these ocular elasto-rigidity factors as well as pharmacologic effects with relevance to migraine pathophysiology is beyond the scope of this article.

Thinning of pRNFL, mGCIPL, mRNFL, and mean and subfoveal choroidal layers recorded via SD-OCT in the inter-ictal headache-free and headache periods, similar to changes in glaucoma also indicate a definitive primary involvement of the posterior pole of the eye [70-75,77,78,85-91,93,95,97] A vasoconstrictive influence on the posterior pole of the eye, as commonly presumed, is highly unlikely to prevail in-between migraine attacks (inter-ictal periods). An 'occult' relative barometric influence coupled with outlier-enhanced corneoscleral distensibility / ocular rigidity is the most likely cause for prolonged alterations of RNFL and choroidal thickness found in migraine, up to 75 days after an attack.

Canonical pathognomonic SS as well as typical headaches of migraine are not experienced after enucleation of the eye(s) or loss of sight [124-130] Absence of relative or absolute elevation of IOP in migraine [Devisogullari, et al. 2014] [131], is the missing evidentiary link. Nevertheless, with the onset of exposure to the trigger or anxiety/post-anxiety phase or onset of headache pain early in the course of the migraine attack, the vasopressin-serotonin-noradrenaline homeostatic nexus is activated. Once pain-

of-headache is triggered, a relatively low IOP would be maintained. As discussed above, in migraine patients, stress- and other migraine trigger-related homeostatic activation of Arginine-Vasopressin (AVP) raises SBP but lowers the IOP – a most characteristic feature maintains antinociception and behavior control to a protean / variable exhaustible point-in-time that varies between migraine patients in any cohort as well as in the same patient on different temporal occasions. [11,15,16,38,83,84,132] This is the true meaning of 'protean' insofar as migraine is concerned, and is invaluable pathophysiologically.

Phase-by-phase phenotypic descriptions and phasic underpinning(s) of discrete pathophysiologic modes for each phase, as is common in migraine literature [1,20,133], is a form of contradictory and artificial individuality or 'reductionalism' – as are nosologic 'hypersplitting' and/or disparate or stand-alone laboratory 'evidence' – operating sans an overarching matrix through a biologically implausible and -an unimaginative mix of speculative but reflexive systemic and /or brain vascular and neuronal theories supporting 'central' and/or 'peripheral' sensitization.

Critical limitations of CSD as the key pathogenetic have been discussed and found obsolete. The adaptive or homeostatic role of CSD in the animal kingdom is clear in lower mammals and insects. [see Box 1, above] Several key migraine preventive or provocative pharmacologic agents do not influence CSD [11,15,16,30,31,38,84,132]. Glyceryl Trinitrate (GTN), the best-defined i.v. experimental model for migraine headache has no basic or critical influence on basic parameters of KCL-induced CSD, with only a decrease in propagation failure compared to controls [134]. The unexplained but characteristic delay (4 hours - 6 hours) between i.v. administration of GNT and onset of migraine-like headache may be linked to early fall in SBP/IOP or concomitant activation of the homeostatic-adaptive AVP-5HT-NA nexus or both. Cilostazol and sildenafil are other vasodilators, that experimentally produce migraine headaches, importantly most without migraine aura, and none with well-formed SS [135-138] Sildenafil alters neither CSD nor the subsequent characteristic effect of nitric oxide synthase (NOS) inhibition, i.e. a marked widening of CSD [139] Sildenafil raises IOP but lowers SBP [140]. In a small highly-selective cohort of 16 MwA patients, of whom 11 patients (69%, > 2/3rd) only experienced MwA sans headache, sildenafil induced aura symptoms -- but not SS. No migraine headache attack generating experimental systemic vasodilator, including GTN or sildenafil or cilostazol or Calcitonin-Gen Related Peptide (CGRP) has induced SS or other major positive aura-linked symptoms of migraine, barring rare anecdotes, thus sustaining the major pathophysiologic disconnect between the aura and the headache of migraine. Despite widespread belief, experimental vasodilator-induced migraine attacks post-NTG infusion is associated with delayed (1.5 hours - 5.5 hours), diffuse, mild, and transient vasodilatation (6.7% - 30.3%, $p < 0.01$), while during migraine attacks blood vessel diameters of cerebral or meningeal arteries were no different from baseline or between headache and non-headache sides [141-143] Major arteries such as internal carotid arteries and basilar arteries showed no change in blood flow during NTG-infusion or migraine [143]. Inconsistent vasodilation of the middle meningeal artery followed systemic diffuse vasodilator-induced generalized vascular dilatation not lateralizing to the side of headache [136,138].



Failure of significant dilatation of cerebral arteries ($\geq 50\%$ - 75%) following vasodilator challenge indicates the operation of an early rapidly adaptive-homeostatic, spontaneous, and sustained vasoconstrictor influence involving a vasopressin-like neurohormone; such failure of key cranial arteries to vasodilate following NTG-challenge also cannot rationalize lateralizing headache or non-homonymous nasal visual-field SS and/or visual field defects of migraine [11,15,16,83,84,132]. Intriguingly, alcohol – one of the commonest precipitants of migraine attacks worldwide – does not dilate but constricts the internal carotid circulation – a feature that has never been underscored in migraine pathophysiology. Ethanol blood concentrations during binge drinking [18 to 80 mM] constrict cerebral arteries in a wide variety of species, including humans, both *ex vivo* and *in vivo*; as reviewed, this cerebral vasoconstrictive action of ethanol results from drug-induced inhibition of cerebrovascular smooth muscular K^+ vasodilator channels (calcium-and voltage-gated potassium channels of large conductance type) [144,145].

High prevalence of migraine in moderate-to-morbid (total-body and abdominal) obesity, with striking prevalence in Congenital Heart Disease (CHD) without right-to-left shunting (43%), and even higher in Ebstein anomaly (EA) (67%) appears to be directly and sequentially linked to the right ventricular dysfunction and/or obstructive impediment of cranial venous return, cranio-ocular-ANS hypofunction-mediated ocular choroidal arteriovenous congestion and retinal venodilatation, the rise of hydrostatic pressure, IOP elevation, ocular globe, and corneoscleral distention, with the genesis of algogenic V1 neural traffic that is self-limited by the ocular tamponade effect (see algorithm, Figure 1) [146-159].

Closure of Atrial Septal Defect (ASD) can generate migraine *de novo* or aggravate pre-existent migraine that is likely consequent to immediate or almost-immediate improvement in left-ventricular filling and the concomitant rise in both cardiac output and ocular blood flow (Gupta 2006) [160]. Rise of ocular blood flow coupled to ANS-hypofunction in migraine patients can lead to ocular choroidal overperfusion, the rise of ocular hydrostatic pressure, and increased formation of AH with a relatively higher IOP. Patients who undergo device-closure of ASD have much shorter recovery than those who require surgery and thus enjoy the benefits of improved hemodynamics and increased systemic cardiac output much earlier. Neuropathologically, there is no conceivable pathogenetic link of EA, other CHD, obesity, or ASD-closure or PFO-closure to CSD [15,16,161]. Migraine attacks speculatively linked to PFO-related right-to-left atrial shunt with systemic transfer of migraine-attack-provoking substances such as neurotransmitters, further suppose episodic/periodic (cyclical or non-cyclical) elevation of right-atrial pressure through VM, similarly cannot logically rationalize the occurrence of recurrent periodic (programmed, regularly appearing, or cyclic menstrual migraine attacks) or non-periodic (irregularly irregular non-cyclic migraine attacks) self-limited (4 hours - 72 hours) and protean (varied frequency, severity, and duration lateralizing headache predominantly confined to V1 or non-homonymous nasal-visual field sparing SS, that appear spontaneously at puberty, adolescence, adulthood, the first trimester of pregnancy, and spontaneously resolve with later trimesters of pregnancy or advancing age, including menopause [11,159,162]. Size of PFO consistently, but paradoxically, increases with age, while migraine prevalence falls with increasing age, including menopause, as reviewed elsewhere [161]. Results of placebo-controlled trials of

PFO closure to prevent migraine attacks and the meta-analyses that follow are not uniform or striking, with the fundamental supporting basis of science lacking and with the primary end-points not being met [161-167] (see below).

Botulinum toxin – type A (BOTOX-A) has no anti-nociceptive or vasomotor-control or behaviour-control role in the management of pain *per se* or that of em [168,169]. Chronic migraine management with onabotulinum toxin-A is largely disappointing, as in RCCT, migraine frequency is marginally reduced only by 2 days/month [170-172]. Botulinum therapy for the prevention of a long-term disorder such as migraine is also not cost-effective. Magnesium is a vasodilator and does not freely cross the BBB under many discrete experimental circumstances, key issues that render its exogenous administration or supplementation useless for migraine prevention [11]. The role of magnesium as a prophylactic for migraine, as a brain neuronal saviour, and as a life-saving drug in the ICU has become obsolete almost 3 decades previously [173].

Outcome

This study reports in real-time and real-world outside of RCCTs the first N-of-1 evidence for the instantaneous and definitive physical displacement of migraine visual aura, including SS and floating 'stars', by the simple measure of guarded and gentle digital self-application of mechanical pressure to both eyeballs alternatively at the inner and outer canthi, thereby establishing beyond doubt that the retina is the source of origin of migraine-related positive visual aura. Monocular non-homonymous distribution of SS confined to the temporal visual field in a migraine patient trained to study her own visual phenomenon is reported for the first time in migraine literature. Such pre-trial training to study participants or volunteers for clinical self-evaluation and self-reporting of visual aura has never been previously made available to migraine patients. Hupp, Kline, and Corbett, in their landmark, ground-breaking, and insightful article three decades ago, suggested that digital / finger displacement of visual phenomena by migraine patients themselves would offer conclusive evidence for retinal or cortical origin of visual aura, uncluttered with statistics; these authors also recommended that migraine patients be trained themselves perform the eye-cover test to determine monocular or binocular distribution of visual aura/phenomena, positive or negative, as well as to distinguish nasal and temporal visual fields of each eye [77].

Migraine attacks can develop unilaterally or bilaterally, and non-homonymous SS or other positive visual aura also may occur in one or both eyes. Bilateral non-homonymous rippled SS-like or floating 'star-like' visual aura can mimic homonymously distributed phenomena and misleadingly suggest brain cortical visual cortex origin, unless checked bilaterally / binocularly for digital / finger displacement. Hence, the digital displacement of positive visual phenomena reported in this study accurately determines its retinal origin, regardless of the underlying retinal-level pathophysiologic mechanism(s). Retinal Spreading Depression (RSD) is a well-established neuro-ophthalmologic phenomenon, that can well explain the spreading nature of SS of migraine [174-176]. CGRP receptors mediate RSD propagation while sumatriptan blocks SD in isolated chick retina; RSD is an efficient *in vitro* approach for assessing anti-migraine drugs targeting CGRP receptors [177,178]. As suggested 2 decades ago, RSD is the only CNS electrical phenomenon that can be activated by mechanical or rheologic pressure (Gupta 2006).



Regardless of underlying cellular/molecular level retinal mechanism(s), [179] absolute clinical evidence regarding displaceable short-lasting neurophysiologic oculo-retinal symptomatic phenomena can be further established with simple but specific training imparted to lay migraine patients without professional knowledge of visual pathway neuroanatomy. Clinical awareness and application of the twin tests of eye cover and self-displacement to determine the side of occurrence and site of origin of visual aura phenomena must be disseminated and improved. Neurologists and headache specialists have the highest incidence of migraine attacks; female headache specialists have 1-year and lifetime migraine prevalence of 74.1% and 81.5% [180,181]. Once the simple but almost-completely ignored neuro-ophthalmologic principle is generally accepted, digital-finger self-displacement of positive migraine aura can be easily replicated and can rapidly establish the precise bio-neural substrate of migraine attacks, including nasal-visual field sparing SS, lateralizing migraine-headache, and painless photophobia versus light-sensitivity. There is no evidence to suggest that the Trigeminovascular 'System' (TVS) directly innervates the neurons of the visual cortex to generate a nasal-visual field sparing SS of migraine [11,182]. Also, it is not known why the visual aura should be the preponderant cerebral component of the aura of migraine. Definitive evidence regarding displaceable nasal-visual field sparing SS/positive visual aura can easily come from neurologists, ophthalmologists, headache specialists, and physicians once the exclusive pathophysiologic turf-like hyperfocus on the brain is resolved.

Unspecific brainstem, hypothalamus, and cortex-related activations or evidence will only then be clarified as secondary phenomenological features of migraine [84,183,]. In maintaining brain neuronal hyper-excitability as the pathogenetic basis of migraine [182], the combined brain neuronal-serotonergic and -noradrenergic activation effected by migraine preventive agents (such as AMT) or drugs of abuse (such as cocaine) is an important caveat [11,15,16,184,185] Caffeine is another brain neuronal noradrenergic stimulant – besides AMT or cocaine -- that delays the onset of migraine / migraine-like headache [30]. Neurotransmitters, like CGRP, in general, work in vivo in a very rapid counter-balancing well-orchestrated manner and never in isolation [6,32,99]. Neurobiological substrate of migraine will become apparent and can be defended robustly against scientific and logical challenges only after the division of its vast phenomenology into primary and secondary components (Gupta 2009). Neurotransmitters or neuropeptides do not constitute the biology of migraine; they simply work as messengers of brain neurons, always in an adaptive-homeostatic mode or concert, never alone. Migraine researchers have divided the whole into parts, all the while, paradoxically, expecting the gestalt to emerge.

This study also reports abnormal retinal arterial tortuosity in migraine for the first time in the scientific literature, first detailed in the Rolex Awards for Enterprise, 1990 [84]. Increased ictal retinal arterial blood flow due to ophthalmic artery overperfusion and ophthalmic venous congestion in migraine may underlie retinal / pre-retinal hemorrhages, papilledema, and glaucomatous optic disc enlargement that have been noted previously in migraine, as part of idiopathic ischemic optic neuropathy [77,186-189]. Such changes are not ischemic but result from over-perfusion. Such choroido-retinal overperfusion, with or without moderate-to-morbid obesity,

CHD without right-to-left shunting, EA, or right heart congestion can also be associated with subtle retinal arterial tortuosity consequent to rheological hemodynamic forces. (see above) Retinal arterial tortuosity and venular dilatation are common in CHD, including EA with tricuspid regurgitation / right heart dysfunction, arrhythmia, progressive central cyanosis from right-to-left atrial level shunting, paroxysmal atrial tachyarrhythmias with or without atrioventricular bypass tracts, conjunctival hyperemia, cyanotic fundus hue, papilledema, and rarely visual snow syndrome [146]. Apparently, CHD, including EA and moderate-to-morbid obesity have no pathogenetic link with CSD/SD or any other brain neuronal network or neurovascular dysfunction. On the other hand, obesity is an independent risk factor for elevated IOP in adults as well as in school children, with higher IOP correlated with body mass index (BMI), waist circumference, and diastolic blood pressure (DBP) (see above). Obesity increases adipose tissue in eye sockets, episcleral venous pressure, and corticosteroid secretion while decreasing aqueous outflow due to excessive blood viscosity, which features an increased IOP. Additionally, obesity is also related to diseases that affect OH, hypertension, diabetes, and dyslipidemia. In individuals with Morbid Obesity (MO), respiratory muscles are inefficient and have low performance. Morbid obesity affects the cardiopulmonary system resulting in lower tidal volume, decreased functional residual capacity, higher respiratory rate, lower lung and chest compliance, higher elastic and muscle work, lower strength and endurance of respiratory muscles, higher oxygen consumption and higher levels of fatigue, shallow breathing post-anesthesia, and subclinical hemodynamic dysfunction with impaired venous return from lower limbs and abdomen notably in gynecoid obesity followed by cardiac decompensation with enhanced preload and afterload and severe physical deconditioning [159,190]. In MO, a prominent upwards displacement or 'splinting' of the diaphragm by a massive increase in abdominal contents and intra-abdominal pressure is likely another major component of positive intrathoracic pressure, besides visco-elastic splinting of the lung/chest wall musculature. Upward displacement/splinting of the diaphragm in MO constitutes, in effect, a near-constant or -persistent VM-like congestive influence on cranio-ocular circulation, rather than a transient effort- or Valsalva Maneuver (VM)-related intermittent pathophysiologic influence. Cranio-ocular congestion is intrinsic to right ventricular dysfunction from any cause, including EA and MO. The 5 - cm canonical indicator of elevated jugular venous pressure is also probably not relevant to MO; a 2 - cm elevation of (Jugular Venous Pressure) JVP is clinically more representative in MO [191]. Valsalva maneuver is relevant to migraine phenomenology, as an IOP-elevating attack-provoking trigger and or headache-worsening factor, as well as to headache- aborting effortful/forceful nausea/vomiting that itself raises IOP but also intensely stimulates AVP release from posterior neurohypophysis [132,161,192,193]. Strikingly, VM involves ocular venous congestion or backpressure but does not directly or primarily affect the ophthalmo-retinal arterial circulation.

A new pelvic-ocular ANS reflex relevant to VM-related straining-at-stools and VM-related migraine is described. The eyes tend to maintain an open position during pelvic straining during passing stools or flatus or during the pelvic delivery of the foetus, possibly as a conserved or evolutionary 'guarding' reflex against social embarrassment and 'fear' of uncontrolled pelvic damage or tear. Nevertheless, maintenance of this pelvic-ocular reflex largely transmits VM-related raised intrabdominal/intrathoracic pressures



directly, repeatedly, and dramatically to the eyes, particularly with breath-holding [194-196] with ocular globe expansion, venous congestion, raised hydrostatic pressure, increased formation of AH, and rise of IOP. Previously, it has been recommended that the eyes be firmly closed as well as the mouth be kept open to short-circuit the ocular hemodynamic effects of VM to prevent primary headache induced by cough (benign cough-induced headache), to prevent migraine attacks, and to prevent reversible cerebral vasoconstriction syndrome-related thunderclap headache during repetitive and most forceful VM known to humans during labour or pelvic delivery [31,197-199]. Blinking of eyes or forceful closure of eyes ('screwing' or 'squeezing' eyes shut tightly) can raise IOP to 10 mmHg or as high as 90 mmHg, respectively [200]. The Tamponade effect of raised IOP / elasto-rigidity of ocular tissue structures does not permit uncontrolled choroido-retinal arteriovenous congestion or triggering of certain headache variants, e.g. migraine and cluster headache do not co-exist commonly, indicating major differences in ocular tissue elasto-rigidity.

- I. Three inter-linked key issues in migraine phenomenology continue to challenge mechanistic insight: Female preponderance;
- II. Age-related decline in prevalence; and,
- III. Biological or dynamic-functional rapidly-developing physiologic processes surrounding the stress/post-stress/depression/or other triggers that precipitate the disorder by generating self-limited nasal-visual field sparing SS and lateralizing self-limited headache (4 hours - 72 hours).

From serotonin (1960s) to the CGRP/CGRP-A in the present era (3rd decade of the 21st Century), a series of biochemical and neuroimaging laboratory events or 'bio-markers' have displaced the biology of migraine [11]. Statistics-based RCCTs allow – and continue to allow -- migraine researchers to perform legitimate science and to mine migraine-related data without clinical validity or commonsense displacing the abstract qualitative from the quantitative [11,161]. RCCTs, paradoxically, in a cart-before-the-horse manner determine the science of migraine, rather than the other way about. The colossal harm done by mathematical statistics to science and scientific thinking, in general, has only recently aroused the scientific community without a personal or philosophical commitment to any or all disciplines, including the science of migraine / primary headaches [201,202]. While decades of journal columns overemphasizing opinions, evidence from animal experiments with almost direct extrapolation to human migraine patients, RCTs, genetics, and epidemiology have been devoted to possible or presumed canonical but mythologic etiologies/pathophysiologies, such as meningeal activation, neuroinflammation, neuropeptide or molecular releases such as cytokines, oxidants-antioxidants, brain neuronal networks and their activations, white-matter hyperintensities, besides SD and CSD, the genuine chicken-egg scientific questions are never formulated. Why should CSD or molecular-substance releases occur in the first instance in a self-limited manner? Nature abhors a vacuum, and science abhors lack of generalization. What is not generalizable in science/medicine is not true. A full detail of all molecular substances implicated in migraine cannot be absorbed in this article.

The meaning of the term 'biology' or 'biological' has been lost in migraine research. The 'biology' of any illness...is a holistic, gestalt,

comprehension... that is not synonymous with 'nonenvironmental', 'organic', 'laboratory' or even 'physiological',...or a 'unifactorial' (PFO- or botulinum toxin- or CGRP-like) or a 'hopelessly complex obfuscation' or frustrating self-defeating Gordian knots in series and in parallel that constitute a grand 'nihilism', but a meticulously orchestrated concatenation of several physiological processes (primary versus secondary stress adaptive/protective/homeostatic physiologic processes) that push or pull the patient towards the disease (migraine-attack or ictal state) or disease-free state (migraine-attack free inter-ictal phase).

Four fundamental physico-biological laws of migraine complete the science of the disorder

1. Migraine is a lateralizing cranial painful disorder -- a 'megrim/hemicranial' headache that is unilateral, bilateral, side-shifting, or side-fixed. From serotonin to SBP to CRGP/CGRP-A, no systemic influence can rationalize the pathophysiology of migraine [173].
2. Migraine is a selective algogenic ophthalmologic nerve (V1) disorder, not a pan-trigeminal disorder. Neck pain in migraine attacks is part of V1 innervation [11].
3. Migraine is frequently aborted by nausea-vomiting, a powerful stimulus for AVP-release from the neurohypophysis with vasomotor, antinociceptive, and behaviour control mechanisms [132].
4. SS (unilateral or bilateral) of migraine spares the nasal-visual field and is physically displaceable by the pressure of the patient's own finger, confirming retinal origin.

No theory for migraine can be complete without rationalizing its highly characteristic sex and age distribution. The futuristic template for female preponderance [Box 2, A] and age-related decline [Box 2, B] |in the prevalence of migraine is presented in the context of the eye model of human migraine, with the pathophysiologic flowchart detailed in this article maintaining hyperfocus on V1 (Figure 1) (Box 2).

Finally, in the present article, the physiologic basis of the psychologic stress / poststress phenomenon in migraine has evolved, through the cause-effect-adaptive pathophysiologic nexus via the AVP-5HT-NA continuum as a generalized neurophysiologic mechanism relevant to neuroscience beyond primary headache. The clinical migraine-IOP-glaucoma continuum has also been elucidated with a substantial wide-based evidentiary base. Cortical spreading depression (CSD) has already been established to subservise an adaptive-protective-homeostatic role in lower mammals (rodents) and insects (Locusts and *Drosophila*). A pathologic role for CSD in human neurologic diseases is purely speculative. CSD/SD suppression in the neurocritical unit cannot be justified.

Conclusion

In summary, this N-of-1 study advances the role of sustained ocular hypotension through topical BOS 0.3% for migraine prophylaxis with a remarkable reduction in the frequency of episodic headache attacks or headache days. Persistent interictal changes in RNFL and choroid with a possible role of intraocular barotrauma are presented. Displaceable, non-homonymous, and temporal visual



Box 2:	
A. Factors Associated with Preponderance of Migraine in Females (human).	
1.	Stress handling is less efficient in females [203].
2.	Perceived thermal stress during exercise hyperthermia is hotter, more uncomfortable, more unpleasant, and more stressful compared to males [204].
3.	Anxiety neurosis / GAD is commoner in females [205,206].
4.	V1 algogenic neural traffic generation potential through corneoscleral distensibility or ocular rigidity is different, with subtle differences such as the size of the globe, age, uveal circulation, state of hydration, connective tissue, angiogenesis, metallic metalloproteinase or hormonal influence (relaxin, elastin, MMP-levels, SB100) [11,207-211].
5.	Pregnancy – vasopressin-vasopressinase (placental) (im)balance; hypervolemia due to vomiting of pregnancy reduces bioavailability/efficacy of AVP (Schrier, 2010) [132].
6.	Different modulation of endogenous pain control systems with more variable and increased pain sensitivity and many more painful diseases commonly reported among women [212].
7.	Larger abundance of renal Na ⁺ transport in the proximal tubules in females [213].
8.	Estrogen has a secondary or permissive role in some factors, with no direct role in V1 pronociceptive neural traffic.
B. Factors Associated with Declining Prevalence of Migraine with Pregnancy (second and third trimesters), Menopause and Advancing Age (human).	
1.	Choroidal thinning [214]. Constituting 80% of ocular blood flow, the choroid is highly labile, and consistent results have not been obtained regarding choroidal thickness during pregnancy [215]. Lack of consistency of results of choroidal thickness indicates critical and overriding relevance of the AVP-5HT-NA continuum.
2.	Hyponatremia, increasing efficacy of arginine vasopressin [216,217].
3.	Non-linear pressure-volume relation in the living human eye with an increase in ocular rigidity (and decrease in corneoscleral distensibility) with age, higher IOP levels, and increasing ocular volume with a fall in pulsatile ocular blood flow. There is increased mechanical resistance of the ocular wall at high IOP levels [218-255].
C. Objectives of Future Advances in creation of Ideal Therapeutic Strategy for Migraine.	
Prophylaxis, Topical or Oral, or Combined	
1.	Focus on V1 neural traffic.
2.	Focus on IOP / choroidal circulation, with long-term combined reduction of both.
3.	Focus on accelerated drainage of aqueous humor, at Schlemm's canal and uveo-scleral outflow.
4.	Focus on increased bioactivity/secretion of the vasopressin-serotonin-noradrenaline continuum.
5.	The focus of the migraine-glaucoma continuum.
Adapted from: Gupta VK. Adaptive Mechanisms in Migraine [16].	

field-localized SS with eye-cover and digital displacement tests is reported, establishing the retina as the source of origin of positive scotomata of migraine. Pathophysiologic role of ANS hypofunction-choroidal blood flow-IOP nexus has been advanced. Key role of subclinical choroido-retinal arterial overperfusion and venous congestion, with primary or rebound increase of hydrostatic pressure generated aqueous humor and, ultimately, IOP in a wide variety of clinical circumstances and human experiments is presented. The basis of the migraine-IOP-glaucoma continuum is discussed in the context of congenital heart disease, including Ebstein anomaly, atrial septal defect, coarctation of the aorta, and patent foramen ovale, as well as in morbid obesity. An idiosyncratic and variable threshold of cumulative algogenic traffic in V1 determines the occurrence of protean migraine attacks. Arteriovenous congestion-mediated selective V1 pronociceptive traffic results in the spontaneous onset of migraine attacks for 4 hours - 72 hours. Self-tamponade mechanism of physiologic systems of eye limits ocular globe-expansion, eventually terminating corneoscleral distention and V1 algogenic traffic, with the spontaneous offset of migraine attacks. The template for female preponderance, menopause- and age-related decline in prevalence, and the fundamental requisites to evolve an ideal strategy for migraine prophylaxis has been proposed.

25 steps to certitude – eye v/s brain -- migraine unveiled

1. CSD, the longest-standing canonical myth in migraine, has an established homeostatic-adaptive influence in lower mammals (rodents), insects, and *Drosophila* which is an evolutionarily conserved neurophysiologic principle.
2. CSD has absolutely no influence on pain, the key limitation and major management concern in migraine therapeutics.

3. CSD has an innate anti-seizure activity.
4. CSD suppression in traumatic brain injury is a counter-intuitive biologically implausible scientifically indefensible reflex-like therapeutic concept.
5. Enucleation of the eye or sightlessness does not allow canonical Scintillating Scotoma (SS) or typically lateralizing headache to manifest.
6. Eye cover tests can establish a non-homonymous distribution of SS confined to the temporal visual field. Non-homonymous visual field defects and SD-OCT detected non-homonymously distributed retinal changes have also been established in the inter-ictal phase without ischemic influence.
7. SS is confined to the temporal visual field and is physically displaceable in real-time by self-digital compression, a phenotypic feature that absolutely confirms retinal origin.
8. Key first- or second-line migraine preventive drugs such as propranolol atenolol, nadolol, or verapamil do not cross the Blood-Brain Barrier (BBB) or have any critical influence on the cortical/visual cortex function.
9. Prototypic β -blockers with Raynaud-like peripheral vasoconstrictive effect that decongest ocular choroido-retinal circulation and maintain relatively low IOP can offer sustained prevention of migraine.
10. Beta-blockers without peripheral vasoconstrictive effect do not lower IOP or offer migraine prophylaxis – a pharmacokinetic absolute, resolving a 50-year-old controversy surrounding hydrophilic/lipophilic beta-blocker drugs and the BBB.



11. The established first-line/second-line migraine-preventing effect of Amitriptyline (AMT) produces cortical hyperactivation and serotonin syndrome by combined reuptake inhibition of 5-HT and NE. AMT is serotonomimetic, a neuro-pharmacologic absolute, that also offers significant Antinociception Via Arginine-Vasopressin (AVP). AMT, melatonin, flunarizine, Angiotensin-Converting Enzyme Inhibitors (ACE-Is), and topical verapamil lower IOP and the migraine threshold. Magnesium is a vasodilator that does not freely cross the BBB and has no role in migraine prevention.

12. Neuropeptides/neurotransmitters like CGRP cannot operate in isolation but always act in nature in a cohesive well-orchestrated manner with simultaneous release of counter-regulatory neuropeptides. CGRP antagonists do not cross the BBB even in physiologically significant amounts. CGRP is a vasodilator, and not unexpectedly, dose-dependently produces a biphasic IOP response, including an early IOP hypertensive phase known for over 2 decades.

13. Delay in onset of migraine attacks, spontaneous or experimental, including alcohol-imbibition or GTN- challenge, is due to a well-orchestrated AVP-5HT-NA homeostatic-adaptive system/continuum that maintains relatively low IOP, antinociception, and behavior control functions.

14. Spontaneous onset of migraine attacks is due to variable exhaustion of the stress or other migraine trigger linked ANS-NA linked AVP system, arteriovenous overperfusion of choroido-retinal circulation, increase in IOP, global volume expansion, and phasic self-limited nociceptive stretch of the elastic corneal envelope.

15. The pain of the head/neck of migraine is selectively confined to the ophthalmic division of the trigeminal nerve (V1) – the new template for future drug discovery and scientific advancement. Migraine is not a pan-trigeminal disorder.

16. Neither brain neuronal networks nor cranial circulations – internal or external – have any role in non-homonymous SS and visual field defects as well as in typically lateralizing headaches of migraine – unilateral, bilateral, side-shifting, or side-locked. This principle holds true for pathognomically side-locked headaches or cluster headaches as well.

17. A spontaneous offset of migraine attacks in 4 hours - 72 hours is due to the tamponade effect of elasto-rigidity of ocular tissues that restricts further choroido-retinal congestion, which ocular tissue features combine to limit and ultimately abort algogenic V1 neural traffic.

18. Spontaneous headache-aborting action of nausea likely involves substantial secretion of AVP from the neurohypophysis.

19. Strikingly high prevalence of migraine in congenital heart disease without right-to-left shunt (43%) including Ebstein anomaly (67%), as well as less commonly with Coarctation of the Aorta (COA), Atrial Septal Defect (ASD), or Patent Foramen Ovale (PFO) has no link to CSD other than speculation.

20. Correction of COA, ASD, or PFO can immediately worsen migraine or generate de novo attacks, that are linked to improved cardiac stroke volume, cardiac output, cranial circulatory flow, and ocular / choroido-retinal overperfusion. Reversal of closed-PFO with worsening migraine requires open-heart surgery.

21. In a long-term prospective N-of-1 trial, topical ocular hypotensive agent bimatoprost ophthalmic solution 0.3% has offered striking migraine prevention. Bimatoprost ocular implants are the future for the management of migraine.

22. Topical timolol maleate long-acting 0.5% at bedtime has prevented weekend migraine in an extended and ongoing N-of-1 clinical trial.

23. Morbid obesity is linked with cranial-ocular venous congestion and relatively higher IOP, which lowers the threshold for developing migraine attacks.

24. Female preponderance of migraine prevalence is based on differential handling of stress, pain, corneal distensibility, ocular rigidity, renal handling of Na⁺ and hormonal influences on the AVP-5HT-NA continuum.

25. Age-related decline in the prevalence of migraine is likely related to declining clinical impact of psychosocial stress, increased choroidal thinning, hyponatremia-related enhanced bioactivity of AVP, and changes in ocular rigidity.

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