

**RISK OF ACUTE ANGLE CLOSURE GLAUCOMA WITH TRIPTAN USE IN
MIGRAINE PATIENTS: A NESTED CASE CONTROL STUDY**

by

Mohit Sodhi

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis/dissertation entitled:

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Submitted by Mohit Sodhi in partial fulfillment of the requirements for
the degree of Master of Science
in Experimental Medicine

Examining Committee:

Dr. Mahyar Etminan, Ophthalmology and Visual Sciences
Supervisor

Dr. Frederick Mikelberg, Ophthalmology and Visual Sciences
Supervisory Committee Member

Dr. Mohsen Sadatsafavi, Pharmaceutical Sciences
Supervisory Committee Chair

Dr. Mary De Vera, Pharmaceutical Sciences
External Examiner

Additional Supervisory Committee Members:

Dr. Claire Sheldon, Ophthalmology and Visual Sciences
Supervisory Committee Member

Abstract

Background: Glaucoma is a chronic, progressive disease that affects over 60 million people worldwide and can lead to either partial or complete vision loss. Similarly, migraines are one of the most prevalent and disabling conditions worldwide. Recent case studies and reports to the Food and Drug Administration have alluded to a link between triptans and an acute angle closure glaucoma (AACG) attack; a true ophthalmic emergency. Given that triptans are a highly prescribed medication, we sought to examine the risk of triptan induced AACG.

Methods: We undertook a nested case-control study. We had access to a random sample of 9,053,240 patients from 2006-2016. Cases were identified by their first diagnosis of AACG. A risk-set of controls matched by age, sex, calendar time, and follow-up time were constructed. Our manner of control selection has shown to generate odds ratios that are close approximations of the risk ratios (RR). RRs for a positive control (topiramate) and negative control (ranitidine) were also calculated. Study drug use was defined as those with a prescription within 7 (current), 14 (recent), and 30 days (past) and any use of the drug within 1 year (0-365 days) prior to the index date.

Results: There were 1,307 cases and 13,070 controls. The adjusted RR for those with any use of triptans was 1.09 (95%CI: 0.56-1.82). The adjusted RR for current, recent, and past use for triptans was 1.37 (95% CI 0.31-6.09), 1.16 (95% CI 0.35-3.92), and 1.19 (95% CI 0.50-2.81) respectively. The adjusted RR for current, recent, past use, and any use for topiramate was 4.44 (95% CI 0.80-24.64), 12.86 (95% CI 5.10-32.42), 6.52 (95% CI 3.34-12.71), and 3.77 (95% CI 2.29-6.20) respectively. The adjusted RR for current, recent, past use, and any use for ranitidine

was 0.66 (95% CI 0.08-5.24), 0.39 (95% CI 0.05-2.91), 0.18 (95% CI 0.02-1.28), and 0.79 (95% CI 0.43-1.44) respectively.

Conclusion: Although a significantly increased risk was not found for triptan induced AACG, we cannot exclude the existence of this risk due to presence of wide confidence intervals.

Therefore, alerting patients on the risk of AACG with triptan use is not currently indicated.

Lay Summary

Migraines are one of the most common and disabling medical conditions in the world. Triptans are a frequently prescribed medication for those suffering from migraines and are associated with a number of adverse events that the Food and Drug Administration (FDA) has warned both prescribing doctors and patients who use this medication. We undertook a large epidemiologic study to determine the risk of suffering from acute angle closure glaucoma (AACG) with use of triptans. AACG is an ophthalmic emergency whereby the sudden increase of pressure within the eye leads to damaging the optic nerve and can ultimately lead to blindness. The results of our study did not find an increase in the risk of AACG with triptan use. These data are reassuring for both patients taking these medications and the clinicians who prescribe it.

Preface

No manuscripts have been submitted for publication or are currently published from any section of this thesis. However, a condensed version of this thesis will be submitted for publication in the near future.

Mohit Sodhi made major contributions to the study design, methodology and statistical analysis. Mohit Sodhi was also responsible for drafting this thesis and will be responsible for drafting and submitting a manuscript on this thesis topic.

All members of the supervisory committee (ME, CAS, FM) assisted with outlining the study methodology and made contributions and edits to drafts of this thesis. Dr. Abbas Kezouh, a biostatistician from the Center for Clinical Epidemiology, Jewish General Hospital, McGill University, was involved with data analysis, SAS coding, and provided the data output for this study.

This project (Risk of Acute Angle Closure Glaucoma with Triptan Use) was approved by the UBC Research Human Ethics Board, UBC CREB Number H18-02119.

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List of Abbreviations

5-HT	Serotonin
AACG	Acute Angle Closure Glaucoma
ACG	Angle Closure Glaucoma
ADE	Adverse Drug Event
AERS	Adverse Events Reporting System
AH	Aqueous Humor
AM	Adrenomedullin
CC	Case Control
CGRP	Calcitonin Gene-Related Peptide
CN	Cranial Nerve
D2R	Dopamine receptor D2
DA	Disproportionality analyses
DM	Drug Monograph
FDA	Food and Drug Administration
GDS	Glaucoma Drainage Surgery
ICA	Iridocorneal Angle
ICD	International Classification of Diseases
IOP	Intraocular Pressure
LGN	Lateral Geniculate Nucleus
MIDAS	Migraine Disability Assessment
NCC	Nested Case-Control
nd:YAG	Neodymium-Doped Yttrium Aluminum Garnet
NSAID	Non-steroidal Anti-inflammatory Drug

NTG	Normal Tension Glaucoma
OAG	Open Angle Glaucoma
OCT	Ocular Coherence Tomography
ON	Optic Nerve
OR	Odds Ratio
OTC	Over the Counter
OV	Open Vigil
PE	Pharmaco-epidemiologic
PRN	Pro Re Nata
RCT	Randomized Controlled Trial
RGC	Retinal Ganglion Cell
ROR	Reporting Odds Ratio
RPE	Retinal Pigment Epithelium
RR	Risk Ratio
Rx	Prescription
SAS	Statistical Analysis System
SD	Standard Deviation
SSRI	Selective Serotonin Reuptake Inhibitor
TG	Trigeminal
TGC	Trigeminocervical
TGV	Trigeminovascular
TM	Trabecular Meshwork

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Dedication

To my family, friends, and research team.

Chapter 1: Introduction to Glaucoma

Chapter 1.1: Synopsis

In this chapter I will be reviewing ocular anatomy and physiology as it pertains to glaucoma. I will then be reviewing the epidemiology and epidemiological risk factors of glaucoma and summarizing the clinical risk factors and diagnosis of glaucoma. I will be exploring different imaging and diagnostic techniques that assist ophthalmologists with glaucoma diagnosis. I will conclude by reviewing both medical and surgical treatments for glaucoma.

Chapter 1.2: Glaucoma Anatomy and Pathophysiology

1.2.1 Relevant Ocular Anatomy and Physiology:

Light enters the eye through the cornea, the transparent anterior aspect of the eye¹. Light then passes through pupil, the opening in the iris (the anterior most colored part of the eye), and then the lens^{1,2}. Aqueous humor (AH) fills the anterior chamber (the space between the innermost portion of the cornea and the iris) and its primary function is to provide nutrients to the cornea and lens, inflate the eyeball itself, as well as maintain intraocular pressure (IOP)³. A few other noteworthy anterior aspects of the eye include the ciliary body and the trabeculae. The ciliary epithelium produces AH while the ciliary muscles help control the shape of the lens and allows it to accommodate to view objects at varying distances and controls the flow of AH into Schlemm's canal^{3,4}. Schlemm's canal is a lymphatic-like vessel that drains AH into the body's main circulation via episcleral veins^{3,5}. These veins help determine the minimum IOP that can be attained through medical therapy⁶. The trabeculae, or trabecular meshwork (TM), lines Schlemm's canal and is the primary resistive power against drainage of AH from the eye⁷. Both the TM and Schlemm's canal are located where the iris and the cornea meet and where the main white of the eye (the sclera) progresses into the cornea, called the iridocorneal angle (ICA)⁷. As

previously mentioned, a primary purpose of aqueous humor is maintenance of the intraocular pressure, the pressure of fluid in the eye measured in millimeters of mercury³. The normal flow of AH in the eye starts at the posterior chamber, where it is produced by the ciliary body, and it flows through the pupil and exits through Schlemm's canal via the TM into the episcleral veins, which then empties into systemic circulation³.

Normal IOP is between 9 and 21 mmHg and acute changes in IOP can be brought upon by exercise, medication and drug consumption, heart rate, respiration, and general day-to-day variation^{8,9}. It is primarily preserved by the coordination of the ciliary muscles and the TM³. When ciliary muscles contract, they move anteriorly and inwards, causing distension of the TM which leads to decreased resistance to outflow, and thus increased outflow of AH³. When the ciliary muscles relax, the opposite occurs which leads to a decrease in mesh pore size, thus decreasing outflow of AH³. Abnormal increases in IOP can indicate pathology, therefore it is critically important for the body to be able to maintain its IOP within the normal range¹⁰.

Light is then passed through the middle of the eyeball called the vitreous body which is filled with vitreous humor that helps give the eye its spherical shape¹¹. The light is focused to the back of the eye called the retina, which contains 6 primary layers of cells¹². The most anterior layer (towards the front of the eye) of the retina contains retinal ganglion cells (RGCs) whose axons cover the surface of the retina and exit the eye as the optic nerve (ON)¹². The optic nerve, carrying the integrated signals, travels to the lateral geniculate nucleus (LGN) of the thalamus, which projects axons to the visual cortex (the occipital lobe) of the brain¹³. This is where the primary vision center of the brain is located and allows us to perceive the images we see¹³. The area where the optic nerve exits the retina and into the brain is perceived as the blind spot in our visual field¹⁴. Moving from anterior to posterior, there are layers containing bipolar, amacrine, and horizontal cells, all of which contribute to light signal transduction in the eye^{13,15}. The

second most posterior retinal layer contains rod and cone cells¹³. Rod cells are most active in situations where there is a lack of light, giving humans vision in dim conditions (scotopic vision)¹⁶. Cone cells are responsible for sensing color and are most active in well-lit conditions (photopic vision)¹⁶. The center of the retina, called the macula, has a high density of cone cells and its function is to provide a high visual acuity¹⁷. At the center of the macula lies the fovea¹⁸. The posterior-most layer of the retina is the retinal pigment epithelial (RPE) layer which has critical functions in: promoting light absorption, phagocytosis (breaking down) of rods and cones that need to be renewed, supporting the health and integrity of the retina via factor secretion, and is a part of the blood-retina barrier, which prevents certain substances from entering the eye¹⁹. As mentioned earlier, the ON (CN II), is critical to light perception and signal transduction to the brain; any damage to the ON can impact eyesight and ultimately lead to blindness²⁰.

It is worth mentioning the sensory and motor innervation of the eye and the orbital space. Cranial nerves (CN) III (oculomotor nerve), IV (trochlear nerve), and VI (abducens nerve) are all involved with the eyeball's motor response and innervate extraocular muscles to provide movement for the eye²¹. The ophthalmic nerve (CN V₁) is a branch of CN V (trigeminal nerve) which carries sensory information from the anterior chamber (ciliary bodies, iris, and cornea), the tentorium cerebelli, posterior area of the falx cerebri, and the dura mater surrounding the brain²². It also carries afferent information from the mucous membranes of the orbit as well as the sphenoid and frontal sinus in addition to the skin of the forehead, scalp, and eyelids²².

1.2.2 Glaucoma Pathophysiology

Glaucoma is a group of ocular diseases that affect the ON, either unilaterally or bilaterally, and subsequently leads to vision loss if left untreated²³. Primarily, RGCs that are critical to transducing light information to downstream processing pathways are damaged in a glaucomatous state, thus highlighting the importance of RGCs²⁴.

Although the underlying etiology of glaucoma is unknown, a cardinal symptom of many forms of glaucoma is increased IOP²⁵. The increased IOP leads to compression of the lamina cribrosa, located posteriorly in the eye, deep within the ON head²⁵. The lamina cribrosa is where axons of the RGCs transverse into the brain, and it is this area that subjects the ON to the greatest potential for damage²⁶. Raised IOP can induce compression and mechanical stress on the RGCs and transporting axons, subsequently reducing signals to the lateral geniculate nucleus (LGN) of the brain and thereby negatively affecting vision²⁴.

1.2.3 Subtypes of Glaucoma

Although there are numerous subtypes of glaucoma, the two most common forms of glaucoma are open angle glaucoma (OAG) and angle closure glaucoma (ACG)²⁴. OAG occurs when the ICA is normal or larger than normal, however there is disruption of AH outflow from the TM²⁴. This can be due to deposition of extracellular debris into the TM, essentially clogging the mesh pores^{24,27}. ACG is characterized by a very narrow ICA, where the iris is the primary obstructing force and induces the closure of the ICA, preventing outflow of AH, and increasing IOP²⁴. Two mechanisms may cause the iris to block the angle: a force pulling the iris towards the TM such as iris neovascularization²⁸, or a force pushing the iris form behind and closing the angle, such as a displaced lens²⁹. Both OAG and ACG can be subdivided into two types: primary and secondary. Primary OAG or ACG occurs for an unknown cause that precipitates the disease while secondary glaucoma occurs “secondary” to another disease, such as inflammation, traumatic injury, or tumor²⁴.

Acute ACG (AACG) is another subtype of glaucoma worth highlighting; it will be heavily focused on in this thesis. Patients present with a rapid onset of significantly increased IOP, blurry vision, nausea and vomiting, headache, fixed dilated pupils, unilateral or bilateral ocular redness, and intense pain in the affected eye(s)²⁴. AACG is a true ophthalmic emergency;

pressure buildup caused by the iris completely blocking AH drainage and can rapidly provoke permanent ON damage³⁰. The most common precipitating factor leading to an attack of AACG is due to a relative pupillary block secondary to pupil dilation either by pharmacological or natural means (such as going into a dark room)²⁹. When the pupil is mid-dilated, the relative pupil block between the posterior and anterior chamber is maximal²⁹. This leads to a pressure differential causing the iris to bow forward²⁹. If the angle is narrow, the bowing forward of the iris will lead to closure of the ICA and IOP elevation²⁹.

The existence of normal tension glaucoma (NTG) highlights the fact that although increased IOP is an important clinical sign of glaucoma, not all forms of glaucoma present in this manner³¹. However, lowering IOP may still be beneficial to NTG patients³¹. NTG involves damage to the ON despite a within normal range IOP and its diagnosis is dependent on a good assessment of patient history, clinical signs and symptoms, and discerning various optic nerve head vulnerabilities³¹.

Chapter 1.3: Epidemiology of Glaucoma and Epidemiological Risk Factors

Glaucoma is one of the leading causes of both visual impairment and irreversible blindness worldwide³². Approximately 6 million people are blind as a result of glaucoma worldwide³³. In 2013, there were approximately 64 million people between the ages of 40 and 80 globally who suffer from primary OAG and ACG, with a global prevalence of 3.54%³². Approximately half of those with glaucoma are undiagnosed, having the vast majority of these patients suffering from undiagnosed OAG³³. It is estimated that due to the rise in the aging population, there will be 76 million people with glaucoma in the year 2020 and 112 million by the year 2040³². In 2013, approximately 69% of glaucoma cases were OAG (~44 million), and 31% of glaucoma cases were ACG (20 million)³². Between 20-30% of these ACG cases are classified as AACG attacks^{34,35}. Ethnicity and age are important factors that influence the

presentation of glaucoma. Indeed, for ACG, the incidence ranges from 4.4/100,000 people to 15.5/100,000 and depends on ethnicity³⁵. Cases of glaucoma for those between 2 and 18 years of age was 0.01% (1 in 10,000) while the estimate for those between 18 and 40 was more than 10 times higher (0.16%), yet evidently very rare³⁶.

Some epidemiological risk factors for OAG include being of African American descent, older age, and having a family history of OAG^{37,38}. Epidemiological risk factors of ACG include being of East Asian or Inuit descent, being of the female sex, and being of older age³⁹.

Chapter 1.4: Risk Factors, Clinical Presentation, and Diagnosis of Glaucoma

There are a number of noteworthy clinical risk factors for glaucoma. Clinical risk factors of OAG include and are not limited to myopia (nearsightedness) and low diastolic perfusion pressure³⁸. For those with increased IOP, having a thin cornea is also considered a major risk factor³⁸. Other risk factors for OAG include elevated systolic blood pressure, diabetes mellitus, and migraines, however current evidence is inconsistent³⁸. Clinical risk factors for ACG include having a shallow anterior chamber, having a thicker lens, having a shorter axial length (distance from the anterior to posterior poles of the eye), and hyperopia (farsightedness)^{39,40}. Clinical risk factors for AACG are generally the same as ACG⁴¹. However, there are risk factors that are more specific to precipitating an AACG attack which include: taking medications that promote mydriasis either intentionally for examination (phenylephrine), as a side effect of medication (antidepressants), or natural causes (entering dark rooms)⁴¹. Other risk factors for AACG include: cataracts, tumors, diabetic retinopathy, ocular ischemia, or an ectopic lens⁴².

Diagnosis of any form of glaucoma involves the physician conducting a thorough patient history. This includes learning the patient's family history in relation to the disease, the patient's past ocular history (noting any prior diseases and procedures), and current and/or past medications²⁴.

A complete ophthalmologic examination is necessary, including measuring visual acuity and pupillary responses⁴³. Tonometry, discerning the patient's IOP, is another critical assessment a physician can perform. This can be done via a Tono-Pen, a probe that lightly taps the cornea and subsequently records the patient's IOP, or a Goldmann applanation tonometer, which is an instrument attached to a slit lamp and calculates the amount of force needed to flatten a particular area of the cornea^{44,45}. Gonioscopy can be performed during a slit-lamp examination to determine the size of the iridocorneal angle, (open, narrow, or closed)⁴⁶. Gonioscopy can allow the physician to clearly visualize relevant ocular structures in relation to the patient's disease⁴⁶. An estimation can also be obtained by illuminating each eye using a penlight⁴⁷.

Objective testing is important, and appropriate tests include ocular coherence tomography (OCT), retinal/ON imaging, and visual field assessments. OCTs are cross section images taken of the retina which allow imaging of the many retinal layers, in addition to the ON nerve and its head⁴⁸. In a glaucomatous state, there is visible thinning of the retinal nerve fiber layer which contains the RGCs, in addition to visible structural changes of the ON and the ON head⁴⁸.

With ON and retinal imaging, the physician can visualize the optic disk, which contains mostly nerve fibers, and its central depression called the cup, which is not composed of neural tissue⁴⁹. In healthy eyes, the size of the cup is relatively small, about 10% the size of the optic disk; a cup to disk ratio of 0.1⁴⁹. This indicates that the neural tissue of the ON has not yet been damaged⁴⁹. In glaucomatous eyes, the ON fibers begin to atrophy, consequently enlarging the cup and shrinking the relative proportion of area containing the disk, therefore increasing the cup-to-disk ratio⁵⁰. When IOP is increased and visual field loss is present, a cup to disk ratio of 0.5 or greater or finding high asymmetry between eyes can be indicative of glaucoma⁴⁹.

Another important clinical examination to perform is perimetry, also known as a visual field test⁵¹. One main finding of glaucomatous patients involves loss of vision within the central

30 degrees of the visual field⁵¹. Perimetry is usually performed using a Humphrey automated perimeter where a patient is told to focus on bright colored light central to their visual field (at 0 degrees) surrounded by a white background^{51,52}. They are then asked to press a button whenever they see a bright white light in their periphery; this can be tracked electronically and can highlight any deficits in a patient's visual field⁵². In a visual field analysis, the darker the section, the poorer the vision is in that area⁵².

Although there are many potential reasons for decreases in peripheral vision, cupping of the ON, and increased IOP, it is important to perform a thorough patient history, assessment of risk factors, and track the progression of any ocular anomalies while considering all factors when determining a diagnosis²⁴.

Chapter 1.5: Glaucoma Treatment

As with most of medicine, there are two avenues of treatment of glaucoma: pharmacological and surgical.

Pharmacological treatment of glaucoma mainly pertains to decreasing the patient's IOP, thus decreasing the risk of damage to RGCs and the ON²⁴. It has been found that even in glaucoma patients with IOPs within normal limits, lowering a patient's IOP may be helpful in reducing glaucoma progression³¹. One method by which physicians can achieve this is by decreasing the volume of AH produced by the patient's eyes⁵³. This can be accomplished through administration of beta blocking agents in the form of eye drops such as timolol, levobunolol, and carteolol⁵³. Alpha-adrenergic blockade, by using drugs such as apraclonidine or brimonidine, can also be used to decrease AH production and are usually prescribed before and after laser treatments⁵⁴. Carbonic anhydrase inhibitors are also frequently used to decrease the formation of AH and are administered in the form dorzolamide hydrochloride and brinzolamide drops⁵⁴. Systemic carbonic anhydrase inhibitors such as acetazolamide are also given in

conjunction with drops in cases of AACG where a high IOP is required to be reduced quickly⁵⁴. Systemic acetazolamide has been found to decrease aqueous humor production by 40-60%⁵⁴.

It is also possible to increase the outflow of aqueous humor using pharmacological agents⁵⁴. This is primarily managed using prostaglandin analogs such as bimatoprost, tafluprost, or travoprost eye drops^{54,55}. These drugs are sometimes prescribed in conjunction with agents used to decrease production of AH⁵⁴. Parasympathomimetic agents such as pilocarpine (a muscarinic receptor agonist) acts by increasing aqueous outflow by contracting ciliary muscle fibers, thus opening the pores of the TM to allow for greater outflow of AH⁵⁴. In patients with AACG, doctors may prescribe hyperosmotic agents such as oral glycerin to reduce vitreous humor volume in addition to drugs that decrease AH production⁵⁴. The goal is to reduce the amount of lens displacement caused by excess vitreous humor behind the lens, thereby allowing the lens to move posteriorly and open a narrowed ICA⁵⁴.

In cases of primary ACG, miotic (pupil constricting) agents are often prescribed to reduce the relative pupil block, thereby reducing the pressure differential and opening the angle⁵⁴. Contrarily, if ACG is a result of the lens displacing anteriorly, mydriatic (pupil dilating) drugs may be prescribed to assist in relaxing ciliary muscles which promotes the lens to move posteriorly⁵⁴.

Surgical treatment of glaucoma has shown to be highly successful in treating glaucoma. Procedures used to treat ACG (in particular, AACG), involves either peripheral iridotomy or iridectomy⁵⁶. An iridotomy involves using a neodymium:YAG laser (nd:YAG) to remove pupillary blocks by directly connecting the anterior and posterior chambers, thus removing pressure buildup^{56,57}. Iridectomy involves surgical removal of the iris in order to decrease pressure and open the ICA⁵⁶. It has been found that prophylactic nd:YAG laser iridotomy has

equal efficacy to surgical iridectomy, however the nd:YAG laser iridotomy is more preferred by patients⁵⁸.

The primary surgical option for OAG is a laser trabeculoplasty, which involves using an nd:YAG laser to stimulate the endothelial cells of the trabecular meshwork leading to upregulation of the production of endogenous matrix metalloproteinase enzymes to digest the excess glycosaminoglycans in order to promote AH outflow^{59,60}. Glaucoma drainage surgery (GDS) is utilized in more serious cases of glaucoma where previous laser treatments were ineffective in decreasing a patient's IOP⁵⁷. The preferred method of GDS is a trabeculectomy, where a flap is produced in the sclera to permit controlled egress of AH to the sub-conjunctival space^{57,61}. In cases where all forms of medical and surgical treatment fail, an ophthalmologist may opt to perform a cyclodestructive procedure, where an nd:YAG laser or ocular cryotherapy can be used to permanently destroy the ciliary body, therefore significantly reducing the production of AH^{57,62}.

From this point forward, I will be shifting my focus to angle closure glaucoma (in particular, AACG), as it is most relevant to my thesis. Any place where the word “glaucoma” is used, assume it is in reference to AACG, unless otherwise specified.

Chapter 2: Introduction to Migraines

Chapter 2.1: Synopsis

The brain is one of the most complex systems known to man. Given the complexity of the brain, it is understandable that the pathophysiology of migraines is also complex; many mechanisms have yet to be elucidated. I will first be exploring the relevant anatomy and physiology of the brain and the meninges with a special focus on the trigeminal (TG) complex. I will then outline both the epidemiological and clinical risk factors while investigating how a typical migraine presents. I will then discuss how migraines can be diagnosed and what tools a physician can use to assist in determining how severe a patient's migraine can be. I will then look into the vast treatments for migraines; in particular, triptans.

Chapter 2.2: Relevant Migraine Anatomy and Pathophysiology

The brain is surrounded by 3 primary layers of membranous tissue called the meninges; the pia mater (closest to the brain), the arachnoid mater, and the dura mater (closest to the skull)⁶³. Within these layers runs numerous extracerebral blood vessels⁶³.

Part of headache pain associated with migraine attacks is due to activation of nociceptors that innervate the blood vessels within the dura, arachnoid, or pia mater⁶⁴. As such, it has been found that stimulating these nociceptors can lead to symptoms very similar to that of a migraine headache such as intense pain, nausea, and photophobia⁶⁴.

The TG complex is of importance when outlining the pathophysiology of a migraine attack⁶⁵. The trigeminocervical (TGC) complex refers to the convergence of cervical and trigeminal neurons in the brainstem⁶⁵. This complex receives neuronal information from the meninges and projects signals to subcortical structures implicated in migraine pathophysiology such as the brainstem and the hypothalamus, which proceed to send information to the cerebral cortex to process the nociceptive signal itself⁶⁶. Stimulation of upper cervical roots can induce

pain similar to that of a migraine headache and stimulation of the ophthalmic nerve (V₁) can lead to pain felt in the cervical (neck) area⁶⁷.

The trigeminovascular (TGV) system refers to the trigeminal nociceptive innervation of blood vessels⁶⁴. Sensory information is carried from the ophthalmic branch (V₁) but may also arise from the maxillary (V₂) and mandibular branches (V₃)⁶⁴. The nociceptive information carried by V₁-V₃ travel through the trigeminal ganglion and reach the dura, arachnoid, or pia matter blood vessels in addition to sending nociceptive signals to the brainstem⁶⁴. Vasodilation or deformation of meningeal blood vessels triggers trigeminal nociception and release of certain transmitters, thereby inducing pain^{64,68}.

The TGV and TGC complex differ in terms of their neuroanatomy and functionality as the TGV complex is implicated in the nociception of a migraine itself via the innervation of blood vessels while the TGC is implicated in passing the neural information along to higher cortical and subcortical structures within the brain via the meninges in addition to the sensation and sensitization of pain^{66,68}.

A cardinal symptom of migraines is photophobia, as 90% of migraine patients report this symptom⁶⁹. There are three classifications of light sensitivity that patients with migraine may experience⁶⁴. In some individuals, the migraines they experience are aggravated by light⁶⁴. It is hypothesized that in these migraineurs, light signals that are passed by RGCs converge with TGV nociceptors on the same thalamo-cortical pathway which leads to allodynia (pain sensitization) extracerebrally; this highlights a direct path from the ON to thalamic nuclei⁷⁰. A second classification of photophobia includes having an increased sensitivity to light⁷⁰. This is believed to be primarily due to the nociceptive signals located within the TGV path which then project to the visual cortex of the brain and enhances the response to light stimuli; this is possibly due to an intermediary step involving light sensitive neurons in thalamic nuclei that receive input

from RGCs which then project to the visual cortex of the brain^{64,70}. Lastly, some migraine sufferers experience intraocular pain caused by bright light^{64,70}. This may be a result of light leading to deformation and/or vasodilation of ocular blood vessels which are innervated by trigeminal nociceptors, leading the individual to feel ocular pain^{64,70}.

The TGV complex nociceptors, when activated, release vasoactive mediators such as calcitonin gene-related peptide (CGRP), which is a potent vasodilator⁷¹. This neuropeptide is heavily distributed throughout the brain, especially in structures critical to migraine pathophysiology such as the brainstem, the periaqueductal grey, the cerebellum, and the hypothalamus^{67,72}. It has been found that when blood samples are taken from the external jugular vein of patients with migraines, CGRP is found to be elevated within this blood during the migraine attack, further solidifying its role in migraine pathophysiology⁷³. Furthermore, when CGRP is injected into migraine patients, it induces a migraine attack, which does not occur in non-migraine subjects⁷³. CGRP also leads to activation of the nociceptors within the meninges in addition to inflammation⁷⁴.

Another potent vasoactive chemical that is hypothesized to be potentially involved in migraine pathophysiology is adrenomedullin (AM)⁷⁵. It is heavily secreted by vascular endothelial and smooth muscle cells (in particular those within cerebral vessels) and its secretion leads to vasodilation⁷⁵. It acts on the same receptors and exhibits a similar mechanism of action as CGRP⁷⁵. The AM relation to migraine has not yet been well elucidated and study results have been contradictory, however it would be worthwhile for future studies to further investigate the relationship⁷⁵.

Serotonin (5-HT) is also heavily implicated in migraine pathophysiology⁷⁶. Serotonin is a known vasoconstrictor within the central nervous system⁷⁷. Research shows that lack of serotonin not only precipitates significant vasodilation within cerebral and extracerebral blood

vessels, but it also may lead to nausea, which is another cardinal symptom of a migraine headache⁷⁸. Furthermore, the standard of treatment for migraine abortion is prescribing triptans, which are strictly serotonin receptor agonists⁷⁹.

For many people, different features about their environment can trigger the onset of an acute migraine attack. These can include the following: stress, not eating, weather, perfume or odor, neck pain, sleep disturbance, lighting, alcohol and smoke, hormones in women, and sleeping late⁸⁰. In terms of genetics, although there have been over 38 different migraine loci located in the genetic code, there has yet to be substantiated evidence with large effect sizes for migraines to determine whether they are familial or not⁶⁷.

Chapter 2.3: Epidemiology of Migraines

Migraine headaches are one of the most prevalent medical conditions in the world. The Global Burden of Diseases, Injuries, and Risk Factors Study has found that migraines are one of the leading cause of disability worldwide, especially for those younger than 50 years of age⁶⁷. Furthermore, symptoms associated with migraines such as depression and neck pain are also among the leading causes of disability worldwide⁶⁷. It is estimated that 1 in 7 people (14.7%) suffer from migraine attacks globally, making it the third most prevalent disease in the world⁸¹. Migraines affect women three times more frequently than men⁸². Although children can be affected by migraines, they are typically diagnosed in individuals aged 25-55⁸³. Episodic migraines have a global prevalence of ~17% for women and ~6% for men while chronic migraines have a prevalence of 1.3% for women and 0.5% for men, but rates can be as high as ~5% for the general population^{84,85}.

Migraines have a high economic burden such that it costs 36 billion USD in lost productivity and overall healthcare costs in the USA alone⁸³. This surmounts to approximately 113 million lost in work days⁸³. It has also been found that the healthcare costs for those

suffering from migraines are 70% greater than those who do not suffer from migraines⁸³.

Episodic migraines tend to have less of an economic burden than chronic migraines, ranging from ~\$700 to \$1,500 annually for those in North America as opposed to ~\$1800-\$4400 lost per sufferer of chronic migraines⁸⁶. Chronic migraines also lead to greater days of lost productivity (~68 days) versus ~13 days for episodic migraine sufferers in a three-month period⁸⁶.

Chapter 2.4: Risk Factors, Clinical Presentation, and Diagnosis of Migraines

Certain aspects of an individual's environment or daily tasks can trigger an acute migraine attack. However, there are different factors that can lead to progression of episodic or acute migraine attacks to become chronic migraines, known as chronification⁸⁷. Approximately 3-14% of episodic migraineurs progress to develop chronic migraines, with risk factors for chronification being increased age, low socioeconomic status, being of the female gender, depression, and stress^{85,87}. One of the best predictors of chronic migraines includes the overuse of medication used to treat acute migraine attacks⁸⁷. This is defined as taking analgesics and triptans on 15 and 10 days per month, respectively⁸⁷. Another risk factor for chronic migraines includes having received ineffective treatment of acute migraine attacks, as it has shown to double the risk of those receiving appropriate treatment⁸⁷. Obesity has also been found to be a risk factor for chronification of migraines⁸⁷. Other risk factors for migraines include: family history of migraines, depression, stressful life events, a variety of craniomandibular disorders, caffeine withdrawal, and snoring/sleep apnea⁸⁸.

The diagnosis of migraine can be straightforward and does not typically require advanced technological methodology, assuming other causes of headache are ruled out. Research has shown that in patients with headache without other neurological symptoms, abnormal MRI findings are discerned in less than 1% of patients⁸⁹. A physician should take a detailed patient history in addition to attentively listening to the patient's symptoms as they relate to the disorder.

Questions regarding prior head trauma, family history, and history of the headache is critical in making a correct diagnosis⁹⁰. Assuming other potential diagnoses are ruled out after a thorough physical examination, the process of elimination can be applied to diagnose a migraine⁹⁰.

Furthermore, follow up visits with the patient after prescribing treatments can allow the doctor to alter the diagnosis given how well the treatment has worked or reassure themselves and the patient that a correct diagnosis was made^{89,90}. Patients are also encouraged to record a diary noting the frequency of their migraine attacks, any medications used, and migraine severity to assist their physician in selecting or modifying their prescribed therapy or to confirm diagnosis⁸⁹.

By describing their symptoms in detail, a patient can help their physician in diagnosing and treating them accordingly. For many patients, a typical migraine consists of four primary, yet non-obligatory phases: the premonitory (prodrome), aura, headache, and postdrome phases⁷⁴. The premonitory phase can occur 12-72 hours before the headache actually occurs⁹¹. It is associated with photophobia, food cravings, fatigue, and muscle tenderness⁹¹. Individuals are typically able to correctly predict that a migraine will occur in the near future during this phase⁹¹. Next is the aura phase, which affects approximately 30% of migraineurs, and typically occurs within minutes prior to the actual migraine attack^{91,92}. It is most commonly associated with disturbance of the patient's vision; however, motor, speech, and language difficulties may also arise⁹¹. The headache phase can last anywhere from 4 to 72 hours and is the phase that most notably affiliated with a migraine⁹¹. It is in this phase where the TGV complex is most active and leads to headache pulsation, throbbing, allodynia, and cognitive dysfunction⁹¹. The last phase of a migraine attack is the postdrome, which typically lasts anywhere between 6 to 48 hours after the headache phase⁷⁴. The most common symptoms of the postdrome phase include difficulty with concentration, stiff neck, persistent photophobia, and fatigue⁷⁴. By describing these symptoms at length, a patient can help guide a physician's diagnosis and treatment.

A useful tool used by clinicians to assess the degree of disability associated with a migraine is called the Migraine Disability Assessment (MIDAS) test⁸⁹. It involves asking the patient a few questions regarding the frequency of their migraines, their symptoms during an attack, how often it affects their productivity, and how often it affects day-to-day tasks⁸⁹. A score is assigned based on the patient's responses⁸⁹. A score of 0-5 days per month warrants a MIDAS grade of I (little or no disability), and goes as high 21+ days, designated a MIDAS grade IV (severe disability)⁸⁹.

Chapter 2.5: Migraine Treatment

The simplest form of migraine treatment involves environmental modification. This includes avoiding the previously discussed triggers for a migraine attack, as it pertains to the patient⁸⁷. If an individual is aware that a particular trigger or activity induces migraine, they are advised to avoid that if possible⁸⁷.

The most common medical intervention for migraine headaches involves drug therapy. Pharmacologic agents can be broken down into two categories: prophylactic agents and abortive treatment⁹³.

2.5.1 Prophylactic Treatment

Prophylactic medications have shown to be very useful in reducing the frequency of migraine attacks in addition to reducing the severity of an attack should it still occur⁹³. Many of these drugs are normally prescribed for other health conditions, however, they can be repurposed to pose a beneficial effect in terms of migraine prevention⁹³. Beta-adrenergic blockers such as propranolol or metoprolol (which have shown to be equally effective)⁹⁴, and antiepileptic agents such as topiramate or valproate have shown to be quite effective migraine prophylactic agents⁹⁵. Metoprolol, propranolol, valproate, and topiramate are considered the best and first-line treatments for migraine prophylaxis⁹⁵. Beta blockers have shown efficacy in preventing

migraines when taken daily over a 6-month period⁹⁴. Topiramate typically takes about 1-2 months to take full effect in reducing migraine frequency if taken daily⁹⁶ while valproate has shown to decrease migraine frequency over a period of 6 months when taken daily⁹⁷. A recent meta-analysis investigating the effectiveness of migraine prevention using tricyclic antidepressants such as amitriptyline, have shown to have relatively favorable outcomes⁹⁸. Depending on the patient, combinations of these drugs can prove to be rather helpful⁹³. Beta blockers have shown favorable results when combined with either valproate or topiramate while nortriptyline has shown to be efficacious while combined with topiramate⁹³.

Many different medications can be taken over the counter or prescribed by a physician as abortive treatments of a migraine attack.

2.5.2 Abortive Treatment

2.5.2.1 Abortive: Acetaminophen and NSAIDs

Many individuals resort to using acetaminophen or over the counter (OTC) non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid, ibuprofen, or naproxen to treat their migraines; they remain the most utilized drugs for migraine abortion⁹⁹. It has been shown that although many NSAIDs (both prescription and OTC) have similar efficacy in treating migraines, they are considered some of the most effective drugs at treating migraines, even more so than acetaminophen⁹⁹. One drawback of using NSAIDs or acetaminophen is that a higher dose is usually required, and this may lead to headaches caused by medication overuse⁹³.

2.5.2.2 Abortive: Ergot Derivatives, D2R Antagonists, and Opioids

Ergot derivatives such as dihydroergotamine or ergotamine and caffeine combination pills can be prescribed for severe, long lasting migraines¹⁰⁰. However, due to their widespread mechanism of action and affinity for many receptor subtypes, ergot derivatives are sometimes not well tolerated¹⁰¹. Although dihydroergotamine typically has a smaller side effect profile, it is

not as effective in migraine abortion as ergotamine¹⁰⁰. Ergot derivatives, nowadays, are prescribed infrequently due to their overuse and poor side effect profile¹⁰⁰.

Physicians may also prescribe anti-emetic drugs that are dopamine receptor-D2 (D2R) antagonists (such as metoclopramide or domperidone) that can be used to treat nausea associated with migraine attacks¹⁰².

Although less frequently prescribed, opioids such as codeine can be used to treat migraines, however opioid use runs the risk of opioid dependence and medication overuse¹⁰³.

2.5.2.3 Abortive: Triptans

The triptan class of drugs, which includes drugs such as sumatriptan or zolmitriptan, are the first line of treatment for those who don't respond to NSAIDs¹⁰⁴. As such, they are a widely prescribed medication to migraine sufferers, with over 1.2 million prescriptions of triptans in the USA alone in 2013¹⁰⁵. Triptans are 5-HT 1B and 5-HT 1D receptor agonists¹⁰⁰. Triptans lead to vasoconstriction via agonism of the nerve endings of extracerebral blood vessels¹⁰⁰. Furthermore, by binding to presynaptic 5-HT 1D receptors, they inhibit vasoactive (vasodilating) peptides and have also been shown to inhibit nociceptive neurotransmission from the dorsal horn of the spinal cord, thus decreasing pain signals sent to the thalamus^{106,107}. Triptans have also been found to lower CGRP levels in blood thereby improving migraine symptoms, thus further strengthening the role of CGRP in migraine pathophysiology¹⁰⁸. Triptans can also be prescribed with NSAIDs, which have shown to have favorable benefits to migraineurs when compared to monotherapies¹⁰⁹. As such, triptans that are prescribed with naproxen have shown to be somewhat superior to triptan monotherapy but significantly superior to naproxen monotherapy¹¹⁰. Typically, triptans are prescribed in conjunction with anti-emetic drugs, such as those mentioned above, or for some individuals, triptans provide some nausea relief¹⁰². Research has shown that although sumatriptan is the most prescribed, eletriptan, rizatriptan, and

almotriptan have the greatest rate of success⁹³. If triptans are not initially well tolerated by the patient, different formulations of triptans can be prescribed in the form of intranasal spray, buccal (dissolving in the cheek), or subcutaneous injection⁹³. Some common reported side effects of triptans include dizziness, sleepiness, muscle weakness, nausea, hot or cold tingling sensations, flushing, and dry mouth¹¹¹.

It is recommended that patients use NSAIDs or acetaminophen for less than 15 days per month⁹³. Should a patient be using triptans or ergot derivatives, they are recommended to use them on less than 10 days per month⁹³. A typical clinical rule of thumb is the “three strike” policy; if a particular treatment does not reduce a patient’s migraine symptomology in at least 2 of 3 attempts, the treatment should be switched⁹³.

2.5.3 Surgical

In very severe cases of chronic migraines, surgery is an option and has shown to be almost 90% effective in treating migraines altogether¹¹². Surgical treatment may involve either injecting botulinum toxin (Botox) or decompressing specific trigger points along either the frontal (supraorbital and supratrochlear nerve branch of the ophthalmic division (V₁) of CN V), temporal (the zygomaticotemporal nerve branch of the maxillary division (V₂) of CN V), or occipital (the greater occipital nerve of the second cervical spinal nerve) trigger points¹¹².

Chapter 3: Relation Between Triptans and AACG

Chapter 3.1: Synopsis

In this chapter I will be reviewing both the published literature and unpublished reports relating triptans to AACG. I will also then highlight proposed mechanisms for why triptans could potentially lead to AACG and then discuss the objective of this study.

Chapter 3.2: Review of Published Literature

To conduct this review, I searched both MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE ®<1946 to Present) and Embase (1974 to present). No other search restrictions were made in either MEDLINE or Embase. Final search results were screened and included or excluded based on abstract content. The exact search strategy can be found in Appendix A.

Based on this review there are only 2 case studies that have alluded to the role of triptans and AACG development. One case study by Hsu et al (2017) reported a sumatriptan induced bilateral AACG attack. A 26-year-old woman presented to the emergency department with a severe headache, photophobia, and nausea after having used one 100 mg tablet of sumatriptan one-week prior for severe unilateral migraines¹¹³. She presented to the ER with loss of vision in both eyes with an elevated IOP (50 mmHg)¹¹³. Upon slit lamp examination, her ICA was found to be closed and she had developed acute myopia¹¹³. She was given mannitol, systemic acetazolamide, and eye drops containing dorzolamide-timolol to reduce her IOP¹¹³. After a few days, her IOP and myopic refractive error both decreased and her ICA opened¹¹³. Sumatriptan use was also discontinued¹¹³.

Although compelling, a limitation of a case report is that it cannot demonstrate a causal relation between X and Y, thus causation is difficult to discern. Furthermore, the authors mentioned that the patient had no prior medical history; however, they did not mention whether

this was in relation to past ocular history or general medical history. The authors also failed to discuss any other medications the patient was taking at the time or failed to discuss the patient's co-morbidities. It is possible the combination of the sumatriptan consumption and a potential co-morbidity had a synergistic effect and led to the AACG attack, or that a co-morbid disease alone acted as to lead to the acute ACG attack. Nonetheless, the authors hypothesized that the sumatriptan was the inciting agent¹¹³.

Another case study by Lee et al. (2017) described a case of a 42-year-old woman who had been using zolmitriptan over a 12-month period, however increased her dosage within a few days prior to the clinical presentation of AACG¹¹⁴. She presented with acute myopia, decreased vision, and increased IOP (34 mmHg) bilaterally¹¹⁴. Zolmitriptan treatment was discontinued and she was prescribed topical anti-glaucoma drugs (brimonidine and brinzolamide)¹¹⁴. After two weeks, her vision and IOP returned to within normal limits and her ICA opened¹¹⁴. Once the brimonidine and brinzolamide was discontinued, she experienced recurrent pressure-related headaches; as such, a laser trabeculoplasty was performed in order to avoid long term topical drug use¹¹⁴.

This study is also limited by its nature as a case study and although the authors hypothesized that zolmitriptan was the culprit inducing the AACG, it is difficult to discern causation. An additional issue with case studies is the lack of unexposed patients, such that we cannot calculate risk or odds ratios with only one or two subjects. Lastly, case reports cannot demonstrate cause and effect but only generate a testable hypothesis that can be examined using an epidemiologic study.

Chapter 3.3: Review of Unpublished Reports

The FDA has also received a number of reports of triptan induced ACG, however these data are unpublished¹¹⁵. No information regarding the individual cases is accessible (such as

patient history, clinical signs and symptoms, co-morbidities, duration of use, number of prescriptions, and number of medications). These FDA frequency reports can be retrieved by accessing Open Vigil FDA 2.1¹¹⁶. This is a project spearheaded by the Universitätsklinikum Schleswig-Holstein (UKSH) Institute of Experimental and Clinical Pharmacology¹¹⁵. It determines information on drugs from the FDA Adverse Event Reporting System (AERS)¹¹⁵. One can search one or multiple drugs and a particular adverse event that may be associated with said drug(s)¹¹⁶. A step by step guide to using the Open Vigil 2.1 database can be found in Appendix B. The Open Vigil system also employs disproportionality analyses (DA). DA are used to investigate drug safety ‘signals.’ Specifically, DA compare the risk of a particular outcome with a specific drug and compares this risk to the risk with all other drugs reported to the FDA¹¹⁶. Although this may be a relatively crude analysis, it is an effective hypothesis generating tool that can be used in large epidemiologic studies to address drug safety questions. Among the disproportionality analyses, an important metric is utilized called the reporting odds ratio (ROR)¹¹⁶. ROR is similar to that of an odds ratio used in epidemiological studies, however since it is calculated using a reporting database, it is referred to as a ROR. The ROR is calculated using the following mathematical formula¹¹⁶:

Formula 1:

$(DE \times de) / (dE \times De)$, where in this study:

DE=number of reported ACG cases with triptans

de = number of reported non ACG cases with all other drugs

dE = number of reported ACG cases with other drugs

De= number of reported non ACG cases with triptans

Figure 3.1 below shows the example calculation of sumatriptan induced ACG. Plugging the labeled values into the formula $(DE \times de) / (dE \times De)$, the answer will provide one with the

ROR. An ROR is deemed significant when the confidence interval does not cross 1 such that lower and upper bounds are greater than one ¹¹⁶. This means that there more reports of ACG with sumatriptan to the FDA than ACG reports with other drugs.

Figure 3.1: Example Screenshot of OV 2.1 Results for Sumatriptan and ACG

	Drug(s) of interest	All other drugs	Σ
Adverse event(s) of interest	12 DE	1214 dE	1226
All other adverse events	15720 De	6522477 de	6538197
Σ	15732	6523691	6539423

Rate (DE/D): 0.076278%

Chi-Squared with Yates' correction: 24.853341

Interpretation: Do the observed frequencies differ from expected frequencies? The greater the chi-squared value, the greater the differences. Chi square values g

Measurements of disproportionality (observed-expected ratios like RRR, PRR, ROR)

Interpretation: Generally, the higher the value, the more likely an association between drug(s) and adverse event(s) has been found. Lower bounds of confidence

Relative Reporting Ratio (RRR) and 95% confidence interval (lower bound; upper bound): 4.068612 (2.304703 ; 7.182533)

Proportional Reporting Ratio (PRR) and 95% confidence interval (lower bound; upper bound): 4.098944 (2.321821 ; 7.236277)

Reporting Odds Ratio (ROR) and 95% confidence interval (lower bound; upper bound): 4.10131 (2.322161 ; 7.243573)

According to the criteria of Evans 2001 (n > 3, chisq > 4, PRR > 2) this combination of drug(s) and adverse event(s) is considered: **likely an adverse reaction**

In this database, each of: sumatriptan, eletriptan, zolmitriptan, frovatriptan, and rizatriptan were searched individually with the adverse event being angle closure glaucoma, as the database does not distinguish between ACG and AACG. Between 2004-2018, the FDA received 22 reports of triptan induced ACG (Table 3.1)¹¹⁵. The results are summarized in Table 3.1.

Table 3.1: Summary of unpublished reports to the FDA regarding various triptans and ACG

Drug	Number of Reports	ROR (95% Confidence Interval)	Likely or Unlikely Association?
Sumatriptan	12	4.10 (2.32-7.24)	Likely
Zolmitriptan	5	11.41 (4.74-27.50)	Likely
Eletriptan	3	5.11 (1.65-15.84)	Likely
Frovatriptan	1	16.07 (2.26-114.56)	Unlikely (just 1 report)
Rizatriptan	1	2.02 (0.28-14.42)	Unlikely (just 1 report)

Chapter 3.4: Proposed Mechanism of Triptan Induced AACG

These data show that there may be an association between ACG and triptan use; sumatriptan, zolmitriptan, and eletriptan all have significant RORs (Table 3.1). Research has shown that 5-HT receptors can be found throughout the human eye, namely within the iris and ciliary bodies¹¹⁷. It has been hypothesized that agonizing these receptors (perhaps even the 5HT 1B and 1D, as triptans do) in the eye induces a forward rotation of the lens–iris diaphragm and the condition is exacerbated by ciliary body swelling and increased curvature of the lens^{113,114}. These events may account for the blockage of aqueous humor (AH) drainage through the trabecular meshwork (TM) by the iris, the induction of myopic shift, and the subsequent narrowing of the anterior chamber^{113,114}. Hsu et al. also postulated that the idiosyncratic drug induced AACG event may be due to the triptan acting as a foreign antigen and binds to the choroid (vascular tissue between the sclera and retina) which leads to an immune reaction and choroidal effusion^{113,118}. It is also possible that agonizing the 5HT 1B and 1D receptors can affect the vasculature of the eye which may have also precipitated an AACG attack¹¹³. In the patient described by the case study, there was supraciliary effusion which may account for the forward rotation of the ciliary processes and indirect angle closure¹¹³. Basic science research has demonstrated that 5-HT receptors are important in control of IOP, however the direct involvement, if any, of the 1B or 1D receptor subtypes has yet to be discovered¹¹⁹.

Chapter 3.5: Why does this Research Question Warrant an Epidemiologic Study?

As vision is the most valued human sense, it is important to identify any risk factors that may compromise this sense. As triptans are heavily prescribed drugs for migraine patients, adverse events from this class of drugs can potentially affect a great number of individuals worldwide¹⁰⁵. Should this study find a signal indicating that triptans increase the risk of AACG, this information will be valuable to clinicians, patients, and policy makers such as the FDA,

Health Canada, and the European Medicines Agency. Should this study not find an association between triptans in relation to AACG, this can be reassuring to clinicians and patients and may avert any concerns about this risk.

As AACG occurs in 4-6 million people every year^{34,35} and is considered an ophthalmic emergency, it is prudent to ensure individuals are not at risk of developing an ocular emergency that can potentially be avoidable. Therefore, since current evidence and a number of case reports provides a strong signal for triptan induced AACG (published reports and FDA reports via Open Vigil) in the absence of a pharmaco-epidemiologic study on the topic, we sought to ascertain the risk of AACG with triptan use in migraine patients using a large health claims database from the USA.

Chapter 4: Methods

Chapter 4.1: Synopsis

This chapter discusses different types of study designs including randomized controlled trials (RCTs) and observational studies, in addition to discussing their advantages and disadvantages. The chapter will conclude by discussing the study design used for this investigation, the nested-case control study, and describing its methodology and statistical analysis.

Chapter 4.2: RCTs

RCTs are a type of clinical trial where the efficacy of a specific intervention (a drug, device, or surgical procedure) is compared to a control group who is given a control intervention or another type of intervention¹²⁰. For example, in drug efficacy research, a control or placebo would be a “sugar pill” with no known biological activity and a comparison group might be a different drug, usually the standard of care¹²¹. RCTs are considered to be the strongest study design for clinical trials because they involve processes of randomization and blinding, also making them true experimental studies¹²². Randomization is where every patient has an equal chance of receiving a control treatment and is critical to reducing bias¹²². As such, each subject in the study has an equal chance of receiving the drug or placebo and study cohorts are equal in terms of their baseline characteristics, which ensures that one of the study outcomes isn’t a result of a difference among the study groups¹²². The second important factor in RCTs involves the process of blinding, where both the investigators and study group participants are unaware of who is receiving an active intervention or a control; this also decreases bias¹²².

RCTs are effective in answering questions about drug efficacy, however, they have many drawbacks when looking into quantifying rare adverse drug events (ADEs). One main drawback is that it would be considered unethical to give a particular intervention to healthy participants

when there is a risk of harming them¹²². Another drawback to RCTs is that depending on the latency of a disease in response to a drug, it may take years to determine if there is a risk of said disease with use of a particular drug¹²³. These long term ADEs cannot be quantified by RCTs because they usually have a follow up period of 1 year or more and by the time the drug is deemed harmful, it may already be marketed to the public¹²³. Additionally, although RCTs may exhibit strong internal validity, assuming variables are well controlled for, they lack external validity; those who enter RCTs tend to be more compliant with drug taking schedules, are healthier and are usually devoid of multiple comorbidities¹²². As such, RCT participants are usually different than patients in a “real life” clinical setting¹²². Lastly, another drawback to RCTs is that very rare ADEs (those with a prevalence of $\leq 1/10,000$) may take millions of patients to attain statistical significance or power; this is not feasible in an RCT as it would require a significant amount of money and human resources¹²². For these reasons, we did not conduct an RCT for this study.

Chapter 4.3: Observational Studies

Observational studies involve researchers investigating a potential link between an exposure (a particular intervention) and an outcome (i.e. a disease) in a large population¹²⁴. Observational studies must adjust for certain variables that can potentially influence the study results using statistical techniques¹²⁴. Observational studies differ from RCTs in that they do not require subject randomization per se because a particular exposure is chosen to be evaluated to ascertain distinct outcomes^{122,124}. RCTs are typically used to assess the efficacy of particular treatments while observational studies are more useful when investigating adverse events and their risks, given a particular exposure^{122,124}. Although adverse events are noted during RCTs on a patient to patient basis, RCTs do not use a large enough sample size to assess the risk of rare events¹²². This problem can be solved using an observational study methodology.

Within the broad category of observational studies, there are three main sub-designs: cross sectional studies, cohort studies, and case-control studies¹²⁴.

Chapter 4.3.1: Cross-sectional studies

In cross sectional studies, investigators attempt to determine an association between the exposure and outcome at a particular point in time¹²⁵.

Chapter 4.3.2: Cohort Studies

In cohort studies, which can be either prospective or retrospective, researchers follow a particular subset of a population who have received the intervention in question (those who are exposed) and controls without the intervention (unexposed)¹²⁴. Researchers can then investigate which patients have developed the disease in question (the outcome)¹²⁴.

Researchers then quantify the rate of disease in those exposed to a particular intervention compared to a group of control individuals that were unexposed, given as a risk ratio (RR).

Chapter 4.3.3: Case-Control Studies

Contrary to cohort studies, case control (CC) studies are usually coined as “research in reverse” as investigators first identify those with the disease in question (cases) and those without the disease (controls)^{126,127}. Researchers can then work backwards by determining exposure to the intervention in question (such as a drug) amongst the cases and controls.

In the present study, we decided to use a nested case-control study (NCC) design, also known as a case-control within a cohort study. This a type of case control study analysis within a well-defined cohort of subjects where cases (those with a particular disease) are matched to controls (those who do not have the disease)¹²⁸. The NCC design is able to account for time varying exposures such as prescription drugs without the complexities of a cohort study; unlike the cohort design, not all subjects need to be followed for the computation of the relative risk¹²⁸. These complexities become more apparent when millions of person-time of data need to be

accounted for, as in the case with cohort studies using large population databases. Like all CC studies, it is effective in studying drugs with rare exposures¹²⁴.

Chapter 4.3.4: Advantages and Disadvantages of Observational Studies

4.3.4.1 General benefits and drawbacks:

It is important to review the advantages and disadvantages of observational studies.

Advantages: One major advantage of observational studies in general is that they are able to quantify rare outcomes that are associated with different types of interventions (i.e. drugs)¹²⁴.

Another major benefit of observational studies is that given the potentially long follow up periods of certain outcomes, researchers are able to quantify rare ADEs that have a long latency¹²⁴.

Disadvantages: A major disadvantage of observational studies however, is that not all pertinent clinical variables may be available to study the participants, which might lead to biased results¹²⁴. This type of bias is referred to as selection bias, whereby the sample that researchers select to be in the study are not representative of the population they are meant to represent^{124,129,130}.

4.3.4.2 Cross Sectional Studies:

Advantages: Advantages of cross sectional studies include the fact that they are 1) cheaper to execute and 2) data can be recycled i.e many different questions can be addressed with one dataset¹³¹.

Disadvantages: A drawback of cross-sectional studies is that a study could lack power if the population being investigated is too small and is a bigger problem if the ADE in question is rare. Like most observational studies, causation cannot be determined through cross sectional studies¹³¹. Another major drawback of cross-sectional studies is that they describe the exposure and outcome at one single point in time, therefore temporality between the exposure and outcome cannot be determined¹³¹. Additionally, cross-sectional studies are subject to recall bias, whereby those who have the disease are more likely to report it than controls¹³¹.

4.3.4.3 Cohort studies

Advantages: Cohort studies allow researchers to determine an association between an intervention and particular outcome¹²⁴. They also allow researchers to assess multiple outcomes for a particular intervention¹²⁴. Furthermore, cohort studies are also useful for inquiring about rare outcomes¹²⁴. Lastly, cohort studies measure the rates of a particular disease, which generate RRs which are easy to interpret.

Disadvantages: A disadvantage of cohort studies is that a large number of research subjects is required to obtain useful information for exposures that are very rare¹²⁴. Some disadvantages of retrospective cohort studies, namely those based on large databases, include inadequate information for all potentially confounding variables which can lead to unmeasured confounding bias¹²⁴. Disadvantages of prospective cohort studies are similar to those of RCTs; it may be hard to follow up on subjects as they may withdraw, and it is quite expensive to run the study^{122,124}. Another disadvantage is that selection bias can occur, such that one group may be healthier than the other, making the results less generalizable^{122,124}.

4.3.4.4 Case-control studies:

Advantages: One advantage of CC studies is that they require a smaller sample size than cohort studies as the design identifies cases and corresponding controls unlike cohort studies where all study subjects need to be followed and analyzed for the computation of the relative risk (RR), therefore making CC studies an efficient study design¹²⁴. When you have a large sample size (i.e. 9 million patients), it is much more complex to follow all patients as opposed to selecting a subset of this sample, in particular for control selection. Another benefit of CC studies is that since a relatively fewer number of subjects (compared to cohort studies) are required to obtain significant statistical power, they are relatively cheap and quick to conduct¹²⁴. Furthermore, CC studies are useful in studying outcomes that are relatively rare or have a long latency period to manifest¹²⁴. Moreover, many exposures can be investigated, and existing records can be used in the study¹²⁴.

Disadvantages: One drawback of case control studies is that since detailed individual patient information may not be available to researchers, in particular with large health claims databases, it may be difficult to control for extraneous variables (unmeasured confounding bias)¹²⁴. This lack of information regarding pertinent confounders could potentially bias study results. Additionally, it is crucial, in particular with NCC studies, to select controls in an unbiased manner such that controls represent the exposure prevalence of the population, as ORs are calculated based on the exposure prevalence of the controls¹²⁴. Therefore, inappropriate control selection can lead to biased results.

Chapter 4.4: Triptans and AACG: Why use the NCC Study Design?

Given that this study will be investigating a relatively rare event (AACG), we did not utilize an RCT or a cross-sectional study. Additionally, triptans, the exposure in question, are

taken as a PRN (as needed basis) and not as a regularly scheduled medication (such as a statin or blood pressure medication would be). Therefore, we elected to utilize a nested case-control study design (NCC) study design over a retrospective cohort design. Since the NCC looks at patterns of exposure use before the index date (the date a case incurred the event) it can better enable investigators to examine drug risks at different risk periods, as opposed to a retrospective cohort study which typically uses the “intent to treat” paradigm. Although the “on treatment” paradigm could also be accomplished using a retrospective cohort study design, it is significantly more complex as one must define the exposure at baseline and look at the first prescription of a particular drug going forward in time, thus making it difficult to look at different exposure (or risk) periods^{124,128}. For example, if the risk of triptans changed over a one-year risk period, it would be possible to identify different risk periods, such as 0-30 days, 31-60 days, and 61-365 days prior to the index date using the NCC design. This makes the NCC design more flexible than a cohort study. The NCC design also makes it easier to look at many prescriptions of the drug in question¹²⁴. An additional benefit to the NCC design over cohort studies is the ability to match cases and controls on possible confounding variables such as calendar time and follow up time^{128,132,133}. Calendar time describes the actual date (i.e. January 1, 2006) when someone entered a cohort and follow up time refers to how long a case was followed for before they received a diagnosis code (i.e followed for 6 or 12 months)^{128,132,133}. Calendar time is an important parameter that can often introduce bias in drug safety studies as the introduction of drugs at different time periods may prompt or dissuade prescribing of that particular drug by clinicians^{132,133}. By matching cases and controls by calendar time one can ensure that this variable does not introduce bias into the study. By matching follow up time, we allow for both cases and controls to have an equal opportunity to have received the particular drug in that time frame^{132,133}. For example, if a case enters the cohort on January 1, 2006, and is followed for one

year and is diagnosed with AACG on January 1, 2007, 10 controls can be selected who also entered the cohort on January 1, 2006 and who were also followed and were alive one year later on January 1, 2007 when their matched case was diagnosed with AACG.

Chapter 4.5: Data Sources

To examine the risk of AACG with triptan use, this study utilized a large health claims database from the United States; the IMS LifeLink PharMetrics Plus Database. We sought to investigate our question with a “real” clinical setting in mind, hence utilizing the IMS LifeLink database, which reports insurance claims data¹³⁴. This de-identified database captures health claims for over 150 million unique enrollees, with fully adjudicated pharmacy and medical claims¹³⁴. The medical claims are comprised of all physician visits and captures medical diagnoses through the international classification of diseases, ninth and tenth editions (ICD-9 and 10)¹³⁴. All prescription drug data includes information regarding the drug name, strength, day supply, and dose quantity dispensed¹³⁴. This database also provides information regarding patient hospitalizations and procedures performed¹³⁴. The database is a good representation of all geographic areas of the United States¹³⁴. We had access to a random sample of 9,053,240 subjects aged 1-80 from 2006-2016. This study was approved by the University of British Columbia Human Ethics Board.

Chapter 4.6: Cohort Entry/Definition

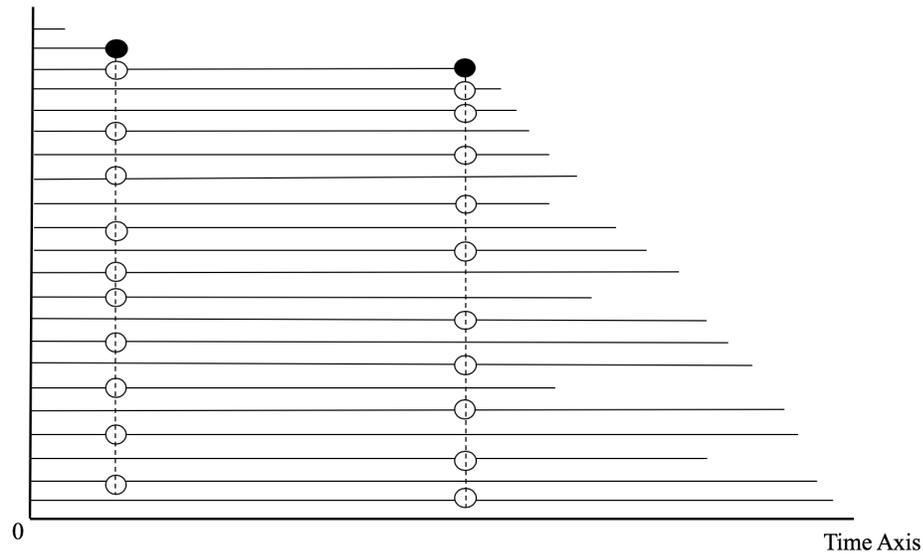
4.6.1. Case and Control Definition

In this study, cases were defined as patients with the *first* diagnosis of AACG (which was required to be coded by an ophthalmologist or optometrist). The date of diagnosis was deemed the index date. We excluded those with a previous diagnosis of any subtype of glaucoma. AACG has an ICD-9 code of 365.22, and this definition has been used in previous studies looking at the risk of AACG with use of topiramate and bupropion¹³⁵. This definition of AACG

is very specific to AACG. For example, an ICD-9 code of 365 indexes glaucoma in general; a code of 365.2 indicates primary ACG and a code of 365.22 indexes AACG¹³⁶. Contrarily, an ICD-9 code of 365.1 indexes OAG¹³⁶.

For each case in the study, a risk-set of controls who had the same follow up time and calendar time to that of the case were identified randomly. Within each risk set, ten controls who had the same age (± 2 years) as cases were randomly selected and matched to a case. Controls could have been selected more than once and were allowed to be at risk until they became a future case¹²⁸. Allowing controls to be future cases would emulate a cohort study where exposed and unexposed subjects are followed in time until they incur the event and become a case. Thus, selecting controls using density based sampling has shown to generate RRs that are very close approximations of the OR¹²⁸. RRs will be used to assess risk as they are generally more intuitive to interpret. Figure 4.1 (below) demonstrates this. Each black circle is a case and the white circles are control subjects (Figure 4.1). The vertical dashed lines represent a particular risk set at a point in time and the horizontal black lines are follow up time (Figure 4.1). This figure highlights that risk sets are defined by a particular point in time (calendar time) and by how long it took to diagnose a case (follow up time). Therefore, it is possible for a control to be selected as a future case should they develop the disease at a later point in time (Figure 4.1)

Figure 4.1: Density Based Sampling

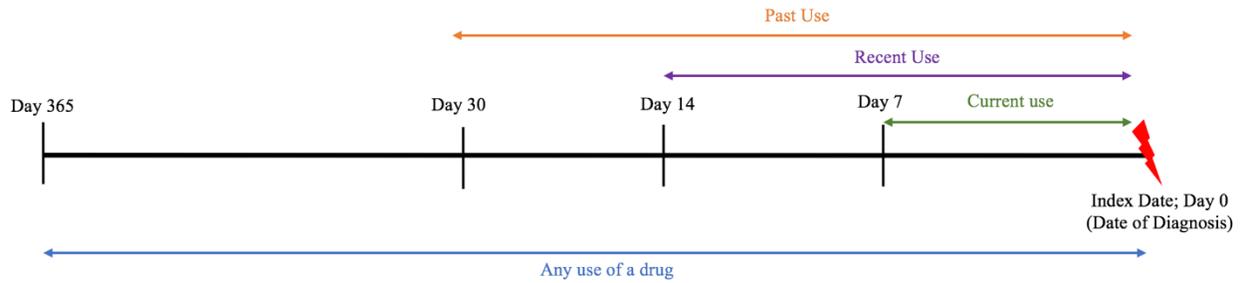


Source: Mohit Sodhi ©, adapted from Essebag et al. 2003¹²⁸

4.6.2. Exposure Definition

Cohort members were followed to the first diagnosis of AACG or the latest date of data availability, whichever date came first. We were then able to identify all triptan prescriptions available in the database (sumatriptan, zolmitriptan, eletriptan, frovatriptan, and rizatriptan) in the year prior to the index date. It is worth noting that in the reported case of sumatriptan induced AACG, the disease onset was within one week of initiating triptan use¹¹³. However, the case study describing zolmitriptan induced AACG described that the patient was consuming zolmitriptan for 1 year prior to the AACG attack, however, the patient was taking an increased quantity of zolmitriptan in the few days prior to presentation¹¹⁴. Therefore, we created different risk periods of exposure as follows: 1) the last dispensed drug at 0-30 days prior to the index date (deemed as “past use”) 2) the last dispensed drug at 0-14 days prior to the index date (deemed as “recent use”) 3) the last dispensed drug at 0-7 days prior to the index date (deemed as “current use”) and 4) any use of the drug within 1 year of the index date (0-365 days) (Figure 4.2).

Figure 4.2: Defining Exposure Risk Periods and Index Date



Source: Mohit Sodhi ©

As triptans are used on an as needed basis, we excluded those who received less than 2 prescriptions of triptans, which may indicate that the patient is consistently consuming a particular triptan on a somewhat regular basis. The triptan prescriptions must have been within 60 days from each other (i.e. the first triptan prescription must have been no more than 60 days prior to the second). In order to validate our results, we calculated the RR for both a positive control drug (topiramate), which has a known association with AACG, and a negative control drug (ranitidine), which is not known to have such an association¹³⁵. The exposure definition that was used for triptans was also used for topiramate and ranitidine. We ensured having one-year prescribing data for all cases and controls.

4.6.3 Statistical analysis

To study the demographics of our cohort, we calculated both categorical variables (gender, covariates) and continuous variables (age, follow up in years) using descriptive statistics. A t-test was utilized for continuous variables and a chi-square test was used for categorical variables. To discern the risk of triptan induced AACG, we computed both crude RRs and adjusted RRs. We adjusted for the following covariates in the year prior to the index date: sex, age, and follow-up years. Additional covariates included adjusting for SSRI, bupropion, and steroid drug users, who were identified at baseline.

We created a conditional logistic regression model to compute RRs. A logistic regression is a type of a regression model that attempts to study the association between an independent and dependent variable¹³⁷. A conditional logistic regression model is a specific type of logistic regression that is utilized when cases in a case-control study are matched to a fixed number of controls, while adjusting for other covariates¹³⁷. An unconditional logistic model would be used if matching is not accounted for, which in the case of our study would lead to many biases as discussed earlier¹²⁸; therefore, conditional logistic regression will be used in this analysis. Continuous variable demographics (age) and binary variables (gender, SSRI, bupropion, and steroid users) were adjusted for at baseline. The reference group for this study were subjects who were not taking any triptans during the one-year period prior to the index date. All analyses were computed using SAS version 9.4.

Chapter 5: Results

Chapter 5.1: Synopsis

In this chapter I will be reviewing the demographics of our source population. Then I will be summarizing both the crude and adjusted risk ratios for AACG that we ascertained for triptans, the positive control (topiramate), and the negative control (ranitidine).

Chapter 5.2: Demographics

Of a random sample of 9,053,240 subjects, we identified 1,307 AACG cases which were matched with 13,070 controls (Table 5.1). The mean age \pm SD (standard deviation) of both cases and controls was 57.0 ± 12.4 years with the follow-up \pm SD being 3.1 ± 2.4 years (Table 5.1). Approximately 61% of both cases and controls were female. ~3% of cases and 2% of controls had taken bupropion, ~20% of cases and ~10% of controls had taken steroids, and ~12% of cases and ~10% of controls had used SSRIs at baseline (Table 5.1).

Table 5.1 Characteristics of AACG cases and their matched controls

	Cases¹	Controls
Number	1,307	13,070
Age in years	57.0 ± 12.4	57.0 ± 12.4
Follow-up in years	3.1 ± 2.4	3.1 ± 2.4
Female gender (%)	61.3	61.3
Covariates (%)		
Bupropion	2.8	2.0
Steroids	19.9	9.8
SSRI	12.4	10.2

¹ The number of controls were weighted according to the number of cases.

5.3: Triptan Distribution by Age

We conducted an age stratification analysis to determine which age groups experienced the greatest number of AACG events, and of those how many had taken any one of our study triptans. As demonstrated in tables 5.1 and 5.2, there were a total of 1,307 AACG events and of those, 88 subjects had at least 2 prescriptions of a triptans. The most AACG events occurred in those aged 60-64 (293 events, ~22% of the total cases) and the least being in those aged 50-54 (172 events, ~13%) (Table 5.2). The most commonly associated triptan with an AACG event was sumatriptan (67 cases) and the least being frovatriptan (1 case) (Table 5.2). The age having the most AACG cases associated with our study triptans was those aged 55-59 (44 cases), and the least being those over 65 years of age (5 cases) (Table 5.2).

Table 5.2 Number of AACG events and triptan use stratified by age

Group age	AACG Events (%)	Eletriptan N (%)	Frovatriptan N (%)	Rizatriptan N (%)	Sumatriptan N (%)	Zolmitriptan N (%)	Total Triptan N (%)
<50	274 (21.0)	3 (100.0)	0	3 (100.0)	1 (1.5)	0	7 (8.0)
50-54	172 (13.2)	0	1 (100.0)	0	14 (20.9)	5 (35.7)	20 (22.7)
55-59	279 (21.4)	0	0	0	44 (65.7)	0	44 (50.0)
60-64	293 (22.4)	0	0	0	8 (11.9)	4 (28.6)	12 (13.6)
65+	289 (22.1)	0	0	0	0	5 (35.7)	5 (5.7)
Total	1,307	3 (100.0)	1 (100.0)	3 (100.0)	67 (100.0)	14 (100.0)	88 (100.0)

Chapter 5.4: Risk Ratios of Study Drugs

The crude RR for any use of triptans (0-365 days prior to the index date) was 1.27 (95% confidence interval (CI) 0.76-2.11) (Tables 5.3.1, 5.3.2, 5.3.3). The crude RR for any use of topiramate and ranitidine was 4.56 (95% CI 2.80-7.43) and 0.97 (95% CI 0.54-1.77), respectively (Tables 5.3.1, 5.3.2, 5.3.3).

The crude RR for current, recent, and past use for triptans was 1.47 (95% CI 0.34-6.49) (Table 5.3.1), 1.32 (0.40-4.40) (Table 5.3.2), and 1.37 (0.58-3.21) (Table 5.3.3) respectively. The crude RR for current, recent, and past use for topiramate was 5.18 (95% CI 0.95-28.30) (Table 5.3.1), 14.24 (95% CI 5.72-35.44) (Table 5.3.2), and 7.05 (95% CI 3.66-13.60) (Table 5.3.3) respectively. The crude RR for current, recent, and past use for ranitidine was 0.94 (95% CI 0.12-7.28) (Table 5.3.1), 0.51 (95% CI 0.07-3.82) (Table 5.3.2), and 0.22 (95% CI 0.03-1.61) (Table 5.3.3) respectively.

Table 5.3.1 Crude RRs of AACG and intake of Study Drugs (Current use)

Number of Subjects	Cases (%) 1,307	Controls (%) 13,070	Crude Rate Ratio	95% CI
No use of 3 Rx Below	95.49	97.39	1	Ref
Triptan (any use)	1.30	1.06	1.27	0.76-2.11
Current Use	0.15	0.11	1.47	0.34-6.49
Topiramate (any use)	1.84	0.42	4.56	2.80-7.43
Current Use	0.15	0.03	5.18	0.95-28.30
Ranitidine (any use)	0.92	0.96	0.97	0.54-1.77
Current Use	0.08	0.08	0.94	0.12-7.28

Rx = prescription

Table 5.3.2 Crude RRs of AACG and intake of Study Drugs (Recent Use)

Number of Subjects	Cases (%) 1,307	Controls (%) 13,070	Crude Rate Ratio	95% CI
No use of 3 Rx Below	95.49	97.39	1	Ref
Triptan (any use)	1.30	1.06	1.27	0.76-2.11
Recent Use	0.23	0.18	1.32	0.40-4.40
Topiramate (any use)	1.84	0.42	4.56	2.80-7.43
Recent Use	0.84	0.06	14.24	5.72-35.44
Ranitidine (any use)	0.92	0.96	0.97	0.54-1.77
Recent Use	0.08	0.15	0.51	0.07-3.82

Rx = prescription

Table 5.3.3 Crude RRs of AACG and intake of Study Drugs (Past Use)

Number of Subjects	Cases (%) 1,307	Controls (%) 13,070	Crude Rate Ratio	95% CI
No use of 3 Rx Below	95.49	97.39	1	Ref
Triptan (any use)	1.30	1.06	1.27	0.76-2.11
Past Use	0.46	0.35	1.37	0.58-3.21
Topiramate (any use)	1.84	0.42	4.56	2.80-7.43
Past Use	1.15	0.17	7.05	3.66-13.60
Ranitidine (any use)	0.92	0.96	0.97	0.54-1.77
Past Use	0.08	0.35	0.22	0.03-1.61

Rx = prescription

The adjusted RR for any use of triptans (0-365 days prior to the index date) was 1.09 (95% CI 0.56-1.82) (Tables 5.4.1, 5.4.2, 5.4.3). The adjusted RR for any use topiramate and ranitidine was 3.77 (95% CI 2.29-6.20) and 0.79 (95% CI 0.43-1.44), respectively (Tables 5.4.1, 5.4.2, 5.4.3).

The adjusted RR for current, recent, and past use for triptans was 1.37 (95% CI 0.31-6.09) (Table 5.4.1), 1.16 (95% CI 0.35-3.92) (Table 5.4.2), and 1.19 (95% CI 0.50-2.81) (Table 5.4.3) respectively. The adjusted RR for current, recent, and past use for topiramate was 4.44 (95% CI 0.80-24.64) (Table 5.4.1), 12.86 (95% CI 5.10-32.42) (Table 5.4.2), and 6.52 (95% CI 3.34-12.71) (Table 5.4.3) respectively. The adjusted RR for current, recent, and past use for ranitidine was 0.66 (95% CI 0.08-5.24) (Table 5.4.1), 0.39 (95% CI 0.05-2.91) (Table 5.4.2), and 0.18 (95% CI 0.02-1.28) (Table 5.4.3) respectively.

Table 5.4.1 Adjusted RRs of AACG and intake of Study Drugs (Current Use)

Number of Subjects	Cases (%) 1,307	Controls (%) 13,070	*Adjusted Rate Ratio	95% CI
No use of 3 Rx Below	95.49	97.39	1	Ref
*Triptan (any use)	1.30	1.06	1.09	0.65-1.82
*Current Use	0.15	0.11	1.37	0.31-6.09
*Topiramate (any use)	1.84	0.42	3.77	2.29-6.20
*Current Use	0.15	0.03	4.44	0.80-26.64
*Ranitidine (any use)	0.92	0.96	0.79	0.43-1.44
*Current Use	0.08	0.08	0.66	0.08-5.24

*Adjusted for variables in Table 5.1
Rx = prescription

Table 5.4.2 Adjusted RRs of AACG and intake of Study Drugs (Recent Use)

Number of Subjects	Cases (%) 1,307	Controls (%) 13,070	*Adjusted Rate Ratio	95% CI
No use of 3 Rx Below	95.49	97.39	1	Ref
*Triptan (any use)	1.30	1.06	1.09	0.65-1.82
*Recent Use	0.23	0.18	1.16	0.35-3.92
*Topiramate (any use)	1.84	0.42	3.77	2.29-6.20
*Recent Use	0.84	0.06	12.86	5.10-32.42
*Ranitidine (any use)	0.92	0.96	0.79	0.43-1.44
*Recent Use	0.08	0.15	0.39	0.05-2.91

*Adjusted for variables in Table 5.1
Rx = prescription

Table 5.4.3 Adjusted RRs of AACG and intake of Study Drugs (Past Use)

Number of Subjects	Cases (%) 1,307	Controls (%) 13,070	*Adjusted Rate Ratio	95% CI
No use of 3 Rx Below	95.49	97.39	1	Ref
*Triptan (any use)	1.30	1.06	1.09	0.65-1.82
*Past Use	0.46	0.35	1.19	0.50-2.81
*Topiramate (any use)	1.84	0.42	3.77	2.29-6.20
*Pas Use	1.15	0.17	6.52	3.34-12.71
*Ranitidine (any use)	0.92	0.96	0.79	0.43-1.44
*Past Use	0.8	0.35	0.18	0.02-1.28

*Adjusted for variables in Table 5.1
Rx = prescription

Chapter 6: Discussion

Chapter 6.1: Synopsis

In this chapter I will be discussing the results of this study and how it relates to other studies investigating the relationship between 5HT 1B and 1D agonists. I will proceed to discuss the relevant biases that may have been present in this study and how we ensured they did not affect our study results, as it pertains to our methodology. I will then conclude by discussing the clinical implications of our results.

Chapter 6.2: Study Results in the Context of Current Evidence

Our results show that those using triptans do not have an increased risk of experiencing an AACG attack. However, the upper bound of the confidence interval does not exclude a potential for risk. Our data also confirmed what was expected; mainly that ranitidine does not increase the risk of AACG and that topiramate increases this risk. Although the confidence interval is also wide for ranitidine and the upper bounds indicate a potential risk, the RRs for all ranitidine exposure periods are noticeably lower than 1; however, the RRs for all triptan exposure periods are notably above 1 (Tables 5.4.1, 5.4.2, and 5.4.3).

As highlighted in chapter 3, there is a paucity of studies investigating the risk of AACG with triptan use. The only two published case reports related to this topic were by Hsu et al. (2017) and Lee et al. (2017)^{113,114}. Additionally, there were 22 reports of ACG with triptan use reported to the FDA (Table 3.1).¹¹⁵ Therefore, to put the present study results into context, we believed it was prudent to review the evidence regarding drugs that have 5HT 1B and/or 1D agonist activity and the risk of AACG to see if they may also increase the risk of AACG.

5HT 1B and 1D agonists, other than triptans, can be prescribed for a number of conditions such as depression, Parkinson's disease, schizophrenia, and bipolar disorder¹³⁸⁻¹⁴⁰. To

date, some studies and reports have alluded to the increased risk of AACG with 5HT 1B and 1D agonist use^{141–146} while others do not show such an association.

As triptans are agonists of the 5HT 1B and 1D receptor, I conducted a search of published studies and reports investigating the risk of AACG and agonists of the 5HT 1B and/or 1D receptor subtypes (Table 6.1)¹⁰⁰. I excluded drugs that are not marketed or prescribed to the public and to verify this, I searched for the existence of the FDA drug monograph for that particular drug. Although the drugs I investigated have 5HT1B and/or 1D activity, it may not be their primary mechanism of action, thus are not prescribed specifically for their serotonergic activity^{138–140}. I also searched these drugs individually in the Open Vigil database to determine if there were any reports to the FDA regarding a particular drug and ACG (see Appendix 2 for the search strategy). As previously discussed, the Open Vigil database does not differentiate between AACG and ACG; they are all searched under the term “angle closure glaucoma.” The list of marketed 5HT 1B and 1D agonists can be found on the Guide to Pharmacology website^{147,148}.

To conduct this literature review, I searched both MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE ®<1946 to Present) and Embase (1974 to present). No other search restrictions were made in either MEDLINE or Embase. Final search results were screened and included or excluded based on abstract content. The exact search strategy can be found in Appendix C.

Table 6.1 Summary of published and unpublished reports involving 5-HT 1B and/or 1D agonists and ACG

Drug	Indicated treatment?	5HT 1B or 1D?	Cases on OV	OR (95% CI), likely?	Any case or PE studies?	Warning in FDA DM?
Oxymetazoline 147,148	Decongestant 149	1B (full), 1D (partial) 147,148	0 ¹¹⁵	N/A ¹¹⁵	No	Yes ¹⁴⁹

Dihydro-ergotamine ^{147,148}	Migraines ¹⁵⁰	1B & 1D (full) ^{147,148}	0 ¹¹⁵	N/A ¹¹⁵	No	No ¹⁵⁰
Ziprasidone ^{147,148}	Antipsychotic ¹⁵¹	1B & 1D (full) ^{147,148}	3 ¹¹⁵	1.18 (0.38-3.66), unlikely ¹¹⁵	No	No ¹⁵¹
Asenapine ^{147,148}	Antipsychotic ¹⁵²	1B & 1D (full) ^{147,148}	2 ¹¹⁵	1.89 (0.47-7.57), unlikely ¹¹⁵	No	No ¹⁵²
Pergolide ¹⁴⁷	Anti-parkinsonian ¹⁵³	1B (full) ¹⁴⁷	0 ¹¹⁵	N/A ¹¹⁵	No	Yes (unspecified glaucoma) ¹⁵³
Vortioxetine ¹⁴⁷	Anti-depressant ¹³⁸	1B (partial) ¹⁴⁷	2 ¹¹⁵	2.77 (0.69-11.09), unlikely ¹¹⁵	No	Yes ¹³⁸
Bromocriptine ^{147,148}	Anti-parkinsonian, High prolactin ¹⁴⁰	1B & 1D (partial) ^{147,148}	0 ¹¹⁵	N/A ¹¹⁵	Case study (but other drugs present) ¹⁴⁶	No ¹⁴⁰
Cabergoline ^{147,148}	High prolactin ¹⁵⁴	1B (full) & 1D (partial) ^{147,148}	4 ¹¹⁵	7.48 (2.80-19.98), likely ¹¹⁵	Case study (within 5 hours) ¹⁴⁵	No ¹⁵⁴
Olanzapine ^{147,148}	Antipsychotic ¹⁵⁵	1B & 1D (full) ^{147,148}	26 ¹¹⁵	3.27 (2.22-4.83), likely ¹¹⁵	Case study ^{143,144}	Yes ¹⁵⁵
Clozapine ^{147,148}	Antipsychotic ¹⁵⁶	1B & 1D (full) ^{147,148}	4 ¹¹⁵	0.44 (0.17-1.19), unlikely ¹¹⁵	No	Yes, because of anti-cholinergic action ¹⁵⁶
Aripiprazole ^{147,148}	Antipsychotic ¹⁵⁷	1B & 1D (full) ^{147,148}	11 ¹¹⁵	1.13 (0.62-2.04), unlikely ¹¹⁵	Yes ^{141,143}	No ¹⁵⁷
Quetiapine ¹⁴⁸	Antipsychotic ¹³⁹	1D (full) ¹⁴⁸	24 ¹¹⁵	1.69 (1.13-2.54), likely ¹¹⁵	Yes ^{142,143}	Yes ¹³⁹

OV = Open Vigil

PE = pharmacoepidemiologic
DM = drug monograph

Published case reports and FDA reports show that although some 5HT 1B and/or 1D agonists allude to an increased risk of ACG, others do not (Table 6.1). In total, between 2004 and 2018, there were 76 reported cases to the FDA for 8 out of 12 5HT 1B and/or 1D agonists (Table 6.1)¹¹⁵. The FDA also warned of the risk of ACG or AACG in 6 out of 12 drug monographs (Table 6.1)^{138,139,149,153,155,156}. Furthermore, the Open Vigil DA determined that only three out of the 12 agonists had a likely risk of ACG, which were cabergoline, quetiapine, and olanzapine (Table 6.1)¹¹⁵. It may be worth investigating these three drugs in the form of a pharmacoepidemiologic study to further validate this risk. No pharmacoepidemiologic studies were found regarding any of the 12 drugs however there were case studies that reported bromocriptine, quetiapine, cabergoline, olanzapine, and aripiprazole being associated with AACG (Table 6.1)¹⁴¹⁻¹⁴⁶.

6.2.1 What do these data mean?

There is discordance between the results of this study and the DA using the FDA AERS data. Although the DA has its strengths, there are a number of limitations that might have contributed to this discordance. First, although Open Vigil's DA may show a signal for some of the drugs investigated in this study (sumatriptan, zolmitriptan, and eletriptan) or in the chapter 6.2 review (cabergoline, quetiapine, and olanzapine), its ability to show a causal link is weaker than an epidemiologic study because the ascertained cases might be subject to reporting bias. Moreover, the derived ROR is a reported effect size from the FDA's AERS database and not from a population based epidemiologic study. Thus, the ROR cannot control for potential confounding variables including adjustment for other drugs that may also have contributed to ACG.

Taking the aforementioned reports and published cases in combination with the results of the present study into account, it is difficult to postulate for certain whether 5HT 1B and/or 1D agonists have an association with precipitation of an AACG attack, therefore further work is needed.

Chapter 6.3: Addressing Bias in this Study

When investigating any drug safety questions using a pharmaco-epidemiologic study design, there are a number of limitations that must be addressed. These limitations pertain to a number of potential biases that I will discuss. These biases include: *misclassification bias*, *calendar time bias*, *time window bias*, *selection bias*, *protopathic bias*, *confounding by indication*, *bias due to unmeasured confounding*, and *sparse data bias*.

6.3.1 Misclassification Bias

Misclassification bias (or misclassification error) describes a situation where cases may be falsely identified (false positive) or those that should be identified as cases but were incorrectly categorized as controls or not included in the cohort to begin with (false negative)¹⁵⁸. Misclassification bias can affect both the outcome and the exposure in observational studies, including NCC studies¹⁵⁸. In light of the present study, misclassification of the outcome might occur if a subject was misdiagnosed with AACG and was identified as a case using the ICD-9 code 365.22 when in fact they had another condition that mimicked AACG. A false negative (misclassification of the outcome) in this context would mean if a subject indeed suffered from AACG but were diagnosed and coded with a different disease or another type of glaucoma, and thus did not become a case in our study and not identifiable using the ICD-9 code for AACG.

Misclassification of the exposure with regard to the present study would be if a subject was prescribed triptans but did not actually take the prescribed medication. Although we mitigated this risk by including only those who had two or more prescription of triptans, it is

possible that a subject did not actually take their medication but did in fact receive a second prescription. This way, they would have been included in our study by our exposure definition. However, this scenario is less probable because a patient who is indeed suffering from migraines would be unlikely to go back to see their physician and request a second prescription if they did not use or finish the medication from their first prescription.

Misclassification bias can be further subdivided into differential and non-differential biases. *Differential misclassification* bias occurs when there is a misclassification difference between the groups who are unexposed versus those who are exposed. *Non-differential misclassification* bias occurs when errors occur across the groups (both exposed and unexposed). Both non-differential or differential misclassification biases are unlikely to affect the study results as AACG is a diagnosis typically made by a licensed ophthalmologist or optometrist and error is unlikely to occur such that it doesn't affect the overall study results. Moreover, since AACG is an ophthalmic emergency, we ensured to look at various risk periods (30, 14, and 7 days) prior to the index date (i.e. the date of AACG diagnosis), therefore it is unlikely a patient would be misdiagnosed with a different form of glaucoma (with a longer disease latency) or a different disease altogether. Furthermore, the PharMetrics Database is a good representation of institutes across the USA; even if a few physicians within the represented institutes misdiagnosed patients with AACG, thus having a patient misclassified within the database, it is unlikely that it would affect the overall results of the study¹³⁴.

6.3.2 Time Window and Calendar Time Bias

As described in chapter 4, time window (follow up) and calendar time bias and are important to control for in NCC studies. Time window bias refers to a situation where the follow time up time before being identified as a case is not equal to that of a control¹³². In this study we matched cases and controls by follow up time, therefore allowing for both cases and controls to

have an equal opportunity to have received the particular drug in that time frame¹³². For example, if we followed one case for two years, the 10 controls that are matched to this particular case were also followed for two years until their corresponding case was diagnosed with AACG. By doing this, we can confirm that both case and controls had an equal opportunity to have been exposed to a triptan.

Calendar time bias refers to a bias where calendar time can differentially affect the prescribing of a particular drug¹³³. Failure to adjust or match for calendar time can introduce bias in pharmacoepidemiologic studies because introduction of drugs at different time periods may prompt or dissuade prescribing of that particular drug by clinicians which may lead to differential prevalence of that drug among the cases or controls^{128,132,133}. For example, if a particular triptan was heavily prescribed in 2012 (possibly due to publication of new guidelines) and a case enters a cohort in 2010 and its corresponding controls enter the cohort in 2012, that case does not have an equal opportunity to have been prescribed that particular triptan. In this study, we matched cases and controls by both follow up and calendar time, to prevent differential prescribing to the cases or controls. Consequently, due to our rigorous methodology, both time window and calendar time bias were unlikely to have affected our study results.

6.3.3 Selection Bias

Selection bias occurs when the study participants or a portion of the participants are selected in such a way that could have affected the outcome and exposure. For example, if we had selected controls from a neurologist's office where there could have been a higher prevalence of triptan use than the cases, this would clearly be an example of selection bias which would have led to biased estimates due to a spuriously high prevalence of triptan use in the controls. We ensured this did not happen in our study by selecting 10 controls for each case from

the entire database (>9 million subjects) using density-based sampling. No other restrictions were implemented in the study design which would have in any way led to selection bias.

6.3.4 Protopathic Bias

Protopathic bias, also known as reverse causality bias, occurs when a particular intervention (i.e. a drug), is prescribed for a condition that happens to be a symptom of the outcome of interest¹⁵⁹. In the context of the present study, protopathic bias may occur if a subject uses a triptan to relieve a headache secondary to AACG alluding to a causal relation between triptans and AACG. Although this type of bias may be present in the clinical setting, this is unlikely to have affected our results. Protopathic bias would only be relevant in the case a harmful association had been observed in this study; this study did not show an increased risk of triptan induced AACG, therefore protopathic bias is not relevant.

6.3.5 Confounding by Indication

Although similar to protopathic bias, confounding by indication occurs when the risk of obtaining the outcome is increased by the disease itself as opposed to the medication that it was prescribed for¹⁵⁹. In context of the present study, this would mean that migraine headaches by themselves increase the risk of AACG as opposed to the use of triptans increasing the risk of AACG. To address confounding by indication, it is useful to underline a recent study by Chen et al. (2016) that demonstrated that migraines are not associated with ACG. This study found that those who suffer from migraines do not have an increased risk of primary ACG when relevant covariates are adjusted for¹⁶⁰. The authors note that it is possible for a few cases of primary ACG, especially AACG cases, to be thought of being “exposed” to migraines as well, given that many patients with AACG present with similar symptoms as migraines¹⁶⁰. However, patients who experience migraines (according to their exposure definitions) are still not at an increased risk of developing primary ACG compared to non-migraine patients¹⁶⁰.

6.3.6 Unmeasured Confounding Bias

Unmeasured confounding bias arises from confounding variables that could not be measured in our study or variables for which we do not have control over because our data do not provide us with that particular set of information, therefore making it difficult to draw causative conclusions¹⁶¹. For example, in our study, we did not have access to OTC medications or illicit drugs that may have influenced the risk of AACG. More specifically, some drugs such as diphenhydramine, a very popular antihistamine, are contraindicated for patients with narrow angles and are associated with AACG¹⁶². Additionally, both marijuana and ecstasy have been reported to be associated with AACG^{163,164}. It is entirely possible that such a bias could have influenced the results but there is no way of confirming or denying this, other than asking the patients themselves, which was impossible to do using ours or any health claims database. Another limitation of the database is absence of patient records containing imaging and diagnostic data to verify glaucoma diagnosis.

6.3.7 Sparse Data Bias

Sparse data bias occurs when there is a small number of events for the exposed group or other covariates adjusted for in the model. This lack of case number in an observational study can lead to a decrease in the overall power of the study¹⁶⁵. Such a bias can even occur in very large datasets, in particular when using regression methods while adjusting for confounders or covariates¹⁶⁵. This is entirely possible in this study, given the small number of events that occurred in our current or recent use exposure periods and when we adjusted for covariates (SSRIs, bupropion, and steroid use). There would be no other way to overcome this bias other than using a larger data set to increase the number of cases and therefore increase the power.

Chapter 6.4: Conclusion

The results in the present study show that those using triptans are most likely not at risk of an AACG attack. However, given the high upper value of the 95% confidence interval, the risk of AACG cannot be excluded and further work is required to elucidate the connection, if any, between AACG and triptans. Future studies can investigate the risk of AACG with triptan use using a larger database that captures more AACG cases, users of triptans, and possibly one that captures information regarding OTC medications.

Given the prevalence of migraines and the high use of triptan drugs, many patients using this class of drug can be put at ease by their prescribing doctors. As drug regulatory bodies like the FDA and Health Canada currently do not have any specific warnings on the risk of AACG and triptans, our findings indicate that such a warning is not necessary based on the results of this study¹⁶⁶⁻¹⁷². As for now, alerting patients on the risk of AACG with triptan use is not indicated, however this might change in the future should a risk is found.

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Appendix A: Literature Review Search Strategies (Triptans)

MEDLINE search strategy: There were a total of 4,394 studies associated with ACG and 96,636 studies were found with triptan related search terms. When all glaucoma and triptan search terms were matched, only 3 studies were found. However, after screening the abstracts, only 2 studies were deemed relevant^{113,114}.

<input type="checkbox"/>	# ▲	Searches	Results	Type
<input type="checkbox"/>	1	exp Glaucoma, Angle-Closure/	3096	Advanced
<input type="checkbox"/>	2	(angle adj5 closure adj5 glaucoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4394	Advanced
<input type="checkbox"/>	3	1 or 2	4394	Advanced
<input type="checkbox"/>	4	exp Tryptamines/	90262	Advanced
<input type="checkbox"/>	5	tryptamine*.mp.	8952	Advanced
<input type="checkbox"/>	6	almotriptan.mp.	274	Advanced
<input type="checkbox"/>	7	triptan*.mp.	1943	Advanced
<input type="checkbox"/>	8	naratriptan.mp.	325	Advanced
<input type="checkbox"/>	9	frovatriptan.mp.	194	Advanced
<input type="checkbox"/>	10	sumatriptan.mp. or SUMATRIPTAN/	3070	Advanced
<input type="checkbox"/>	11	rizatriptan.mp.	499	Advanced
<input type="checkbox"/>	12	zolmitriptan.mp.	608	Advanced
<input type="checkbox"/>	13	5-Hydroxytryptophan/	4061	Advanced
<input type="checkbox"/>	14	oxitriptan.mp.	6	Advanced
<input type="checkbox"/>	15	eletriptan.mp.	279	Advanced
<input type="checkbox"/>	16	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	96636	Advanced
<input type="checkbox"/>	17	3 and 16	3	Advanced

Embase Search Strategy: In Embase, 20,878 studies were found for triptan related search terms and 6559 studies were found for ACG. When all triptan and glaucoma search terms were matched, 41 studies were found. However, after screening the abstracts, the same 2 studies that were found in MEDLINE were deemed relevant^{113,114}.

<input type="checkbox"/> # ▲ Searches	Results	Type	Actions	Annotation
<input type="checkbox"/> 1 exp closed angle glaucoma/	5762	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 2 (angle adj5 closure adj5 glaucoma).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3757	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 3 1 or 2	6565	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 4 exp tryptamine derivative/	1688	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 5 tryptamine/ or tryptamine*.mp.	5889	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 6 oxitriptan.mp. or 5 hydroxytryptophan/	6128	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 7 4 and 5	1688	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 8 triptan.mp. or triptan derivative/	4048	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 9 eletriptan.mp. or eletriptan/	1389	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 10 naratriptan.mp. or naratriptan/	1675	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 11 almotriptan.mp. or almotriptan/	1188	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 12 sumatriptan.mp. or naproxen plus sumatriptan/ or sumatriptan/ or sumatriptan succinate/ or naproxen plus sumatriptan succinate/	8868	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 13 zolmitriptan.mp. or zolmitriptan/	2801	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 14 frovatriptan.mp. or frovatriptan/	987	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 15 rizatriptan.mp. or rizatriptan/	2333	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 16 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	20878	Advanced	Display Results More ▼	<input type="checkbox"/>
<input type="checkbox"/> 17 3 and 16	41	Advanced	Display Results More ▼	<input type="checkbox"/>

Appendix B: Searching the Open Vigil Database

Step 1: Go to the Open Vigil Website at <http://openvigil.sourceforge.net/>. The home screen is shown below. Since Open Vigil 2.1 was used in this study, click on the link right under the **Open Vigil 2.1** heading and input the username and password provided.

OpenVigil - open tools for data-mining and analysis of pharmacovigilance data



Quick access:

[Search drugs and adverse events with OpenVigil 2!](#) [Search drugs and adverse events with OpenVigil FDA!](#) [Explore AERS with OpenVigil 1!](#)
[Search German pharmacovigilance data!](#) [Calculate 2x2 contingency tables!](#) [Map drugnames using RxNorm!](#)

Documentation:

Welcome	About Pharmacovigilance	How to use OpenVigil
Technical docs and other resources	Further Literature	News & project roadmap

What is OpenVigil?

OpenVigil 1 and 2 are software packages to analyse pharmacovigilance data. There are several national and international databases of so called spontaneous adverse event reports, e.g., the U.S. american FDA Adverse Event Reporting System (AERS, mostly domestic data) or the WHO Uppsala Monitoring Centre (international). Currently, analyses of FDA AERS (LAERS & FAERS) pharmacovigilance data are available. In addition to U.S. american data, we have also imported German pharmacovigilance data. Data mining features include highly configurable search criteria filters and output filters. Analyses include disproportionality analyses for signal detection like Proportional Reporting Ratio (PRR) calculations. Results can be viewed, sorted and filtered in the webbrowser or saved for further analyses in statistical software packages. Both projects aim at integrating these and other pharmacovigilance sources to pharmacoepidemiological data like prescription data. OpenVigil 2 is designed for complete case analyses.

OpenVigilFDA is a front-end to the openFDA-interface which is being developed by the FDA since 2014. It allows extraction of the latest reports. Due to technical limitations, the beta-version status and the ongoing changes to the API of openFDA, OpenVigil 2 is more stable and superior for analyses of disproportionality. OpenVigilFDA provides available case analysis, e.g., some records are not complete but still considered.

Where can I access OpenVigil?

 There are live installations with **U.S. american FDA pharmacovigilance data** of both versions of OpenVigil with FDA AERS data and OpenVigilFDA freely available at Christian Albrecht University (CAU) of Kiel, Germany:

OpenVigil 2.1-MedDRA (data 2004Q1-2018Q2):

<https://www.is.informatik.uni-kiel.de/pvt/OpenVigilMedDRA17/search/>

OpenVigil 2.1 (data 2004Q1-2018Q2): <https://www.is.informatik.uni-kiel.de/pvt/OpenVigil2.1/search/>

OpenVigil 2.0 (data 2004Q1-2012Q2): <https://www.is.informatik.uni-kiel.de/pvt/OpenVigil/search/>

username: dgpt password: dgpt

Step 2: Input the exposure (drug) of interest. Sumatriptan was used in this example, but any triptan (or drug) can be input here.



FDA data from Q4/2003-Q2/2018 Are now included in OpenVigil 2.1.
If you want to restrict the data basis to the former data set (Q4/2003-Q2/2014) please apply advanced search.
Furthermore, the latest drugbank data have been used for completing the drug and pharma product tables.

[Search](#) [Show Report](#) [Browse](#)

OpenVigil Search

Drug: Drug +

Adverse event: LLT

Advanced search

Data presentation and statistics

Evaluation method: Raw_data Frequency Frequentist_methods

Drug

- sumatriptan
- ↳ sumatriptan (sumatriptan)
- ↳ sumatriptan (sumatriptanum)
- ↳ sumatriptan (sumatriptanum [inn-latin])

Step 3: Input the outcome (the adverse event). Notice how the database does not discern between “angle closure glaucoma” and “acute angle closure glaucoma.”



FDA data from Q4/2003-Q2/2018 Are now included in OpenVigil 2.1.
If you want to restrict the data basis to the former data set (Q4/2003-Q2/2014) please apply advanced search.
Furthermore, the latest drugbank data have been used for completing the drug and pharma product tables.

Search

Show Report

Browse

Open Vigil Search

Drug: Drug +

Adverse event: LLT +

Advanced search

Show advanced search

LLT

angle closure glaucoma

Data presentation and statistics

Evaluation method: Raw_data Frequency Frequentist_methods i

Counting records according to: ISR (unique reports) ↓

Output items

Show output items

Search

Step 4: Now we are ready to search the database. No advanced search criteria were used in this thesis to maximize exposure.



FDA data from Q4/2003-Q2/2018 Are now included in OpenVigil 2.1.
If you want to restrict the data basis to the former data set (Q4/2003-Q2/2014) please apply advanced search.
Furthermore, the latest drugbank data have been used for completing the drug and pharma product tables.

[Search](#) [Show Report](#) [Browse](#)

OpenVigil Search

Drug: +

Adverse event: +

Advanced search

[Show advanced search](#)

Data presentation and statistics

Evaluation method: Raw_data Frequency Frequentist_methods ⓘ

Counting records according to:

Output items

[Show output items](#)

Step 5: The results page is shown below. There are a few important aspects to highlight on this page. The first is the 2x2 contingency table. The first value (12) is the number of those taking sumatriptan and suffered the adverse event of angle closure glaucoma (DE; see formula 1). The value next to it (1,214) is the number of people who suffered angle closure glaucoma as a result of all other drugs (dE; see formula 1). The number of patients who suffered from all other adverse events while taking sumatriptan is 15,720 (De; see formula 1). The number of all adverse events with all drugs in the database is 6,522,477 (de; see formula 1).

The next aspects to highlight are the metrics for the disproportionality analyses. These include the Reporting Ratio (RRR), the Proportional Reporting Ratio (PRR), and Reporting Odds Ratio (ROR). The ROR is of most significance to this study. This is calculated by the values in the contingency table: $(DE \times de) / (dE \times De)$.

The last line is also noteworthy. According to the database, sumatriptan induced angle closure glaucoma is a likely association.

snow query

	Drug(s) of interest	All other drugs	Σ
Adverse event(s) of interest	12	1214	1226
All other adverse events	15720	6522477	6538197
Σ	15732	6523691	6539423

Rate (DE/D): 0.076278%

Chi-Squared with Yates' correction: 24.853341

Interpretation: Do the observed frequencies differ from expected frequencies? The greater the chi-squared value, the greater the differences. Chi square values gi

Measurements of disproportionality (observed-expected ratios like RRR, PRR, ROR)

Interpretation: Generally, the higher the value, the more likely an association between drug(s) and adverse event(s) has been found. Lower bounds of confidence

Relative Reporting Ratio (RRR) and 95% confidence interval (lower bound; upper bound): 4.068612 (2.304703 ; 7.182533)

Proportional Reporting Ratio (PRR) and 95% confidence interval (lower bound; upper bound): 4.098944 (2.321821 ; 7.236277)

Reporting Odds Ratio (ROR) and 95% confidence interval (lower bound; upper bound): 4.10131 (2.322161 ; 7.243573)

According to the criteria of Evans 2001 (n > 3, chisq > 4, PRR > 2) this combination of drug(s) and adverse event(s) is considered: **likely an adverse reaction**

Appendix C: Literature Review Search Strategies (Other 5HT 1B and/or 1D Agonists)

MEDLINE search strategy: In MEDLINE, there were a total of 4,396 studies associated with ACG and 30,819 studies were found with the 5HT 1B and 1D agonist search. When all glaucoma and 5HT 1B and 1D search terms were matched, only 4 studies were found. However, after screening the abstracts, only 3 studies were deemed relevant^{143–145}.

<input type="checkbox"/>	# ▲	Searches	Results	Type
<input type="checkbox"/>	1	exp Glaucoma, Angle-Closure/	3099	Advanced
<input type="checkbox"/>	2	(angle adj5 closure adj5 glaucoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4396	Advanced
<input type="checkbox"/>	3	1 or 2	4396	Advanced
<input type="checkbox"/>	4	OXYMETAZOLINE/	627	Advanced
<input type="checkbox"/>	5	DIHYDROERGOTAMINE/	1388	Advanced
<input type="checkbox"/>	6	ziprasidone.mp.	1910	Advanced
<input type="checkbox"/>	7	asenapine.mp.	369	Advanced
<input type="checkbox"/>	8	PERGOLIDE/	781	Advanced
<input type="checkbox"/>	9	vortioxetine.mp.	312	Advanced
<input type="checkbox"/>	10	BROMOCRIPTINE/	6894	Advanced
<input type="checkbox"/>	11	cabergoline.mp.	1601	Advanced
<input type="checkbox"/>	12	olanzapine.mp.	8614	Advanced
<input type="checkbox"/>	13	CLOZAPINE/	7734	Advanced
<input type="checkbox"/>	14	ARIPRAZOLE/	2095	Advanced
<input type="checkbox"/>	15	Quetiapine Fumarate/	2572	Advanced
<input type="checkbox"/>	16	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	30819	Advanced
<input type="checkbox"/>	17	3 and 16	4	Advanced

Embase search strategy: In Embase, 99,624 studies were found for 5HT 1B or 1D search terms and 6,566 studies were found for ACG. When all 5HT 1B and 1D drugs and ACG search terms were matched, 91 studies were found. However, after screening the abstracts, only 6 studies were deemed relevant (3 of which were the same as the MEDLINE search)^{141–146}.

<input type="checkbox"/>	# ▲	Searches	Results	Type
<input type="checkbox"/>	1	exp closed angle glaucoma/	5763	Advanced
<input type="checkbox"/>	2	(angle adj5 closure adj5 glaucoma).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3758	Advanced
<input type="checkbox"/>	3	1 or 2	6566	Advanced
<input type="checkbox"/>	4	oxymetazoline.mp. or oxymetazoline/	2860	Advanced
<input type="checkbox"/>	5	dihydroergotamine/ or dihydroergotamine.mp.	5583	Advanced
<input type="checkbox"/>	6	ziprasidone.mp. or ziprasidone/	8706	Advanced
<input type="checkbox"/>	7	asenapine.mp. or asenapine/	1313	Advanced
<input type="checkbox"/>	8	pergolide.mp. or pergolide/	4936	Advanced
<input type="checkbox"/>	9	vortioxetine.mp. or vortioxetine/	809	Advanced
<input type="checkbox"/>	10	bromocriptine mesilate/ or bromocriptine/ or bromocriptine.mp.	21771	Advanced
<input type="checkbox"/>	11	cabergoline.mp. or cabergoline/	5476	Advanced
<input type="checkbox"/>	12	olanzapine/ or olanzapine.mp.	32456	Advanced
<input type="checkbox"/>	13	aripiprazole lauroxil/ or aripiprazole.mp. or aripiprazole/ or aripiprazole cavoxil/	14107	Advanced
<input type="checkbox"/>	14	quetiapine.mp. or quetiapine/	22149	Advanced
<input type="checkbox"/>	15	clozapine.mp. or clozapine/	32298	Advanced
<input type="checkbox"/>	16	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	99624	Advanced
<input type="checkbox"/>	17	3 and 16	91	Advanced