THE IMPACT OF OCCLUSION THERAPY AND PREDICTORS ON AMBLYOPIA
DOSE-RESPONSE RELATIONSHIP AND SUCCESS OUTCOMES

by

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Abstract

Amblyopia is a decrease in visual acuity caused by abnormal binocular interaction or pattern vision deprivation in one or both eye(s) with no organic abnormalities which is reversible by therapeutic measures. Current research on amblyopia treatment lacks dose standardization, dose-response rate estimates, and age limits. One common treatment is occlusion therapy. This study aimed to determine the success outcomes of occlusion therapy, dose-response rate of visual acuity to occlusion therapy, and explore predictors for occlusion therapy success and dose-response rates. Results showed 90.3% treatment success and dose-response rate of 224hours/0.1 logMAR increase. To reach outcome visual acuity, a total dose of 1344 hours (FTO) and 504 hours (PTO) was required. Classification of amblyopia, age, visual acuity chart used, initial distance vision in the amblyopic eye, and treatment dose predicted dose-response rate. Significant variables for treatment success included initial distance vision in the amblyopic eye and initial interocular visual difference.

List of Abbreviations Used

VA: Visual Acuity

DVA: Distance Visual Acuity

Pd: Prism Diopters

PI: Primary Investigator

VPC: Vision Progress Chart

ETDRS: Early Treatment Diabetic Retinopathy Study

LH: Lea Symbols

LGN: Lateral Geniculate Nucleus

PEDIG: The Pediatric Eye Disease Investigator Group

WHO: The World Health Organization

PTO: Part-Time Occlusion

FTO: Full-Time Occlusion

GLM: General Linear Model

Glossary

Amblyopia: A decrease in visual acuity caused by abnormal binocular interaction or pattern vision deprivation in one or both eye(s) with no organic abnormalities which is reversible by therapeutic measures

Anisometropic amblyopia: A difference of refractive error between the eyes of at least 1 diopter of hyperopia, 3 diopters of myopia, or 1.5-2 diopters of astigmatism causing pattern vision deprivation, resulting in a unilateral reduction in visual acuity

Age at treatment onset: The age in months of the patient when occlusion therapy was initiated

Cycloplegic refraction: The refractive error that is solely based on the properties of the eye, excluding accommodative factors. Performed with the aid of cycloplegic agents which dilate the pupil and paralyze accommodation of the ciliary body

Cycle: 1 week per year of age follow-up to a maximum of 4 weeks

Dose: The number of hours per day the non-amblyopic eye is occluded by an adhesive patch

Dose-response rate: Visual acuity gain per hours of occlusion over the same period

DVA: Distance Visual Acuity

ETDRS: Early Treatment Diabetic Retinopathy Study

LH: Lea Symbols

Mild amblyopia: DVA of 6/9 or better or 0.2 logMAR or better

Mixed amblyopia: A combination of strabismic and anisometropic amblyopia

Moderate amblyopia: DVA 6/12-6/30 or 0.3-0.7 logMAR

Occlusion therapy: Covering the non-amblyopic eye to force the use of, and reliance on, the amblyopic eye in an attempt to improve vision using an adhesive patch

Pre-treatment level of VA: The level of DVA at the initial clinical visit, before any occlusion therapy treatment, and following at least 12 weeks of refractive adaptation for participants wearing spectacle correction

Post-treatment level of VA: The level of DVA after either three consecutive cycles of no visual acuity improvement, or equal vision following occlusion therapy

Severe amblyopia: DVA worse than 6/30 or >0.7 logMAR

Strabismic amblyopia: A constant, non-alternating or unequally alternating manifest alignment of the eyes always resulting in a unilateral reduction in visual acuity due to an abnormal binocular interaction, preventing fusion

Stereopsis: Three dimensional vision

Total dose: The total number of hours patched (non-amblyopic eye) to reach maximum visual acuity (defined as 3 consecutive cycles of no visual acuity improvement or equal vision in both eyes following occlusion therapy)

ACKNOWLEDGEMENTS

1.0 Chapter 1 Introduction

1.1 Amblyopia Definition(s) and Prevalence

Amblyopia has been classically defined as a "decrease of visual acuity for which no causes can be detected by physical examination of the eye, caused by vision deprivation or abnormal binocular interaction" (Von Noorden, 1996). This vision reduction is due to one or more amblyogenic factors such as refractive error, visual deprivation, or strabismus in visually immature children (Stein et al., 2014; C. Williams et al., 2008). Clinically, unilateral amblyopia is defined as a two-line and/or 10 optotype interocular difference in best-corrected visual acuity (Von Noorden, 1996). Unilateral amblyopia is commonly associated with strabismus (19-50% of cases) and anisometropia (46-79% of cases) (The Pediatric Eye Disease Investigator Group, 2003d, 2017; Xiao et al., 2015). It is during the critical period of visual development that the amblyopic eye, with appropriate therapeutic intervention, can be successfully managed. Basic science research using animal models provided some clarity of the pathophysiology of amblyopia and the critical period in the development of the visual system (Torston N. Wiesel, 1963).

Amblyopia has a prevalence of 1-5% (DeSantis, 2014; Friedman et al., 2009; A. Pai & Mitchell, 2010; C. Williams et al., 2008) and is the most common visual deficit in children in the developed world (Friedman et al., 2009; A. Pai & Mitchell, 2010; C. Williams et al., 2008). In both adults and children, amblyopia is the leading cause of monocular vision loss and doubles the lifetime risk of binocular vision loss (Delpero et al., 2019; A. Pai & Mitchell, 2010; Van Leeuwen et al., 2007). The prevalence of amblyopia in school-aged children is dependent on the population, ranging from 0.7-1.9% (Flom & Neumaier, 1966; A. S. I. Pai et al., 2012). Other studies have reported that in children over age 7 years and adults, the prevalence of amblyopia increases to around 1-

5.5% (Attebo et al., 1998; Flom & Neumaier, 1966; McKean-Cowdin et al., 2013). Although more often a unilateral condition, amblyopia can also be a bilateral process consisting of 5-14% of cases (The Pediatric Eye Disease Investigator Group, 2017; Xiao et al., 2015).

1.1.2 Critical Period of Visual Development

It would be impossible to discuss most aspects of amblyopia and its management without a brief discussion on the pathophysiology of amblyopia and critical periods of visual development. The critical period for visual development has been reported to peak around age 2-3 years with new-onset amblyopia and treatment efficacy gradually decreasing after this point until visually maturity is reached, believed to around 7 years of age (Holmes, Lazar, Melia, Astle, Dagi, Donahue, Frazier, Hertle, Repka, Quinn, & Weise, 2011; Holmes & Levi, 2018; The Pediatric Eye Disease Investigator Group, 2019). Animal-based research has been pivotal in helping clinicians and researchers better understand amblyopia in humans. Hubel and Wiesel, using animal-based models, described the pathophysiological changes that occur within the lateral geniculate nucleus (LGN), resulting from the introduction of amblyogenic factors (Hubel & Wiesel, 1970). As to structural changes, cells in the LGN and binocular cells in the occipital cortex receiving information from the amblyopic eye have reduced volume (Gunton, 2013). The cells were 25-40% smaller, paler, and more densely packed. Atrophy, thinning, and loss of Nissl substance within all layers of the LGN were also linked to the amblyopic eye (Gunton, 2013). Additionally, in research involving cats, ocular dominance column distribution was different, with more monocularly divided columns, and fewer binocular columns (Hubel & Wiesel, 1970). Hubel and Wiesel also reported on the reversibility of

these anatomical changes prior to visual maturity (Hubel & Wiesel, 1970). In 1970, Wiesel and Hubel investigated the reversibility of amblyopia in cats by suturing the preferred eye to force the use of the amblyopic eye. After 3 months of monocular deprivation, limited recovery of the LGN and cortical physiologic changes were found. However, a return of normal function in vision of the amblyopic eye was observed behaviourally following monocular deprivation (Hubel & Wiesel, 1970).

1.2 Amblyopia Risk Factors

Although no genetic link has been found, a family history of amblyopia, strabismus and hypermetropia are significant predictors of amblyopia risk in children (Williams et al., 2008). Other risk factors include anisometropia, >1 diopter of astigmatism, and strabismus. Patients with esodeviations are at greater risk of developing amblyopia than exodeviations. Exodeviations more often have intermittent control whereas esodeviations are more often manifest which could explain the lower amblyopia rates in this population (McKean-Cowdin et al., 2013; Sjöstrand & Abrahamsson, 1990; The Pediatric Eye Disease Investigator Group, 2011, 2017). Additionally, premature birth, developmental delay, maternal smoking, drinking, and drug use during pregnancy also increase the risk of amblyopia and strabismus (The Pediatric Eye Disease Investigator Group, 2017; Williams et al., 2008).

1.3 Classification of Amblyopia

Historically, Chavasse created a classification of amblyopia and its pathogenesis which to some extent continues to be the foundation for the more modern classifications of the disorder (Worth et al., 1959). Chavasse divided amblyopia into two main

categories: amblyopia of arrest and amblyopia of extinction. Amblyopia of arrest was said to occur when a deviation was present during the "plastic period of macular development", essentially from birth to 6 years of age, such that the macular development in the deviating eye was stopped. This suppression of the deviating eye and the resulting loss of visual acuity was also believed to be irreversible after this formative critical period (i.e. after the age of 6) (Worth et al., 1959). Chavasse also reported that any visual acuity loss at the onset of the ocular misalignment could be recovered if the intervention was within this critical period. Amblyopia of extinction referred to conditions in which visual acuity had already developed yet was lost through lack of use or inhibition. Chavasse's theory on this type was based on the concept that for visual acuity to remain at a normal state, continual use must take place (Worth et al., 1959). These older theories on the etiology of amblyopia carry over into the more traditional classifications such as strabismic, refractive, visual deprivation, and occlusion or reverse amblyopia, depending on the primary amblyogenic factor(s) present.

1.3.1 Strabismic Amblyopia

This form of amblyopia is caused by "a constant, non-alternating or unequally alternating manifest misalignment of the eyes". Strabismic amblyopia always results in a unilateral vision decrease due to an abnormal binocular interaction of the eyes (Committee, 2012; DeSantis, 2014; Von Noorden, 1996). Strabismus creates either competition between the eyes or active inhibition of the retinocortical pathway of the deviating eye that leads to the abnormal development of dominance columns in the visual cortex of the brain, favoring the fixating eye and decreasing responsiveness to the deviating eye (Hubel & Wiesel, 1965; The Pediatric Eye Disease Investigator Group,

2017). The prevalence of strabismic amblyopia is higher in acquired and accommodative esotropia and less common in intermittent exotropia and congenital esotropia (DeSantis, 2014; Raab et al., 2010). Treatment of strabismic amblyopia includes full refractive correction, and/or surgical intervention to manage the residual strabismus, attempting to eliminate ocular misalignment as an amblyogenic factor (Committee, 2012; DeSantis, 2014; Von Noorden, 1996). Traditionally, amblyopia treatment is done prior to strabismus surgery however, a few studies have illustrated effects on treatment success when strabismus surgery was performed before amblyopia treatment (DeSantis, 2014; Lam et al., 1993). The elimination of any amblyopia prior to surgical intervention is believed to enhance the post-operative fusional potential (Repka et al., 2005; The Pediatric Eye Disease Investigator Group, 2017).

1.3.2 Refractive Amblyopia

Like strabismic amblyopia, refractive amblyopia creates an abnormal binocular interaction and pattern vision deprivation between the eyes due to an unequal or bilateral high refractive error. The refractive error produces retinal blur, thus provoking a decrease in visual acuity of the corresponding eye. Typically, depth of amblyopia correlates with the amount of refractive error with a higher error causing deeper amblyopia (DeSantis, 2014; Raab et al., 2010; Von Noorden, 1996). Refractive amblyopia is often sub-classified into anisometropic, ametropic, and meridional types (DeSantis, 2014; Raab et al., 2010; Von Noorden, 1996).

Anisometropic amblyopia results from an unequal refractive error in both eyes creating pattern vision deprivation and abnormal binocular interaction. The eye with the lesser refractive error can focus an image while the other eye remains in a constant

defocussed state, resulting in unilateral vision loss. As with strabismic amblyopia, active cortical inhibition (suppression) of the defocussed eye ensues to eliminate the sensory interference and image blur (DeSantis, 2014; Raab et al., 2010; The Pediatric Eye Disease Investigator Group, 2017). Active cortical inhibition results from the blocking of neural impulses by higher-level processing centers in the visual cortex (Cassin, 1995). It has been reported that with hyperopia, an interocular difference of one diopter can lead to anisometropic amblyopia (DeSantis, 2014; Raab et al., 2010). Anisometropic amblyopia most commonly occurs in the more hyperopic eye as it is not able to fully accommodate under binocular conditions. Anisometropic amblyopia is less common in myopia. This is thought to occur as the less myopic eye is used for distance work while the more myopic eye is used for near work (DeSantis, 2014; Raab et al., 2010; Von Noorden, 1996). In myopic eyes > 6 diopters, severe amblyopia can result without refractive correction as the eye remains chronically unfocussed. Treatment for this form of amblyopia includes prescribing the full refractive error for 12-18 weeks and then treating any amblyopia that remains (DeSantis, 2014; The Pediatric Eye Disease Investigator Group, 2012a). A period of refractive adaption is completed before other treatments as refractive correction alone can correct amblyopia in as many as 32% of cases (The Pediatric Eye Disease Investigator Group, 2012a; Wang, 2015).

Ametropic amblyopia is another form of refractive amblyopia. Unlike anisometropic amblyopia, ametropic amblyopia is always bilateral, resulting from a high, approximately equal refractive error and pattern vision deprivation of both eyes (The Pediatric Eye Disease Investigator Group, 2017). Commonly, ≥5 diopters of hyperopia, ≥6 diopters of myopia, or ≥2 diopters of astigmatism create enough retinal blur that bilateral vision loss can occur. Prescribing full refractive correction is the common

treatment for this form of amblyopia (DeSantis, 2014; The Pediatric Eye Disease Investigator Group, 2012a).

Less common than the previous two forms of refractive amblyopia, meridional amblyopia is caused by a unilateral or bilateral astigmatic refractive error of ≥1.5-2 diopters (Von Noorden, 1996). As the eye(s) cannot focus through the astigmatic error, there is constant retinal image blur and pattern vision deprivation leading to a decrease in visual acuity in the affected eye (DeSantis, 2014; Raab et al., 2010; Von Noorden, 1996). This form of amblyopia is treated using the same modalities as anisometropic amblyopia (DeSantis, 2014; Raab et al., 2010; Von Noorden, 1996).

1.3.3 Mixed Amblyopia

Mixed amblyopia is a monocular or binocular decrease in visual acuity caused by more than one amblyogenic factor. Most commonly, it is a combination of strabismic and refractive amblyopia (Jefferis et al., 2015). This form of amblyopia is treated using the same modalities as anisometropic amblyopia (DeSantis, 2014; Raab et al., 2010; Von Noorden, 1996).

1.3.4 Visual Deprivation Amblyopia

Visual deprivation amblyopia is the least common form of amblyopia but often the most severe and difficult to treat (Beller et al., 1981; The Pediatric Eye Disease Investigator Group, 2017). This form of amblyopia can be unilateral or bilateral and results from "complete or partial obstruction of the visual axis" during visual immaturity resulting in a degraded or absent retinal image (The Pediatric Eye Disease Investigator Group, 2017). Congenital cataracts are the primary cause but severe congenital ptosis,

orbital lesions, corneal opacities, eyelid hemangiomas, media opacities, vitreous

hemorrhages, and infectious or non-infections interocular inflammation can also result in

visual deprivation amblyopia (DeSantis, 2014; The Pediatric Eye Disease Investigator

Group, 2017; Von Noorden, 1996). Visual deprivation occurs much earlier in life than

other forms of amblyopia and happens much more quickly. Visual deprivation amblyopia

can result in secondary sensory strabismus and nystagmus (Committee, 2012; DeSantis,

2014).

1.3.5 Reverse Occlusion Amblyopia

Occlusion amblyopia is a form of visual deprivation amblyopia that results in a

decrease visual acuity of the non-amblyopic eye caused by amblyopia treatment

(patching, visual deprivation, optical and/or pharmacological penalization) (Koc et al.,

2006; Repka et al., 2005; Scott et al., 2005; Scott & Dickey, 1988; The Pediatric Eye

Disease Investigator Group, 2014, 2017). Statistically, it can occur in 1% of children

patched ≥6 hours/day and in 9% of children on atropine treatment of one drop/day after 6

months of treatment (The Pediatric Eye Disease Investigator Group, 2017).

Discontinuation of amblyopia therapy has been reported to be a successful treatment,

allowing the affected eye to return to baseline vision. Conversely, others have reported

failures in the treatment of iatrogenic amblyopia (Sprunger et al., 2006). As reported by

PEDIG (2017), a shorter duration of treatment reduces the risk of occlusion amblyopia

(Scott et al., 2005; The Pediatric Eye Disease Investigator Group, 2017).

1.4 Natural History of Untreated Amblyopia

Previous literature, although minimal, on the natural history of untreated amblyopia has revealed that the amblyopic eye rarely improves without early intervention. Vision in the amblyopic eye has also been reported to continue deteriorating and even develop acutely throughout childhood and into adolescence (Simons & Preslan, 1999). There has also been evidence that amblyopic patients have an increased rate of vision loss in their sound eye following disease or injury, leaving these individuals with significant visual impairment (Delpero et al., 2019; A. Pai & Mitchell, 2010; Van Leeuwen et al., 2007). These reports further emphasize the importance of early detection and treatment of amblyopia.

During the first 3 months of life, visual deprivation amblyopia produces permanent severe visual acuity reduction to 20/200 or worse and permanent reduction of high contrast sensitivity (Mohindra et al., 1979; The Pediatric Eye Disease Investigator Group, 2017; Vaegan & Taylor, 1979). Amblyopia developing in infancy is often associated with the development of congenital nystagmus and strabismus that can further deteriorate binocularity and stereoacuity (The Pediatric Eye Disease Investigator Group, 2017). Even brief visual deprivation during childhood can cause amblyopia (Mohindra et al., 1979; The Pediatric Eye Disease Investigator Group, 2017; Vaegan & Taylor, 1979). After 3 months of age, visual acuity reduction from amblyogenic factors can be less severe, though present. Amblyopia that develops in later childhood results in a slower decline in visual acuity and a quicker response to treatment (The Pediatric Eye Disease Investigator Group, 2017; Vaegan & Taylor, 1979).

As to the severity of amblyopia, untreated refractive errors or strabismus commonly produce less severe levels of vision loss. The severity of anisometropic and

strabismic amblyopia depends on the age of onset of the amblyogenic factor as well as the timing of intervention, with younger children being more at risk of amblyopia development than older children. The critical period of developing amblyopia, subnormal binocularity, and subnormal stereoacuity is 2-3 years of age (Mohindra et al., 1979; The Pediatric Eye Disease Investigator Group, 2017). An approximate age of 8-9 years has been generally agreed upon as the upper age limit where amblyopia treatment can be successful, with no or minimal visual acuity improvement after this age from treatment (DeSantis, 2014; Keech & Kutschke, 1995).

1.5 Rationale for Treatment

Treatment of amblyopia during the critical period of development often improves visual acuity and can improve binocularity in some types of amblyopia (The Pediatric Eye Disease Investigator Group, 2002, 2003a). Early intervention decreases the likelihood of binocular vision loss, and is reportedly cost-effective, being less expensive to treat rather than treat conditions later in life caused by amblyopia (Membreno et al., 2002). Though cost-effectiveness standards have not been well established, in general, a $/QALY (dollars expended per quality-adjusted life-year) gained of <$20,000 is considered cost-effective. When considering amblyopia treatment including any required surgical intervention the $/QALY gained with a 3% discount rate in U.S. dollars in 2001 was $2,281 (Membreno et al., 2002). More recent studies have shown the $/QALY to be US$3,638 as of 2018 (Malvankar-Mehta et al., 2018). Even considering inflation to the present year, this dollar amount is well under $20,000 making amblyopia treatment very cost-effective.

Amblyopia has been reported to double the risk of developing binocular vision loss throughout one's lifetime. Therefore, treating amblyopia during visual immaturity can prevent future low vision and or/blindness and the burden these conditions pose on the patient and healthcare system (Delpero et al., 2019; A. Pai & Mitchell, 2010; Van Leeuwen et al., 2007). Treatment of amblyopia in childhood also decreases the likelihood of losing the normal eye to workplace injury, accidental trauma, or injury in both childhood and adulthood (Simons, 1996; Tommila & Tarkkanen, 1981). Also, the World Health Organization (WHO) found an increase in age-related low vision such as cataracts, age-related macular degeneration, glaucoma, and diabetic retinopathy with the growth in the aging population, increasing the risk of low vision in people with previous amblyopia (Pascolini & Mariotti, 2012).

Although there is not enough evidence to support a negative impact of amblyopia on career performance, educational outcomes, or behavioral difficulties, it does impact career prospects (Chua & Mitchell, 2004; J. S. Rahi et al., 2006; Jugnoo S. Rahi et al., 2009; The Pediatric Eye Disease Investigator Group, 2017). Some careers such as law enforcement, fire fighting, and military service require minimum levels of visual acuity, stereopsis, and binocular single vision which can be unobtainable due to amblyopia (The Pediatric Eye Disease Investigator Group, 2017). Amblyopia has also been associated with colour vision defects, with more severe defects correlating with deeper amblyopia. Colour vision defects could prevent career opportunities in the previously mentioned careers and careers such as electricians, chemical titration analysers, and gem-quality analyzers (Simons, 1996; Von Noorden, 1996). Furthermore, over half of all bilateral vision loss cases related to amblyopia lose vision in their non-amblyopic eye in

workplace injuries, which could deter hiring as amblyopia poses a higher liability (Simons, 1996).

As to morbidity, amblyopia induces a reluctance in operating on the non-amblyopic eye from surgeons as they fear creating bilateral vision impairment (Simons, 1996). In turn, this leads to longer waiting periods for amblyopic patients to receive cataract removals and other ocular surgeries. Again putting them at a higher risk of bilateral vision loss and impairment while also decreasing their quality of life satisfaction (Simons, 1996). Treatment of amblyopia during visual immaturity can therefore reduce the morbidity attributed to amblyopia.

A final rationale for amblyopia treatment is to improve the success rate of strabismus surgery. By eliminating or decreasing the visual acuity interocular difference through amblyopia treatment, better binocularity can be achieved which promotes stability in post-surgical strabismus angles (Repka et al., 2005; The Pediatric Eye Disease Investigator Group, 2017). Therefore, children with binocular potential should receive amblyopia treatment along with strabismus surgery (Repka et al., 2005; The Pediatric Eye Disease Investigator Group, 2017).

1.6 Treatment of Amblyopia

Although extensive literature on amblyopia treatment exists, there is a lack of standardization and consensus on the most effective therapeutic modality. Before the initiation of additional forms of amblyopia treatment, it has been suggested that partial or complete refractive correction be given (The Pediatric Eye Disease Investigator Group, 2017). Across studies, refractive correction alone has had greater effects on patients with milder anisometropia, better stereopsis, strabismus, and mixed amblyopia with lower

visual acuity (Maconachie & Gottlob, 2015). A standard refractive adaptation period of 12 weeks has been suggested (The Pediatric Eye Disease Investigator Group, 2006, 2017). Although refractive correction alone can correct amblyopia in 32% of cases, the lack of randomized controlled studies makes the use of this as a standalone treatment modality unclear (The Pediatric Eye Disease Investigator Group, 2012a; Wang, 2015).

Traditionally, occlusion therapy has been the most widely accepted amblyopia treatment and continues to be the mainstay modality although newer forms of treatment exist (Maconachie & Gottlob, 2015; Taylor & Elliott, 2011; Yazdani et al., 2017). Occlusion therapy involves covering the non-amblyopic eye to force the use of, and reliance on, the amblyopic eye in an attempt to improve vision (Yazdani et al., 2017). It is usually initiated following a period of refractive adaptation (The Pediatric Eye Disease Investigator Group, 2017). Among researchers, varying amounts of occlusion hours have been deemed successful, spanning from 2-6 hours/day for part-time occlusion (PTO) to full-time occlusion (FTO) consisting of all-waking hours (Hug, 2004; Scott et al., 2005; Von Noorden, 1996; Yazdani et al., 2017). Occlusion therapy can last a few months to a few years and is effective for mild, moderate, and severe forms of amblyopia (Wang, 2015).

1.6.1 Compliance and Amblyopia Treatment

Amblyopia is one of the most common visual disorders in children and has a narrow treatment time window. A major component contributing to the lack of treatment success is noncompliance from children and parents, with noncompliance ranging from 11.7-54% (Cathy Williams & Harrad, 2006). Lack of compliance also creates doubts about the responsiveness to treatment in children ages 7 years or older. Older patients

have a higher rate of missed appointments, which negatively impacts treatment success (Fronius et al., 2009, 2014). Compliance is reported to be as low as 46% (Stewart et al., 2004), decreasing from 81% in the first month of treatment to 56% after 3 months (Fronius et al., 2009). Mean compliance has also been reported to be 2.8h/d with only 14% of participants patching within .5 hours of the treatment dose (6h/d) (Stewart et al., 2004).

In the literature, social stigma is thought to be a significant factor in the success or failure of treatment. Both children and adults who wear glasses for amblyopia treatment report lower self-esteem, physical attractiveness, and motivation (Harter & Bosacki, 1999; Webber et al., 2008). Removal of glasses or contacts did not alleviate negative psychosocial effects (Terry et al., 1997). Furthermore, children receiving amblyopia treatment report feeling ashamed or self-conscious of their treatment (Choong et al., 2004; Hrisos et al., 2004; The Pediatric Eye Disease Investigator Group, 2003d), with 35% being more likely to be physically or verbally bullied (Horwood et al., 2005). However, it has also been reported that no significant psychosocial impacts of amblyopia treatment of children or caregivers exist (Choong et al., 2004).

Another reported cause of poor compliance is the cost of treatment. Overall, the cost of glasses during amblyopia treatment ranges from $521 for anisometropic to $1820 for congenital cataract patients. At this cost threshold, a significant financial burden is posed on low-income families, increasing the lack of compliance as treatment is not affordable (Malvankar-Mehta et al., 2018). In this case, mitigation of treatment costs should be considered to promote higher compliance.

To address the problem of noncompliance, one study provided an increased amount of education on treatment, success, and improvement of the amblyopic eye to the

parents and children (Maconachie & Gottlob, 2015). This study revealed a statistically significant dose-response rate between treatment education and visual outcome (Maconachie & Gottlob, 2015). The lack of a truly objective measure of compliance is a consistent flaw across all amblyopia research.

1.6.2 Stability of Visual Acuity after Treatment

Due to the dominance of the non-amblyopic eye following treatment, regression of visual acuity in the amblyopic eye is likely to occur during and after treatment (Lunghi et al., 2016). Previous studies on visual acuity regression have failed to identify any common, predictive, and influencing factors necessary for the maintenance of visual acuity after cessation of therapy (Walsh et al., 2007).

1.7 Amblyopia Treatment Dose-Response Rate

Another area that lacks evidence-based quantitative research, is the dose-response rate of amblyopia therapeutic modalities. This information is essential to determine the effectiveness of amblyopia treatment modalities. The evaluation of therapeutic effectiveness may be the true indication of successful treatment.

1.8 Study Purpose

Although a plethora of literature related to treatments of amblyopia and treatment success predictors exists, research involving the dose-response rate of individual amblyopia therapeutic modalities is lacking. Empirical research on amblyopia treatment effectiveness and dose-response rate is needed. Additionally, previous research on the

dose-response rate of amblyopia treatment has inconsistencies in methodology, study population, and visual acuity assessment tools.

The present study aimed to expand empirical findings on the dose-response rate of occlusion therapy and address limitations of previous literature. It explored retrospective data of a sample of amblyopic children in the population of the IWK Health Centre, Eye Care Clinic. A secondary study outcome measure was to explore predictors for treatment success and dose-response rate. By establishing occlusion therapy dose-response rates, treatment duration estimates, and success rates, this information can be presented to amblyopia patients and families as well as inform clinical practice based on dose-response rate predictors. Determining what predictors are most effective in improving dose-response rate has the potential to improve orthoptic practice, patient outcomes, and compliance. This study will pave the way for future clinical trials and research on the dose-response rate for occlusion therapy. Thus, allowing the most effective treatment of amblyopia to be developed and to shape clinical practices.

2.0 Chapter 2 Literature Review

Amblyopia treatment in children has been an ongoing discussion in the orthoptic and ophthalmic communities. Although there is a wide range of literature related to occlusion therapy in the treatment of amblyopia, few studies have explored dose-response rate. Furthermore, previous research on the dose-response rate of amblyopia treatment had inconsistencies in methodology, study population, and visual acuity assessment tools. Using the findings from the literature, study hypotheses and design were formulated. By reviewing both treatment success and dose-response rate, a more detailed evaluation of therapeutic effectiveness of occlusion therapy may be determined.

2.1 Amblyopia Treatment Success Definitions

Success rates of amblyopia treatment vary widely in the literature from 23-82% (Hiscox et al., 1992; Stein et al., 2014; The Pediatric Eye Disease Investigator Group, 2003a). The definition of treatment success is also inconsistent, making it difficult to draw any conclusions. Equal visual acuity has been used in previous reports as the definition of amblyopia treatment success. Success rates using this definition range from 60-73% (Scott et al., 2005; Stein et al., 2014). Other studies define success based on the final level of visual acuity achieved following amblyopia therapy. The final acuity ranges widely from 6/7.5 – 6/18, depending on the individual investigations (Hiscox et al., 1992; Hug, 2004; The Pediatric Eye Disease Investigator Group, 2003a). Success rates under this definition range from 23-82% (Hiscox et al., 1992; The Pediatric Eye Disease Investigator Group, 2003a). Functional success is a subset of the level of visual acuity obtained for certain careers. As mentioned in chapter 1, some careers such as law enforcement, fire fighting, and military service require minimum levels of visual acuity

which can be unobtainable due to untreated amblyopia (The Pediatric Eye Disease Investigator Group, 2017). Lastly, other studies have used absolute visual acuity gain to define successful amblyopia treatment. Success in these studies ranging from 1-3 logMAR gain with success rates between 23-77% (Hiscox et al., 1992; Kirandi et al., 2017; Seol et al., 2017; The Pediatric Eye Disease Investigator Group, 2006).

For the purposes of this study, amblyopia treatment success will be defined as achieving visual acuity of 6/12 or better in the previously amblyopic eye, without having occlusion amblyopia in the non-amblyopic eye. The level of monocular vision required for non-commercial driving in most jurisdictions is 6/12 by law in Nova Scotia. Additionally, as some patients at the IWK Eye Clinic are ages 2-4 years, 6/12 is the average maximum level of visual acuity for these age groups (Iannelli, 2020). This definition of success will act as the dependant variable. Additionally, final post amblyopia treatment levels of 6/9, 6/7.5, 6/6, and equal visual acuity will be analyzed to allow a wider range of outcome comparisons.

2.2 Amblyopia Treatment Success Predictors

To understand amblyopia treatment success, variables impacting success must be investigated. These variables include age at treatment initiation, classification of amblyopia (ie. mixed, strabismic, anisometropic), the severity of amblyopia, the success of previous treatment, duration of treatment, and type of treatment.

2.2.1 Age at Treatment Initiation

A number of studies have investigated the impact of age on treatment success. All found that the rate of successful amblyopia treatment decreased with increasing age

(Fronius et al., 2014; Holmes, Lazar, Melia, Astle, Dagi, Donahue, Frazier, Hertle, Repka, Quinn, Weise, et al., 2011; The Pediatric Eye Disease Investigator Group, 2005, 2017). It is generally accepted that success of treatment greatly reduces after the age of 7 years (Fronius et al., 2014; Holmes, Lazar, Melia, Astle, Dagi, Donahue, Frazier, Hertle, Repka, Quinn, Weise, et al., 2011; The Pediatric Eye Disease Investigator Group, 2005). However, some studies have found success is still obtainable in the age range of 7-15 years (Mohan et al., 2004; The Pediatric Eye Disease Investigator Group, 2005). Yet, in these studies, participants were included who had previous amblyopia treatment at an undetermined younger age, preventing accurate conclusions from the results (Mohan et al., 2004; The Pediatric Eye Disease Investigator Group, 2005). Although most authors believe that the treatment of amblyopia is unsuccessful after visual maturity, there continues to be debate about this issue.

2.2.2 Classification of Amblyopia

As was noted previously, there are many types of amblyopia. Some research suggests that the type of amblyopia may impact treatment success by influencing outcome and stability of visual acuity. Mixed amblyopia reportedly has worse success outcomes and higher occurrence of visual acuity regression following treatment when compared to other amblyogenic factors such as strabismus and anisometropia (Cleary, 2000; Hiscox et al., 1992; Levartovsky et al., 1995; Woodruff et al., 1994). However, another study reported the highest occurrence of visual acuity regression following treatment with anisometropic amblyopia (Ohlsson et al., 2002). Although the classification of amblyopia is suggested to influence success, there is evidence to the contrary. A retrospective case series study by Seol (2017) investigated the use of 1% atropine penalization twice a week

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over 4 months in children for whom patching had previously failed. This study found no statistically significant difference in success across anisometropic (n=17), strabismic (n=15), or mixed (n=9) amblyopic patients (Seol et al., 2017). These results have been confirmed by other studies finding no difference in visual acuity improvement following occlusion therapy across anisometropic, strabismic, or mixed amblyopia (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a). Though some evidence does exist showing the classification of amblyopia treatment to impact success, the literature also reveals no statistically significant effect.

2.2.3 Severity of Amblyopia

The severity of amblyopia prior to treatment has also been suggested to influence amblyopia treatment success. In the literature, it has been concluded that lower initial visual acuity correlates to lower final visual acuity after treatment (Fronius et al., 2009, 2014; Scott et al., n.d.; Scott et al., 2005; Scott & Dickey, 1988; Stewart et al., 2004, 2007a). Post-treatment visual acuity in those with lower visual acuity is also reportedly less stable (Levartovsky et al., 1995). In summary, outcome visual acuity appears to correlate to initial visual acuity before amblyopia treatment.

2.2.4 Treatment Duration

There are conflicting results in the literature on the correlation between treatment duration and treatment success. Publications have determined both a highly significant relationship (Cleary, 2000; Dorey et al., 2001) or no correlation between hours of treatment and gain in visual acuity (The Pediatric Eye Disease Investigator Group, 2003c). Even an inverse correlation has been reported (Hiscox et al., 1992). Additionally,

the highest visual acuity improvement has been shown to occur in the first 6 weeks of treatment (Cleary, 2000; Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a). Comparatively, Walsh et al. (2006) reported that improvement has also been shown to occur for up to 12 weeks of treatment. However, other longitudinal studies have found no statistically significance effect of treatment duration on outcome visual acuity (PEDIG, 2002). PEDIG (2002) performed a randomized clinical trial of 419 patients ages 3 to 7 years of age with follow-up at 6 months and 2 years after part-time occlusion. No significant difference in success outcomes was found between the 6-month and 2-year groups, with both improving about 3 lines in visual acuity and producing similar sensory outcomes (The Pediatric Eye Disease Investigator Group, 2002). In summary, the highest visual acuity gain appears to be within the first 6 weeks of treatment.

2.2.5 Full Time Occlusion versus Part Time Occlusion

Amongst clinicians, there continues to be controversy on the amount of occlusion and the effectiveness of amblyopia treatment (Scott et al., n.d.; Scott et al., 2005; Scott & Dickey, 1988; The Pediatric Eye Disease Investigator Group, 2003c, 2003b; Yazdani et al., 2017). Some studies have suggested that FTO results in more rapid and higher levels of visual acuity gain, whereas others report similar final acuity outcomes with lower levels of occlusion. The majority of the studies aimed at comparing FTO with PTO have significant limitations making true comparisons difficult, if not impossible.

The Pediatric Eye Disease Investigator Group (PEDIG) conducted several multicentre, randomized controlled studies in an attempt to provide some clarity on this clinical dilemma. In 2003, PEDIG performed a clinical trial of 189 children younger than 7 years with moderate amblyopia (20/40 to 20/80). The patients were randomly assigned

to 2 hours or 6 hours of daily occlusion, in addition to 1 hour of near visual acuity activities while patching. Before the initiation of occlusion, optimal spectacle correction was worn for a minimum of 4 weeks. Treatment adherence was assessed by having the parents record daily occlusion hours on a calendar. The following scale was used to determine adherence to prescribed treatment: excellent (76-100%), good (51-75%), fair (26-50%), and poor (25% or less). The results of this investigation reveal similar visual acuity gains in both groups. This study did have many strengths such as randomization of treatment groups, masked examiners, standardized visual acuity testing protocols, and moderate sample size. However, the limitations of this investigation bring many of the study conclusions into question. One of the main study limitations was the lack of compliance to the prescribed treatment. In the 2-hour group, just slightly over half of the study population (58%) reported excellent adherence to treatment. The patients in the 6-hour per day group, had even lower compliance rates with only 37% reporting excellent compliance, with 63% of this group performing less than 4.5 hours of daily occlusion. Although the authors did acknowledge that the study's conclusions were based on the prescribed patching program, and not the actual amount of occlusion reported, the results for the treatment groups were analysed as though all patients in each group had complete adherence to their prescribed treatment regimen. All patient data was analyzed based on the assigned group, regardless if the prescribed amount of occlusion was actually achieved. This type of data analysis, referred to as intention-to-treat, compares different treatment outcomes, even if that treatment was not actually carried out. Unfortunately, analysing the data in this manner can reduce the validity of the results. Other limitations of this study include a short refractive adaptation requirement (4 weeks minimum) which could have resulted in overestimation of visual acuity gain from occlusion alone as visual

acuity has been found to improve for up to 18 weeks of refractive adaptation (The

Pediatric Eye Disease Investigator Group, 2006, 2012b). One hour of near activities was

prescribed to all patients, however, the compliance to this additional intervention was not

included in the data analysis. The addition of this secondary intervention could confound

the outcome visual acuity results. Allowing individual site investigators to alter the

amount of occlusion between weeks 5-17 at their discretion, adds further ambiguity to

this study's conclusions. As primary outcome visual acuity was measured at the 4-month

visit, occlusion amounts may have already been changed by the investigators. Yet results

were analysed based on the initial prescribed treatment group.

A follow-up study by the PEDIG group in the same year (2003c) looked to

compare FTO (defined as all hours or all but 1 hour per day) to 6-hours of patching per

day in the treatment of severe amblyopia (20/100 to 20/400) in children younger than 7

years. The patient demographics and study methodology, with the exception of the

occlusion hours in the two treatment groups, were similar to the PEDIG investigation

mentioned above. One hundred and seventy-five children were randomized to either the

FTO or 6-hours per day, each combined with 1 hour of near visual activities during

patching. The main outcome measure was visual acuity at the 4-month site visit. The

authors concluded that 6 hours of prescribed patching produces similar visual acuity gains

as prescribed full-time patching in severe amblyopia. Like the previous PEDIG

investigation, this study's results were based on the intention-to-treat analysis and not the

actual amount of daily occlusion worn by the patients. The lack of treatment adherence

was again the most significant limitation of this study, greatly weakening this study's

findings. In the FTO group, approximately two-thirds of the patients may have only worn

their patch half of their waking hours. Only 32% in the FTO group reported excellent

compliance, increasing to only 53% in the 6-hour per day group. Based on these findings, the amount of actual occlusion worn in the two treatment groups may not have been different. The short refractive adaption time (4 weeks minimum) could also result in overestimation of outcome visual acuity improvement, especially in the anisometropic amblyopes, which accounted for approximately one-third of each group. One finding that is certainly of interest is that the majority of the visual acuity gain in each group occurred within the first 5 weeks of treatment.

The final comparison study on amblyopia management by the PEDIG (2003) investigated the effectiveness of atropine penalization vs patching. This was another multicenter, randomized control study of children younger than 7 years with mild to moderate amblyopia (20/40 to 20/100). The primary outcome measure was visual acuity level after 6 months of treatment. Patients were randomly assigned to daily atropine in the non-amblyopic eye or daily patching for a minimum of 6 hours per day, up to FTO. The initial level of occlusion prescribed was at the discretion of the investigator. If the patients had not achieved 20/30 or an acuity gain of 3 lines or more by the fourth treatment month, occlusion was increased to full-time and a plano lens was used to augment the atropine penalization to create a total penalizing effect. The authors concluded similar improvement in visual acuity in both the atropine and patching groups. There was a correlation between the speed of improvement and the increased hours of patching. The patching group achieved 20/30 by week 5 in 56% of the patients, reducing to 33% in the atropine population. The investigators could change the dose of treatment in either group throughout the study at their discretion, making reproducibility and generalizability problematic. This study's conclusion, like the previously mentioned PEDIG studies, was based on the intention-to-treat analysis and not the actual reported treatment amount.

Other studies that compared FTO to PTO found similar results to the PEDIG series. Stewart et al. (2007b) conducted an unmasked randomized trial of 97 amblyopic children from two London, England Hospitals between February 2002 and May 2004. Inclusion criteria included children between the ages of 1-8 years, with anisometropic, strabismic, or mixed amblyopia, with at least 0.1 logMAR interocular difference. Patients with prior history of amblyopia therapy, ocular pathology, or learning disabilities were excluded from this investigation. Eighteen weeks of refractive adaptation was performed prior to the initiation of any occlusion therapy. Participants were randomly sampled into 2 occlusion groups: 6 versus 12 hours/day (n=40 both groups). Study results found no mean difference in outcome visual acuity between groups, with both having an improvement of 0.24 logMAR units. However, a major study limitation is that the actual mean daily dose (hours of patching per day) received did not significantly differ between both groups. The 6-hour group actually patched a mean of 4.2 hours/day and the 12-hour group had a mean of 6.2 hours/day. Given this limitation, comparisons can not be made between the FTO and PTO treatment groups. Another limitation is that participants with only 0.1 logMAR interocular difference in visual acuity were included in this study. A one-line (0.1 logMAR) difference in visual acuity can simply be a result of normal test-retest clinical variability (DeSantis, 2014; Shiamir et al., 2016), limiting this study's results as some non-amblyopic participants could have been included.

Singh et al. (2008) conducted a prospective interventional case series across 100 children with strabismic, anisometropic, and mixed amblyopia between the ages of 7-12 years to compare the efficacy of FTO to PTO. Refractive adaptation of 6 weeks was conducted prior to occlusion therapy. Participants were divided into 4 groups (n=25 each): PTO of 2 hours/day, PTO of 4 hours/day, PTO of 6 hours/day, and FTO (all

waking hours). In addition, all children were asked to perform 1 hour of near work while patching. Study results found significant visual acuity improvement in all four groups following treatment (p<0.001). No significant difference was found between the FTO and PTO groups performing 4 (p=0.068) and 6 hours of occlusion (p=0.284). However, a statistically significant difference did exist between the 6 hour and FTO groups compared to the PTO group patching only 2 hours/day (p=0.015). Study limitations are similar to previous studies. The most notable limitation is that FTO was described as only 6 hours/day, preventing comparisons to FTO of all waking hours. Additionally, only occlusion of 2-6 hours was included, and compliance not reported, possibly leading to a lack of difference between groups and type II error. Type II error occurs when a null hypothesis is accepted when it is actually false. In the case of Singh et al. (2008), possibly finding a lack of difference in treatment groups when a difference exists due to lack of variability between groups. Additionally, near work while patching was prescribed but not well defined, possibly presenting a confounding variable to outcome visual acuity.

In contrast to studies finding no significant difference in outcome visual acuity between PTO and FTO, one study did find a significant difference. Arikan et al. (2005) retrospectively reviewed 128 pediatric patients, ages 3-12 years, from the Dokuz Etlul University School of Medicine from March 1992-2003. Inclusion criteria included patients with anisometropic, strabismic (esotropic only), and mixed amblyopia who had visual acuity measured on a Snellen acuity chart. Participants were divided into 2 groups: PTO (n=70, 2-6 hours) and FTO (n=39, all waking hours) using subjectively (parental) reported occlusion doses. Success was defined as ≤1 line interocular difference following treatment. Compliance was measured using parental diary reports. Study results found statistically significant different mean improvement between FTO and PTO, FTO mean

improvement of 0.58 logMAR and PTO mean improvement of 0.35 logMAR (Arikan et al., 2005). Study strengths included enough sampling between PTO and FTO to allow statistically significant group comparisons although not equal. Study limitations include that although compliance was attempted to be measured through parental reports, the retrospective nature of the data prevented any attempts at objective compliance monitoring. Additionally, limited sampling between groups prevented comparisons of classification of amblyopia on success as statistical power was limited. Finding mean visual acuity improvement of 0.38 logMAR for strabismic amblyopia, 0.46 logMAR for mixed amblyopia, and 0.35 logMAR for anisometropic amblyopia. Although visual acuity improvement appeared better in the mixed amblyopic group, the lack of equal sample sizes between classifications of amblyopia prevented significance in the analysis of variance (p=0.371).

A retrospective review performed by Hug (2004) was performed to compare the success results of FTO to PTO. 45 participants (24 PTO, 21 FTO) were included from charts of the Children's Mercy eye clinic between 2002 and 2003. Inclusion criteria included amblyopic children between the ages of 3-7 years with no organic cause of their amblyopia. All patients received an undefined amount of refractive adaptation prior to occlusion therapy. FTO was defined as ≥12 hours/day of occlusion and PTO <6 hours/day. Success was determined using the level of vision obtained with two brackets of success, 6/9 or better and 6/12 or better. The FTO group trended towards higher success with 76% of participants achieving 6/9 or better compared to 58% of PTO and 67% achieving 6/12 or better compared to 46% of the FTO. Though this was not a statistically significant result as the sample size was small, it should still be acknowledged that FTO trended towards better overall visual acuity (Hug, 2004). The most significant

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study limitation is the small sample size, preventing statistical power. Additionally, length of refractive adaptation was not provided, possibly confounding outcome visual acuity results. Lastly, compliance was not documented, possibly increasing type II error as poor compliance could result in a lack of difference between treatment groups when a difference exists due to lack of variability between groups.

In an attempt to add clarity to the occlusion dose uncertainty, Yazdanni et al. (2017) conducted a meta-analysis comparing FTO and PTO. Six studies were included in the analysis, three of the studies were randomized controlled studies (RCT). Although the investigation revealed no statistical difference in the acuity gain with FTO vs PTO, the authors reported that 6hrs/day of occlusion is the minimal amount needed to achieve maximum improvement. All six studies included in this meta-analysis have been mentioned previously, including the critical flaw in each study's methodology and conclusions. Notably, that all studies used intent-to-treat for statistical analyses.

In summary, the debate continues as to whether FTO or PTO is more effective in the management of amblyopia (Scott et al., n.d.; Scott et al., 2005; Scott & Dickey, 1988; The Pediatric Eye Disease Investigator Group, 2003c, 2003b; Yazdani et al., 2017). Overall, the majority of studies reviewed found no statistically significant difference between the two groups (Hug, 2004; Singh et al., 2008; Stewart et al., 2007b; The Pediatric Eye Disease Investigator Group, 2003d, 2003b). However, a persistent limitation existed across these studies. In each, compliance was poor, limiting group differences in the number of hours patched and making any real comparisons challenging.

2.3 Dose-Response Rate of Treatment

Although there has been extensive literature on the management of amblyopia, little research exists involving the dose-response rate to the amblyopia treatment.

Stewart et al. (2004) conducted one of the first studies aimed to investigate the dose-response rate of visual acuity to amblyopia occlusion therapy. This prospective cohort study investigated dose-response rate, compliance, refractive adaptation, and effectiveness of occlusion therapy. Ninety-four participants (23 anisometropic, 34 strabismic, and 37 mixed amblyopes) diagnosed with amblyopia, with the mean age 5.2 years, were divided into 3 phases: baseline visual acuity measurements, refractive adaptation, and 6 hours/day occlusion therapy. Inclusion criteria included children aged 3-8 years with anisometropic, strabismic, or mixed amblyopia, and interocular difference in visual acuity of 0.1 logMar. Patients with a history of previous amblyopia treatment, ocular disease, or learning difficulties were excluded from this study. All participants had a full ophthalmic and orthoptic examination before study entry and received 18 weeks of refractive adaptation. Participants not requiring refractive correction or those with residual amblyopia post-refractive adaption began occlusion therapy (n=75). Visual acuity for each subject was measured every 6 weeks on ETDRS crowded and single optotype logMAR charts. Following refractive adaption, participants with at least 0.1 logMAR interocular difference received 6 hours/day of occlusion. Follow-up was done every 2 weeks. Occlusion was monitored using an Occlusion Dose Monitor (ODM) with 2 electrodes to monitor compliance. Statistical analyses included a non-parametric modeling LOW-ESS regression and parametric and nonparametric linear regression. The LOW-ESS regression was used to plot scatter points of visual acuity to determine the

dose-response rate. Regression was used to apply covariates to the dependent variable to see their interaction.

Study results found a mean visual acuity improvement of 0.65-0.22 logMAR units in the amblyopic eye during refractive adaptation alone. During occlusion treatment, visual acuity improved from 0.50-0.15 logMAR. Mean compliance was 2.8h/d with only 14% of participants patching within 0.5 hours of 6h/d. The dose-response rate of visual acuity was linear and monotonic with patching over 2 hours increasing dose-rate response but not final visual acuity outcome. However, a higher daily dose did lead to shorter treatment outcomes. The mean dose-response rate for 0.1 logMAR improvement in visual acuity was 120 hours of occlusion therapy. The dose-response rate was not statistically different across the three classes of amblyopia included in the study. However, initial visual acuity, total dose, and age were significant predictors of dose-response rate (R^2=0.87). The highest dose-response rate occurred within the first 6 weeks of occlusion therapy (82% of improvement) and in children under the age of 4. In total, a dose of 200 hours resulted in less than a 0.2 logMAR interocular difference and more than 75% of the amblyopia corrected.

Following the initial study on dose-response rate, Stewart et al. (2009) conducted a second study that investigated the dose-response rate of occlusion therapy and derived an empirical mathematical model of treatment dose-response rate. This study mirrored the first in methods and analyses, including 72 amblyopic participants ages 3-8 years (mean age 5.2 years). The same inclusion, exclusion, and study methodology were used as the previous study. What differed in this study from the first is that additional covariates were included: initial visual acuity, type of amblyopia, age at treatment onset, and severity of amblyopia. Additionally, an empirical mathematical model of treatment dose-response

rate was calculated. Statistical analyses included linear regression and multivariate regression. Linear regression was found to be insufficient to analyse the covariates. Therefore, multivariate regression was used to analyse the effect of covariates on the outcome variable. A LOW-ESS regression plotted scatter points of visual acuity to determine the dose-response rate.

Study results found mean visual acuity improved from 0.65-0.22 logMAR units during refractive adaptation alone. Dose-response rates differed across age with a dose-response rate of 0.20 logMAR acuity gain requiring 170 hours of occlusion for children age 2 and 236 hours at age 3 years. The authors concluded that overall, a 0.35 logMAR improvement in visual acuity is expected to take 150-250 hours of occlusion. Covariates included treatment dose, treatment duration, age at treatment onset, and severity of amblyopia, finding all statistically significant ($p<0.0001$). However, treatment duration is an outcome variable, limiting this model's clinical significance.

As to study strengths, Stewart et al. (2004) was the first study to investigate the dose-response rate of occlusion therapy. Both studies were prospective with well-defined population, inclusion, and exclusion criteria. Other strengths include obtaining statistical power and finding dose-response rate of visual acuity improvement was fastest in the first 6 weeks of treatment and in younger patients (Stewart et al., 2004). These studies also attempted to objectively monitor compliance using the ODM system to address the common limitation of lack of compliance across amblyopia research (The Pediatric Eye Disease Investigator Group, 2003c, 2003e). Lastly, a refractive adaptation of 18 weeks was completed prior to occlusion therapy treatment. This attempts to eliminate confounding results from refractive error (Stewart et al., 2004).

In contrast to the study strengths, limitations across both studies include only

measuring PTO (dose of 6hours/day). Full-time occlusion and other dose rates were not

included limiting result application and generalizability to varied amounts of occlusion.

Another limitation is poor compliance across participants (compliance rate of 48%

(Stewart et al., 2004)) possibly causing type II error in dose-response rate calculations as

treatment was not being followed. Additionally, a 0.1 logMAR difference in visual acuity

was used as inclusion criteria. A 0.1 logMAR difference in visual acuity is clinically

considered standard day-to-day variability. Clinically, a 0.2 logMAR interocular

difference is used to define amblyopia to avoid issues with test-retest reliability across

visual acuity charts (DeSantis, 2014; Shiamir et al., 2016). Additionally, it is not stated

how many participants had only a 0.1 logMAR interocular difference prior to treatment

initiation. The use of ODM for compliance also has its limitations as the sensors are

placed in the center of the patch, allowing the patient to peak from the side. Lastly, only

some covariates were included such as age at treatment, and type of amblyopia limiting

analyses of the impact of confounding variables on treatment. In summary, these

limitations prevent the generalizability of results to patients with amblyopia and present

opportunities for future research (Stewart et al., 2004).

Fronius et al. (2009) continued research on the dose of treatment and age limits

for success for amblyopia treatment (Fronius et al., 2009). Nine amblyopic participants

ages 7-16 years (n=3 anisometropia, n=1 strabismic, n=5 mixed) were included in a small

sample prospective cohort study. Five patients had no prior amblyopia treatment and 4

had prior occlusion therapy with residual amblyopia. Study participants were recruited

from the Pediatric Ophthalmology Department of the University of Frankfurt. Inclusion

criteria included participants over the age of 7 years with strabismic, anisometropic, or

mixed amblyopia who had a minimum 0.2 logMAR interocular difference on crowded

optotypes, after 6 weeks of refractive adaptation. Anisometropic amblyopia was defined as amblyopia with a >1D difference in spherical equivalent and/or >1.5D of difference in astigmatism between the eyes. Exclusion criteria excluded patients with other eye disorders, visual deprivation amblyopia, brain damage, organic amblyopia, or who lived too far away from the research center to travel in for study visits. All participants had full ophthalmic and orthoptic examinations completed. All patients received at least 6 weeks of refractive adaptation using their full cycloplegic correction and were prescribed 5-7 hours of patching per day. Follow-up assessments were scheduled every 3-6 weeks regardless of patient age. The dose-response rate was measured using the 2002 and 2005 versions of the ODM developed in the Netherlands to record the dose of treatment. The dose was defined as the number of hours of occlusion per day with the dose-response rate being cumulated hours occlusion/0.1 logMAR acuity gain. Near visual acuity was recorded using Crowded Landolt ring charts with optotype separation of 2.6minarc at 40cm, and Landolt ring charts at 5m or ETDRS charts at distance. Diaries were also kept by the patient family to record occlusion amounts in cases of technology failure during the study. Statistical analyses included the Wilcoxon matched-pairs tests and Wilcoxon tests. The Wilcoxon matched-pairs tests compared visual acuity gain in the amblyopic eye and inter-eye acuity difference at the start of the study and after 4 months of treatment. The Wilcoxon test compared acuity gain across age (Fronius et al., 2009).

Study results found initial visual acuity ranged from 1.7-0.3 logMAR units, with a mean of 0.9 logMAR units. LogMAR distance visual acuity significantly improved at both 1 and 4 months of treatment, with a median gain of 0.17 logMAR at 1 month, and 0.19 logMAR at 4 months. A total acuity gain of -0.1-0.4 logMAR (mean 0.19) units on crowded optotypes was documented. At the 3-month treatment mark, the ODM recorded

the dose to be an average of 3.47h/d of occlusion across the participants. Compliance was measured as 85% at 1 month and 56% at 3 months of treatment, with 2 patients not patching at all after the first month of treatment. There was no significant difference between age and dose received. The dose-response rate was a mean of 77.63h/0.1 logMAR increase in visual acuity at 1 month and a mean of 234.15h/0.1 logMAR increase at 4 months of treatment. However, two patients were excluded after 1 month of treatment due to lack of compliance.

Strengths of the Fronius et al. (2009) study include well-defined study population, inclusion and exclusion criteria. Like the previous Stewart et al. studies, although no objective measurement of compliance was used, compliance was attempted to be measured using ODM and patient diaries. However, no correlation between diary entries and ODM results was made.

The main study limitation is the small sample size (n=9), limiting statistical power, the applicability of results, and generalizability. Additionally, 4 participants had prior amblyopia treatment, possibly confounding results. Study methodology also varied with 6+ weeks of refractive adaptation used, possibly varying dose-response rate results. Other weaknesses include that only a dose of 3 hours of patching/day was measured. Full-time occlusion and other dose rates were not included. Lastly, compliance was poor with only 56% of participants being compliant to treatment at 3 months. As compliance was poor, dose-response rate calculations may be inaccurate or skewed presenting type II error, preventing findings of group differences.

Fronius et al. (2014) then completed a second study on the dose-response rate of visual acuity following occlusion therapy. This was a small sample prospective cohort study that included 31 amblyopic participants (12 anisometropic, 8 strabismic, and 7

mixed amblyopes) between the ages of 5.4-15.8 years. The data of participants over age 7 years was calculated in a separate study. Study participants were recruited from an outpatient clinic located at the Pediatric Ophthalmology Department of the University of Frankfurt and several other external ophthalmology offices. The same inclusion, exclusion, and study methodology from the prior study (Fronius et al. 2009) were used, with the exclusion of patients that had previous amblyopia treatment other than spectacles prior to study initiation. Visual acuity was measured every 3-5 weeks regardless of age with acuity at 1 and 4 months of treatment used for statistical analyses. The timespans of 1 and 4 months were chosen as these timeframes were found to have the most improvement in the visual acuity in the previous literature (Kracht et al., 2010; Pediatric Eye Disease Investigator Group, 2003; Stewart et al., 2007b). The dose-response rate was measured using the newest version of the ODM, developed in the Netherlands, to record the dose of treatment. Near visual acuity was recorded on Crowded Landolt ring charts with optotype separation of 2.6minarc at 40cm. A range of statistical analyses were included in this study. First, a one-way repeated measures ANOVA compared the dose-response rate at 1 and 4 months of treatment. Next, a Wilcoxon matched-pairs test analyzed changes in occlusion dose-response rate between the treatment periods of 1 and 4 months. One-way ANOVAs with multiple Scheffe comparisons, Kruskal-Wallis one-way analyses of variance, and Wilcoxon-Mann-Whitney Tests compared different groups of patients. Lastly, a Spearman's rank correlation and multiple regression determined the relationships between variables and factors influencing treatment efficiency.

Study results found initial visual acuity ranged from 1.8-0.2 logMAR units, mean 0.77 logMAR units. LogMAR distance visual acuity significantly improved at both 1 and 4 months of treatment, with a median gain of 0.1 logMAR at 1 month and 0.3 logMAR at

4 months. All but 7 patients, all over age 6 years, continued to have visual acuity improvement after 1 month of treatment with a median gain of 0.1 logMAR units. There was no significant difference between patients with (n=15) and without (n=12) strabismus in acuity improvement. Both age and visual acuity gain at 4 months of treatment were reported to be statistically significant. Children under age 7 years had higher gain (n=8, mean age 6 years, median gain 0.4 logMAR units) and children over age 7 lower improvement (n=10, mean age 8.4, median gain 0.25 logMAR units). The dose was measured, using the ODM system, finding 4.19h/d of occlusion at the 4-month treatment mark across all participants. There was no reported significant difference between age and the daily dose received. The dose-response rate of median of 58.25h/0.1 logMAR increase in visual acuity at 1 month and median 169.19h/0.1 logMAR increase at 4 months of treatment was calculated. Dose-response rate became slower with increased age, with children age 6 or older having a dose-response rate of 220h/0.1 logMAR increase in visual acuity. Results also showed a decreased dose-rate response of acuity as a function of age, with no visual acuity gain after age 11 and a maximum gain of 0.3 logMAR units over 100 hours in children under the age of 7 years. The significant variables affecting dose-response rate were initial acuity (p=0.023), the recorded dose rate using ODM results (p=0.001), and age at treatment (p=0.003).

Study strengths include a well-defined study population and study rationale. Like the previous Stewart et al. studies, compliance was attempted to be measured using ODM and patient diaries. However, no correlation between diary entries and ODM results was made. Using ODM also unfortunately does not prevent or have the ability to monitor for peeking while wearing the patch. There really is no true objective measure of compliance. Lastly, a larger sample size was obtained, allowing for statistical power and a wider range

of appropriate statistical analyses.

The weaknesses of this study are numerous, including that only a dose of 6 hours of patching/day was measured. FTO and other dose rates were not included limiting comparisons to other occlusion treatment regimens. Study methodology also varied with 6+ weeks of refractive adaptation used, possibly varying dose-response rate results. Additionally, total dose-response rate to treatment outcome was not calculated. This limitation could be addressed by performing dose-response rate calculations at treatment outcome. Furthermore, Landot C was used to measure visual acuity which has limitations such as guessing and overestimating visual acuity. Additionally, visual acuity was only measured at near whereas distance acuity is typically used to diagnose and measure amblyopia. Another limitation is the source of bias created by some participants being excluded due to a dose-response rate division by 0 as there was no improvement in acuity of some patients between visits. Lastly, only one form of amblyopia treatment was included, preventing comparisons between types of amblyopia treatments. This could be addressed by including more types of treatment.

2.3.1 Dose-Response Study Result Summary

Across studies, a visual acuity improvement of 0.1-0.17 logMAR at 1 month and 0.19-0.3 logMAR at 4 months was found (Fronius et al., 2009, 2014). In all four studies, the dose-response rate was consistently analyzed at months 1 and 4 of treatment. All found the fastest dose-response rate occurred in the 4-6 weeks of treatment, ranging from 58.25-77.63h/0.1 logMAR at 4 weeks, and 169.19-234.15 logMAR at 16 weeks (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a). Dose-response rate per 0.1 logMAR increase ranged between 120-250 hours (Fronius et al., 2009, 2014; Stewart et al., 2004,

2007a). Dose-response rate was also compared across age at treatment initiation finding dose-response rate quickened significantly with younger age. Dose-response rate across classification of amblyopia was also investigated finding no significant differences (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a). Lastly, statistically significant covariates affecting dose-response rate included treatment dose, treatment duration, age at treatment initiation, severity of amblyopia, and initial visual acuity ($p<0.05$) (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a). The total dose-response rate for final visual acuity in the amblyopic eye was not calculated across any of the previous studies.

2.4 Study Objectives

Although amblyopia treatment and its success predictors have been widely studied, dose-rate response of amblyopia treatment lacks empirical review. Additionally, universally accepted best treatment practices as to dose and age for occlusion therapy are lacking. Across the four articles on amblyopia treatment dose-response rate (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a) similar limitations existed including limited doses of occlusion therapy, poor compliance, limited covariates, and small sample size (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a).

The present study aimed to determine the dose-response rate and success of visual acuity improvement following amblyopia treatment across multiple covariates (age, treatment dose, treatment duration, severity of amblyopia, and classification of amblyopia). To address limited dose variation, the present study will include varying hours of occlusion from 2-12 hours/day. The present study will include 134 participants as per the sample size calculation using Cohen (1992) for regression analyses. Several covariates, detailed in the data collection form, will be examined throughout this research.

This will allow the calculation of a predictive model of the covariates that could potentially influence the dose-response rate of visual acuity to occlusion therapy. Lastly, as compliance was only 45% in previous studies, the actual number of reported hours patched versus prescribed will be used.

The present study will add to dose-response rate research for occlusion therapy and address previous limitations. As empirical evidence of dose-rate response to amblyopia treatment is scarcely reported in the current literature, this study will be one of the first of its kind on this topic. It will optimistically pave the way for future clinical trials and research on the dose-response rate for occlusion therapy.

2.5 Hypotheses and Research Questions

Before presenting the research hypotheses and questions, total dose, treatment outcome, treatment cycle, dose, and dose-response rate will be defined. The total dose is defined as the total number of hours patched (non-amblyopic eye) to reach maximum visual acuity (defined as 3 consecutive cycles of no visual acuity improvement or equal vision in both eyes following occlusion therapy) (Stewart et al., 2004). One cycle is defined as 1 week per year of age follow-up to a maximum of 4 weeks. The dose is defined as the number of hours per day the non-amblyopic eye is occluded by an adhesive patch (Fronius et al., 2009). Dose-response rate is defined as visual acuity gain per hours of occlusion over the same period (Fronius et al., 2009).

2.5.1 Research Hypotheses

For all research hypotheses, when referring to significance, the study means statistical significance ($p<0.05$).

Null hypothesis 1: Dose and total dose of occlusion therapy do not significantly predict the success of amblyopia occlusion therapy.

Alternative hypothesis 1: Dose and total dose of occlusion therapy significantly predict the success of amblyopia occlusion therapy.

Null hypothesis 2: Dose and total dose of occlusion therapy do not significantly predict the dose-response rate of visual acuity improvement.

Alternative hypothesis 2: Dose and total dose of occlusion therapy significantly predict the dose-response rate of visual acuity improvement.

Null hypothesis 3: Predictors identified in the literature (listed below) will not have an individual effect on the outcome variables of amblyopia treatment success and dose-response rate of visual acuity.

Alternative hypothesis 3: Predictors identified in the literature (listed below) will have an individual effect on the outcome variables of amblyopia treatment success and dose-response rate of visual acuity.

Predictors:

- Age (integer/continuous): Age at beginning of treatment

- Treatment schedule (categorical): FTO, PTO

- Classification of amblyopia (categorical): Strabismic, Anisometropic, Mixed

- Visual acuity on crowded optotypes (continuous) on a logMAR scale

- Treatment duration (continuous): Any duration length

- The severity of amblyopia (continuous): Measured in initial visual acuity

- Refractive error (continuous): Diopters in + or -

- Follow up schedule (continuous): In weeks

- Angle of strabismus (continuous): in prism diopters

2.5.2 Research Questions

1. What is the dose-response rate of occlusion therapy and outcome visual acuity in patients with strabismic, anisometropic, and mixed type amblyopia?

2. What 'dose' and 'total dose' of occlusion therapy are required to achieve outcome visual acuity in patients with amblyopia?

3. What combination of variables predicts the dose-response rate of visual acuity to occlusion therapy?

4. What combination of variables predicts the outcome of achieving at least 0.3 LogMAR visual acuity and final visual acuity in the amblyopic eye following occlusion therapy?

3.0 Chapter 3 Methodology

Chapter 3 details the methodology of the present study. Study design, methods rationale, population, sample size, inclusion/exclusion criteria, sampling, and data collection are all discussed.

3.1 Study Design

This is a retrospective chart review of IWK Health Centre Eye Clinic amblyopia vision progress charts (VPC) and the MEDITECH patient medical record database (patient records from 2012 to 2019). IWK VPCs document the level of monocular vision in both eyes and treatment type at each visit for amblyopic patients (see Appendix C). Ethical approval was obtained from the IWK Health Centre Research Ethics Board (REB) for the use of orthoptic and ophthalmology reports for patients diagnosed with amblyopia. 458 patient VPCs, between the dates of January 2012 and December 2019, were reviewed. Only amblyopic patients able to accurately perform optotype visual acuity have vision progress charts. Therefore, VPCs capture a population of amblyopic patients with documented optotype visual acuity (see Glossary). As this is a retrospective chart review, patients were not contacted for the study, and all information was anonymized. There is no direct participation of subjects in this study. The methodology and statistical analyses maintained confidentiality and anonymity of all patient data used.

3.2 Rationale for Methods

A retrospective chart review was chosen for the design of this study to maximize the number of eligible amblyopic participants. The benefits of a retrospective design include ease of data collection and the elimination of issues of attrition. The nature of this

design increases the likelihood of obtaining enough participants to reach statistical power. Amblyopia management can take years to complete, making single site-based prospective studies time-consuming and challenging. As this study was set in a 1-year completion timeframe, a retrospective analysis was more appropriate. The present study may provide the foundation for future prospective research and consequently, shape amblyopia practice patterns in this institution and elsewhere.

3.3 Study Population

This was a retrospective chart review of amblyopic patients managed by four IWK Health Centre pediatric ophthalmologists between January 2012 and December 2019. The IWK Health Centre is situated in Halifax, Nova Scotia, Canada. It is a tertiary institution that manages patients from Nova Scotia, Prince Edward Island, New Brunswick, and Newfoundland and Labrador. The IWK Eye Clinic developed and implemented an evidence-based standardized amblyopia treatment protocol in 2010. This protocol continues to be the foundation for amblyopia management at this institution.

Initially, the principal investigator (PI) screened all available VPCs for prospective participants. VPCs of participants who performed occlusion therapy and obtained either equal distance visual acuity (DVA) or three consecutive cycles of stable DVA in the amblyopic eye were sampled for further review. After potential participants were identified using VPCs, Meditech patient data for these participants was reviewed to assess if they met the inclusion/exclusion criteria. Following the VPC review, the sample size was determined to be insufficient using sample size predictions needed for regression statistical analyses (Cohen, 1992). In an effort to identify more potentially eligible participants, a billing code was filed for patients diagnosed with amblyopia. The PI then

reviewed the resulting list for all patients coded for amblyopia to determine which patients met the study's inclusion criteria. Patients who met the inclusion criteria were selected for recruitment. Participants meeting the inclusion criteria were sample retrospectively in order from December 2019 to January 2012 to include the most recent patients to avoid confounds of varying treatment across time.

In the initial screening phase, 458 patient's VPCs were reviewed for sampling. Of these, 98 met the inclusion criteria. The billing code search captured approximately 364 patient names per year coded with the diagnosis of amblyopia, including patients sampled from the VPCs. Of these, every third patient meeting inclusion criteria was selected, adding an additional 60 patients to the sample. In total, 134 patients (66 females and 68 males) ranging in age from 31 months to 132 months (mean of 59.32 months) were included in the study. Only patient data pertaining to independent, dependent, and demographic variables was collected.

3.4 Power Calculation

A power analysis was calculated for the statistical comparison of successful and unsuccessful participants, with the assistance of the IWK Health Centre Consulting Scientist (Ph.D. Health Psychology), using Cohen (1992) as a reference. Based on a linear regression analysis, with a medium effect size, a preferred sample size of 107+50 participants with alpha at 0.05 and power=0.80 was calculated.

3.5 Predicted Sample Size

To ensure the feasibility of the sample size, a pre-study amblyopia billing review was conducted for the year 2019. The sample size is feasible as the IWK Eye care team

sees 350 patients per year based on a calculation of billings for amblyopia patients in 2019. Therefore, from 2010-2019 the IWK Eye Clinic has potentially seen and treated approximately 3150 amblyopic patients, making the sample size of 134 feasible.

3.6 Inclusion Criteria

Patients between the ages of 2 and 11 years with a diagnosis of strabismic, anisometropic, or mixed amblyopia were included in the present study. Additionally, all patients had to have been treated for amblyopia with occlusion therapy that was initiated and discontinued by clinicians at the IWK Eye Clinic. All patients had to be doing consistent occlusion amounts +/- one hour of the reported amount. Any patient with amblyopia treatment prior to referral to the IWK was excluded from the study including refractive adaptation. Treatment was considered complete when three consecutive cycles of no DVA improvement in the amblyopic eye on a consistent optotype VA chart or equal vision following occlusion therapy was documented (Stewart et al., 2004). A cycle is considered amblyopia treatment for 1 week per year of age up to a maximum of 4 weeks (Hardesty, 1959). For the purpose of this study, amblyopia was defined as a minimum of two-line and/or 10 optotype interocular difference in best-corrected visual acuity for which no cause was detected by physical examination of the eye (Von Noorden, 1996). Strabismic, anisometropic, and mixed amblyopia are defined in Chapter 1 and will be redefined later.

All participants had their logMAR optotype DVA recorded by clinicians on either Lea Symbols (LH) for preliterate, and Early Treatment Diabetic Retinopathy Study (ETDRS) for older participants. The chart type was recorded as the VA chart used at the initial visit and could change from LH to ETDRS doing the study timeframe. The LH VA

chart was developed in 1976 and combines the advantages of both optotypes and pictures using the identifiable shapes of a heart, house, circle, and square. It is ideal for the preliterate population as shapes are standardized and are identifiable by children younger than age 2 years (Becker et al., 2002). The ETDRS chart was developed in the 1980s to address the limitations of the Snellen chart. It employs an equal number of optotypes per row, a logarithmic progression between successive lines, and optotypes of consistent difficulty. ETDRS is considered the gold standard in the ophthalmic community (Shiamir et al., 2016). Both LH and ETDRS vision charts contain optotypes of identical size, crowding, and equal distance between optotypes. There is a geometric progression of letter height from line to line equal to 1.2589x the height of the letter on the line below. These VA charts range from 0.1 to -0.3 logMAR and are tested at a distance of 8 feet (Engin et al., 2014). The acuity charts are illuminating using the Vector Vision, CSV-1000 light box. The CSV–1000 is a self-standardized vision-testing instrument that has the ability to self-calibrate in all types of surrounding illumination. All of the examining lanes at the IWK Eye Clinic are equipped with this VA assessment system to ensure consistency in testing results. The calibrated testing distance for the CSV-1000 is 8 ft/2.44 m (*Website VectorVision: https://www.vectorvision.com/*).

   All participants had a cycloplegic refraction within 12 months prior to treatment initiation, with at least 12 weeks of refractive adaption prior to the initiation of occlusion therapy. For all participants, occlusion therapy was only commenced once DVA improvement plateaued following at least 12 weeks of refractive adaptation. Initial DVA was recorded as the visual acuity in the amblyopic eye following refractive adaptation. The outcome DVA used for statistical analysis was defined as three consecutive cycles of

no visual acuity improvement in the amblyopic eye or equal vision following occlusion therapy (Stewart et al., 2004).

3.7 Exclusion Criteria

Participants diagnosed with organic amblyopia, neurologic impairments/abnormalities, history of intraocular or refractive surgery, and unable to accurately perform optotype visual acuity were excluded. Patients with previous amblyopia treatment of any type prior to referral to the IWK Eye Clinic including refractive adaptation or those with less than 12 weeks of refractive adaptation prior to occlusion therapy were also excluded from this study.

3.8 Data Collection

Every third patient conforming to inclusion criteria was included in the study. Data pertaining to amblyopia treatment dose (daily full-time or part-time patching), treatment duration, classification of amblyopia (strabismic, anisometropic, mixed), logMAR DVA at each visit, the severity of amblyopia (the recorded initial DVA), refractive error spherical equivalent from the full cycloplegic refraction (diopters in – or +), follow-up schedule (in weeks), and ocular alignment (in prism diopters), were recorded for each participant. The time between clinical examinations, sex, and age at the time of assessments were also documented. All variables were documented on an excel data collection spreadsheet with anonymized patient identifiers.

3.9 Clinical Measures

This section will define the present study's pertinent variables and how they were measured. Variables included classification of amblyopia, age at treatment onset, initial DVA, post-treatment DVA, and treatment dose.

3.9.1 Classification of Amblyopia

Three forms of amblyopia were included in this study. These included strabismic, anisometropic, and mixed amblyopia. Strabismic amblyopia is caused by "a constant, non-alternating or unequally alternating manifest alignment of the eyes" always resulting in a unilateral reduction in visual acuity due to an abnormal binocular interaction, preventing fusion (Committee, 2012; DeSantis, 2014; Von Noorden, 1996). Any participant with a manifest or intermittent strabismus was documented as strabismic amblyopia. Anisometropic amblyopia was defined as a difference of refractive error between the eyes of at least one diopter of hyperopia, three diopters of myopia, or 1.5-2 diopters of astigmatism causing pattern vision deprivation, resulting in a unilateral reduction in visual acuity (DeSantis, 2014; Raab et al., 2010; Von Noorden, 1996). Myopic, hyperopic, and astigmatic patients with anisometropic but no strabismus were documented as having anisometropic amblyopia. Lastly, mixed amblyopia is a monocular or binocular decrease in visual acuity caused by more than one amblyogenic factor. Most commonly, it is a combination of strabismic and anisometropic amblyopia (Jefferis et al., 2015). Any participants strabismus, anisometropia, and unilateral amblyopia were classified as mixed amblyopia.

3.9.2 Severity of Amblyopia

For the purpose of the present study, the severity of amblyopia was categorized as either mild, moderate, or severe based on initial DVA. Mild amblyopia was defined as DVA of 6/9 or better or 0.2 logMAR or better. Moderate amblyopia was defined as DVA 6/12-6/30 or 0.3-0.7 logMAR. Lastly, severe amblyopia was defined as DVA worse than 6/30 or >0.7 logMAR (Scott et al., 2005).

3.9.3 Age at Treatment Onset

It is generally accepted that success of treatment decreases after age 7 years (Fronius et al., 2014; Holmes, Lazar, Melia, Astle, Dagi, Donahue, Frazier, Hertle, Repka, Quinn, Weise, et al., 2011; The Pediatric Eye Disease Investigator Group, 2005). Visual acuity following amblyopia treatment has been reported to significantly improve in participants age 2-3 years (71%), compared to age 4-5 years (44%) (Scott et al., 2005). The present study defines age at amblyopia treatment onset as the age in months of the patient when occlusion therapy was initiated (Holmes, Lazar, Melia, Astle, Dagi, Donahue, Frazier, Hertle, Repka, Quinn, Weise, et al., 2011). Age in months was selected to correlate with the documentation on patient VPCs and in Meditech documents.

3.9.4 Pre-Treatment Level of Distance Visual Acuity

Pre-treatment level of visual acuity was defined as the level of DVA at the initial clinical visit, before any occlusion therapy treatment, and following at least 12 weeks of refractive adaptation for participants wearing spectacle correction (Levartovsky et al., 1995). This definition was chosen to avoid potential confounding variables, with improvement in visual acuity, secondary to prior amblyopia treatment, and/or refractive

error correction alone. The pre-treatment level of visual acuity was measured on the LH or ETDRS visual acuity charts. All DVA measurements were converted to logMAR for statistical analyses.

3.9.5 Post-Treatment Level of Distance Visual Acuity

Post-treatment level of visual acuity or maximum DVA was defined as either three consecutive cycles of no visual acuity improvement, or equal vision following occlusion therapy (Ronald V. Keech et al., 2002; Stewart et al., 2004). The DVA level matching this definition was recorded as final visual acuity for all statistical analyses. Like the pre-treatment DVA levels, all post-treatment acuities were converted to logMAR for statistical analyses.

3.9.6 Treatment Type

Occlusion therapy was the only amblyopia treatment modality captured in this study. Previous research has reported varying numbers of hours of occluding the non-amblyopia eye to be successful, ranging from 2 hours a day to all-waking hours (Hug, 2004; Yazdani et al., 2017). In this institution, FTO refers to prescribing occlusion for all waking hours minus one hour daily. PTO would be considered anything less than FTO.

3.9.7 Dose of treatment

To answer our research questions, total dose and treatment dose-response rate were investigated. The total dose was defined as the total number of hours occluded (non-amblyopic eye) to reach outcome VA (defined by 3 consecutive cycles of no VA improvement or equal vision following occlusion therapy) (Stewart et al., 2004). In

regards to total dose calculations, all patients must have consistent daily hours patched within +/- 1 hour. Total dose was calculated at the 3 consecutive cycles of no visual acuity improvement or equal vision. The dose was defined as the number of hours per day the non-amblyopic eye was occluded (Fronius et al., 2009). Dose-response rate was defined as VA gain per number of hours of occlusion in the same period (Fronius et al., 2009). Dose, total dose, and dose-response rate were all measured using the optotype VA recorded on patient charts.

3.10 Defining Success

Several definitions have been used to describe amblyopia treatment success. For the purpose of this study, driving level DVA (at least 6/12), as regulated by the province of Nova Scotia was used to define treatment success (Service Nova Scotia and Municipal Relations, 2019). This was chosen as it is the minimum level of vision needed to allow patients to drive if the vision in the non-amblyopic eye ever falls below driving level vision. This definition of success will act as the dependant variable. Additionally, VA levels of equal vision, 6/7.5, and 6/9.6 were investigated to allow comparisons to previous literature.

3.11 Statistical Analysis

A combination of statistical analyses were conducted to answer the four research questions. Initially, data was explored to determine the main effects of identified predictors on the relevant outcome variables. This exploratory phase then informed further analyses to test interactions of relevant predictors and build models to shape future clinical treatment efforts of amblyopia. Descriptive statistics were calculated to describe

how many of the patients had successful/unsuccessful treatment outcomes. An analysis of variance was then conducted to determine data normality. Given the non-normal distribution of the sample data, non-parametric statistics (Mann-Whitney U, Chi-square, Wilcoxon Signed Ranks, Kruskal-Wallis Test) were used to compare variables. A correlation table of all covariates was then calculated to determine significant variables to include in the following regression and General Linear Modeling (GLM) analyses. Regression analyses were performed to determine predictive variables on the outcomes of success and dose-response rate. Finally, GLMs were run to analyse both fixed (categorical) and general (continuous) factors on success and dose-response rate to answer research questions 3 and 4 and calculate predictive models. Dose-response rate was calculated using the formula from the Fronius et al. (2014) study: acuity gain [log units] * 100/recorded occlusion [h] in the same period.

3.12 Data Management and Ethical Considerations

As this was a retrospective chart review, patients were not contacted for the study, and all information was anonymized. Therefore, there was no direct participation and the risk to participants was minimal. Patient identifying information was immediately converted to a unique study ID to preserve anonymity within the data set. One copy linking patient identifying information with study IDs was stored on a password-protected computer located at the IWK Eye Clinic on the IWK Health Centre U drive. Anonymized data was only opened in an encrypted environment following IWK Health Centre standards and stored on a password-protected computer located at the IWK Eye Clinic on the IWK Health Centre H drive. The master list connecting to the patient IWK Health identification numbers (K numbers) was kept in a separate drive within the IWK

computer system (The U drive as opposed to the H). The IWK computer used is an IWK encrypted computer with Global Protect[TM] firewall by Palo Alto Networks.

Any identifying information that would link participants back to their original health records was not stored or collected. No patient names, health card numbers, phone numbers, addresses, or ethnicity were recorded. Also, age rather than birth date was collected. Most data collected and stored was limited to non-identifying assessment and procedural outcomes. Personal health identifiers were recorded based on variables identified in the study design. The PI signed the IWK confidentiality agreement.

All included variables were standardly documented across included participants so no aggregate cell sizes less than 5 were included. An aggregate cell size is defined as the number of participants for each variable. To prevent patient identification, patient history was recorded without personal details, and all information that is not relevant to the study was excluded. Lastly, electronic records will be deleted. Any paper records will be shredded with other confidential paper documents. Records will be destroyed/erased as per IWK Health Centre policy at that time. This study received approval from the IWK Research Ethics Board.

3.13 Expenses

This study includes no additional expenses and is within the circle of care of the Eye Care team at the IWK Health Centre. A circle of care is the group of healthcare providers caring for a patient who require patient information to provide care. The study was performed by the principal investigator with the assistance of her supervisor, IWK Health Centre statistician, and thesis committee.

4.0 Chapter 4 Results

The following section includes a range of analyses that explore the core research questions of the study. First, descriptive statistics were calculated. Next, correlations and comparison models were run. Finally, regression models and non-parametric general linear models (GLM) were performed for the outcome variables of success, outcome DVA, and dose-response rate of VA.

4.1 Descriptive Statistics

Descriptive statistics were performed to understand the distribution of data across both categorical and continuous variables. To start, frequency and percentage descriptive statistics were run on patient demographics and categorical variables as illustrated in Table 1. The sample included 68 males and 66 females. Patient amblyogenic factors included 57 strabismic, 30 anisometropic, and 47 mixed amblyopes. 82 (61%) of participants performed FTO while 52 (39%) of participants performed PTO. Ideally, all of the participants in this study would have been wearing the prescribed FTO, all waking hours (minus one hour). However parental reports showed that due to various reasons, occlusion of all waking hours was not performed by all of the patients. Therefore, the reported/recorded occlusion amount was used for data analysis. FTO was defined as ≥ 8 hours/day and PTO as ≤ 7 hours/day of the non-amblyopic eye. The study attempted to use >8 hours of occlusion as FTO, however, the sample of PTO < 8 hours was too small for inferential statistics. Additionally, 8 hours of occlusion was where the groups differed to allow group comparisons. For the purpose of power for statistical analyses, FTO was defined as ≥ 8 hours of occlusion of the non-amblyopic eye while <8 hours of occlusion was used for PTO.

Success results to occlusion therapy are also included in Table 1. Treatment

success was 90.3% when defined as the final DVA of 6/12 in the amblyopic eye with

only 9.7% of participants not obtaining success. When narrowing the definition of

success, 76% of participants obtained DVA better than 6/12, 35% DVA better than 6/9.6,

and 6% better than 6/7.5 in the amblyopic eye following occlusion therapy. When

defining success as equal vision to the sound eye following occlusion therapy, 69% of

participants were successful. Although success was defined at 6/12 DVA or better, 10 of

13 (76.92%) participants who did not obtain this level did improve at least 0.1 logMAR

following occlusion therapy. Initial DVA of unsuccessful participants included 0.4 (n=1),

0.5 (n=2), 0.6 (n=1), 0.7 (n=1), 0.9 (n=2), 1.0 (n=2), 1.1 (n=1), 1.3 (n=2), and 1.4 (n=1)

logMAR. 8 of 13 (61.53%) unsuccessful participants reached 0.4 logMAR DVA, 1 of 13

(7.70%) 0.7 logMAR DVA, 2 of 13 (15.38%) 0.8 logMAR, and 2 of 13 0.9 logMAR

DVA (15.38%). Overall DVA improvement across unsuccessful participants was 0.34

logMAR units.

Table 1

Frequency Statistics for Categorical Variables

Variable	Level of Variable	n	%
Sex	Male	68	50.70
	Female	66	49.30
Follow Up Schedule in Weeks	4	102	75.00
	5	15	11.00
	6	14	10.30
	7	1	0.70
	8	1	0.70
	9	1	0.70
Classification of Amblyopia	Strabismic	57	42.50
	Anisometropic	30	22.40
	Mixed	47	35.10
Severity of Amblyopia	Mild	14	10.40
	Moderate	70	52.20
	Severe	50	37.30
Vision Chart Used	ETDRS	64	47.80
	LH	70	52.20
Amblyopic Eye	Right Eye	59	44.00
	Left Eye	75	56.00
Non Amblyopic Eye	Right Eye	75	56.00
	Left Eye	59	44.00
Control of Strabismus	Phoric	33	24.60
	Intermittent	24	17.90
	Manifest	77	57.50
Strabismic Eye	Right Eye	43	32.10
	Left Eye	56	41.80
	Alternates	2	1.50
Treatment Success	Yes	121	90.30
	No	13	9.70
Final VA Level in the Amblyopic Eye (LogMAR)	<0.3	102	76.12
	<0.2	47	35.10
	<0.1	8	6.00
	Equal OU	92	68.70
Occlusion	Full-time	82	61.20
	Part-time	52	38.80
Treatment Dose (Hours/Day)	2	4	2.99
	3	6	4.48
	4	8	5.97
	5	8	5.97
	6	14	10.45
	7	5	3.73
	8	5	3.73
	9	4	2.99
	10	9	6.71
	11	4	2.99
	12	64	47.76

Note. This table illustrates frequencies across categorical variables in the present sample.

After completing frequency analyses on categorical variables, descriptive statistics were run on continuous variables. Means, minimum, and maximum values were assessed to ensure no entry errors in data collection were made. All descriptive statistics for continuous variables are provided in Table 2. Following the calculation of descriptive statistics, continuous variables were assessed for skewness based on the Kolmogorov-Smirnov test of normality ($p < 0.05$) to determine whether to use parametric or nonparametric tests in the following analyses. Almost all variables were significantly skewed ($p < 0.05$), excluding age at the initial visit and Rx in the amblyopic eye as marked in Table 2. As variables were significantly skewed (as is expected for clinical data), nonparametric statistical analyses were used for inferential statistical analyses.

Table 2

Descriptive Statistics for Continuous Variables

Variable	N	Minimum	Maximum	Mean	Std. Deviation	Variance	Median	Skewness Statistic	Skewness Std. Error	Kurtosis Statistic	Kurtosis Std. Error
Age at Initial Visit (Months)	134	31	132	59.49	18.19	331.02	57.00	1.12*	0.21	2.05	0.42
Age at Treatment Outcome (Months)	134	35	141	64.31	18.31	335.36	63.00	1.15	0.21	2.36	0.42
Age at Initial Visit (Years)	134	2	11	4.53	1.56	2.45	4.00	1.04	0.21	1.89	0.42
Rx Spherical Equivalent in the Amblyopic Eye (Diopters)	134	-8	8	3.30	2.75	7.57	3.56	-0.97*	0.21	2.45	0.42
Rx Spherical Equivalent in the Non-Amblyopic Eye (Diopters)	134	-5	8	2.50	2.05	4.20	2.13	0.11	0.21	0.35	0.42
Treatment Dose (Hours/Day)	134	2	12	9.14	3.38	11.40	11.00	-0.68	0.21	-1.08	0.42
Treatment Duration (Weeks)	134	4	64	18.42	11.38	129.51	16.00	1.79	0.21	4.62	0.42
Angle of Strabismus at 1/3m (Prism Diopters)	134	-45	54	9.60	16.66	277.72	6.00	0.08	0.21	1.18	0.42
Angle of Strabismus at 6m (Prism Diopters)	134	-40	45	5.97	14.37	206.62	4.00	-0.24	0.21	1.69	0.42
Intraocular Visual Optotype Difference for Distance VA at Initial Visit	134	10	70	25.02	15.42	237.87	19.50	0.97	0.21	0.20	0.42
Intraocular Visual Optotype Difference for Distance VA at Outcome Visit	134	0	40	4.65	7.59	57.61	1.50	2.71	0.21	8.54	0.42
Visual Acuity in the Non amblyopic Eye Near Initial (LogMAR)	72	0	1	0.13	0.15	0.02	0.10	0.69	0.28	0.30	0.56
Visual Acuity in the Amblyopic Eye Near Initial (LogMAR)	71	0	2	0.58	0.38	0.15	0.50	0.98	0.28	0.58	0.56
Visual Acuity in the Non ambyopic Eye Distance Initial (LogMAR)	134	0	1	0.16	0.12	0.02	0.15	0.87	0.21	0.91	0.42
Visual Acuity in the Amblyopic Eye Distance Initial (LogMAR)	134	0	2	0.69	0.36	0.13	0.60	1.26	0.21	1.30	0.42
Visual Acuity in the Non amblyopic Eye Distance Final (LogMAR)	134	0	0	0.13	0.09	0.01	0.10	-0.15	0.21	-0.31	0.42
Visual Acuity in the Amblyopic Eye Distance Final (LogMAR)	134	0	1	0.21	0.15	0.02	0.20	2.39	0.21	7.99	0.42
Total Dose of Occlusion Therapy (Hours)	134	56	5376	1138.81	771.67	595471.89	1008.00	1.88	0.21	7.14	0.42
Total Dose Response Rate (Hours/0.1 LogMAR Increase)	131	22	2016	335.08	324.28	105158.18	224.00	2.40	0.21	7.47	0.42

Note. All skewness statistics are significantly skewed based on Kolmogorov-Smirnova Test of Normality ($p < 0.05$) except for variables that are marked by an asterisk, which are not significantly skewed.

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For continuous data, the study sample had an initial mean age of 60 weeks (5 years) and a median age of 57 weeks (4.75 years). The mean age at the outcome visit was 64 weeks (5.33 years) and the median age was 63 weeks (5.25 years). Although the mean for the data is the average value for the continuous variables, medians are also reported as they are a more appropriate measure of central tendency for skewed data.

Refractive error for the amblyopic eye in the sample varied from -8.00D of myopia to +8.00D of hyperopia in the amblyopic eye with a mean of +3.30D and median of +3.56D. Refractive error was similar in the non-amblyopic eye, ranging from -5.00D to +8.00D, with a mean value of +2.50D and median of +2.13D.

When considering the daily dose of occlusion therapy and treatment duration, the total dose of occlusion therapy was calculated by multiplying the two variables together with the formula: total dose = daily dose x treatment duration. The total dose of occlusion therapy ranged from 56-5376 hours with a mean of 1138.81 hours and a median of 1008 hours. The total dose to achieve outcome DVA with FTO ranged from 336-5376 hours with a mean of 1405 and a median of 1344. Dose to achieve outcome DVA for PTO ranged from 56-2520 hours with a mean of 719 and median of 504 hours. A histogram of the total dose required to reach outcome DVA is presented in Figure 1 to illustrate the distribution of total dose across the sample.

Figure 1

Histogram of Total Dose Required to Reach Outcome Visual Acuity
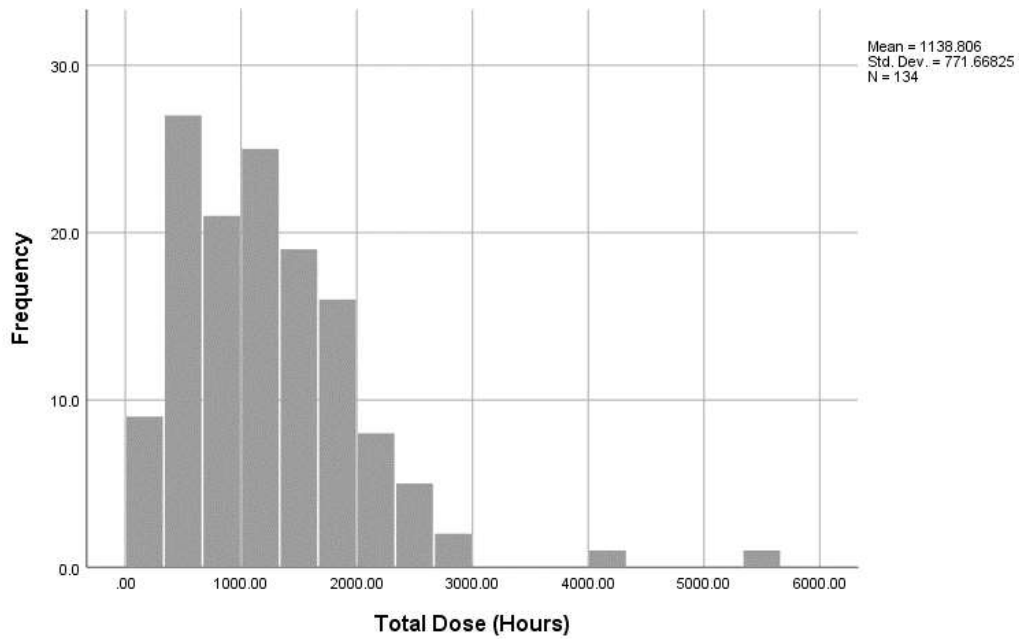
The total dose was also calculated across age as illustrated in Table 3. The total dose required to achieve final VA in the amblyopic eye did not vary much across age ranging from a mean 1110-1164 hours and a median of 840-1120 hours.

Table 3

Total Dose to Achieve Final VA in the Amblyopic Eye per Age Across Participants

Age	N	Min Dose	Max Dose	Mean	Median	Standard Deviation	Skewness	Kurtosis
2	6	392	2016	1110.67	840.00	729.65	0.66	-1.95
3	31	448	2240	1164.26	1120.00	450.26	0.40	-0.32
4	38	168	5376	1148.00	924.00	1062.35	2.36	7.13
5	26	224	2688	1143.69	994.00	732.15	0.80	-0.44
6	23	56	2856	1118.78	1008.00	673.30	0.73	0.64
7	3	1120.00	1764.00	1428.00	1400.00	322.91	0.39	
8	4	168.00	1680.00	882.00	840.00	743.45	0.13	-4.77
9	2	336.00	2352.00	1344.00	1344.00	1425.53		
11	1	252.00	252.00	252.00	252.00			

Next, the daily dose to achieve final VA in the amblyopic eye was analyzed across all participants and successful participants as shown in Tables 4 and 5 respectively. Based on reported patching of the non-amblyopic eye, daily dose ranged from 4-12 hours, with a mean of 9.07 for successful and 9.14 hours for all patients and median of 10 hours for successful and 11 hours for all patients. As illustrated in the categorical data, our sample contained more FTO than PTO which is also reflected in the frequencies shown in Table 1 (FTO n=82, PTO n=52). Of the FTO group, 64 participants (74%) were performing 12h/d of occlusion.

Table 4

Total Dose Descriptive Statistics of the Amblyopic Eye In all Patients

Variable	N	Minimum	Maximum	Mean	Median	Standard Deviation	Skewness	Kurtosis
Total Dose Response Rate to Achieve 0.1logMar VA Improvement	131	22.40	2016.00	335.08	224.00	324.28	2.40	7.47
Total logMar Increase in VA	134	0.20	1.80	0.48	0.40	0.35	1.43	2.01
Total Dose to Achieve Final VA (Hours)	134	56.00	5376.00	1138.80	1008.00	771.67	1.89	7.14
Total Daily Dose to Achieve Final VA (Hours/Day)	134	2.00	12.00	9.14	11.00	3.38	-0.69	0.21
Total Treatment Duration to Achieve Final VA (Weeks)	134	4.00	64.00	18.42	16.00	11.38	1.79	4.62

Table 5

Total Dose Descriptive Statistics of the Amblyopic Eye In Successful Patients

Variable	N	Minimum	Maximum	Mean	Median	Standard Deviation	Skewness	Kurtosis
Total Dose Response Rate to Achieve 0.1logMar VA Increase	119	22.40	1344.00	299.86	224.00	251.23	1.71	3.10
Total logMar Increase in VA	121	0.20	1.80	0.49	0.40	0.36	1.43	2.00
Total Dose to Achieve Final VA (Hours)	121	56.00	5376.00	1109.36	1008.00	785.44	2.05	7.12
Total Daily Dose to Achieve Final VA (Hours/Day)	121	2.00	12.00	9.07	10.00	3.41	-0.63	-1.20
Total Treatment Duration to Achieve Final VA (Weeks)	121	4.00	64.00	18.18	16.00	11.76	1.83	4.54

In addition to the dose of occlusion therapy, treatment duration was also recorded. For the given sample, treatment duration ranged from 4-64 weeks with a mean of 18.4 weeks and a median of 16 weeks. Across successful participants, duration was similar to all patients with a range of 4-64 weeks, mean of 18.18 weeks, and median of 16 weeks. Therefore, most of the sample achieved outcome DVA in the amblyopic eye at 18.4 weeks with a median of 16 weeks or 4 months of treatment.

Following treatment dose and duration, the total logMAR increase of VA over the treatment duration was calculated for all participants and successful participants respectively. Based on the sample obtained, the interocular difference upon the initial

visit ranged from 10-70 optotypes of VA with a mean of 25 optotype difference and a

median of 19.5 optotype difference. This coincides with the initial DVA of the amblyopic

eye which varied from 6/9.6 to 6/120 with a mean of 6/30 (0.69 logMAR) and a median

of 6/24 (0.60 logMAR). Across all participants and successful participants, logMAR

increase in final DVA of the amblyopic eye ranged from 0.2-1.80 logMAR units over the

treatment duration with a mean of 0.48 and a median of 0.40 logMAR units. Following

occlusion therapy, the interocular DVA difference decreased to a mean of 1.65 optotypes

and a median of 1.50 optotype difference. In relation to interocular difference, DVA of

the amblyopic eye also increased with occlusion therapy. The final DVA of the

amblyopic eye ranged from 6/6 to 6/48 with a mean and median of 6/9.6 (0.21 logMAR).

In Table 2, the angle of strabismus at 1/3m and 6m was documented for all

participants. At 1/3m, strabismic angles ranged from 45prism diopters (pd) exodeviations

to 54pd esodeviations with a mean of 9.6pd esodeviation and median of 6.0pd

esodeviation. At 6m, strabismic angles varied from 40pd exodeviation to 45pd

esodeviation with a mean of 6.9pd esodeviation and a median of 4pd esodeviation.

Overall, no notable changes existed between the successful and all participants

illustrated in Tables 4 and 5. This is not surprising given that only 13 patients were

unsuccessful of the 134.

4.1.1 Dose-Response Rate

Dose-response rate descriptive statistics including minimum, maximum, mean,

and median values were calculated across both successful participants (DVA better or

equal to 6/12) and all participants. The dose-response rate was calculated using the

formula from Fronius et al. (2014): cumulated hours occlusion*100/0.1 logMAR acuity

gain. A LO-ESS curve using polynomial regression was attempted to align with previous analytic strategies (Stewart et al,.2004). However, given that data was not polynomial, this analysis did not provide any useful information for the present study. To simplify reporting of dose-response rate and to allow comparison to the Fronius et al. (2009, 2014) studies, dose-response rate per 0.1 logMar increase in DVA of the amblyopic eye was reported. To calculate the dose-response rate per 0.2 logMAR increase, values can be multiplied by 2.

To start, the total dose-response rate was calculated per 0.1 logMAR VA increase of the amblyopic eye across all participants and successful participants. For all participants, the total dose-response rate ranged from 22.40-2016 with a mean of 335 and a median of 224 hours. Across successful participants, the dose-response rate was on average quicker with a range from 22.40-1344, a mean of 199.86, and a median of 224 hours as illustrated in Table 5. Additionally, dose-response rate varied across FTO and PTO with FTO having a slower dose-response rate and PTO quicker as illustrated in Table 6. Initial DVA for both groups was similar with FTO having median 0.74 logMAR and PTO 0.6 logMAR acuity. A histogram of the dose-response rate is presented in Figure 2 to illustrate the distribution of dose-response rate across the sample.

Table 6

Total Dose Response Rate to Achieve 0.1logMar Increase in VA in the Amblyopic Eye with FTO and PTO

Variable	N	Minimum Dose	Maximum Dose	Mean	Median	Standard Deviation	Skewness	Kurtosis
FTO	80	48.00	2016.00	398.83	308.00	366.21	2.19	5.75
PTO	51	22.40	1008.00	235.00	168.00	211.69	1.93	3.91

Figure 2

Histogram of Dose-Response Rate Frequencies
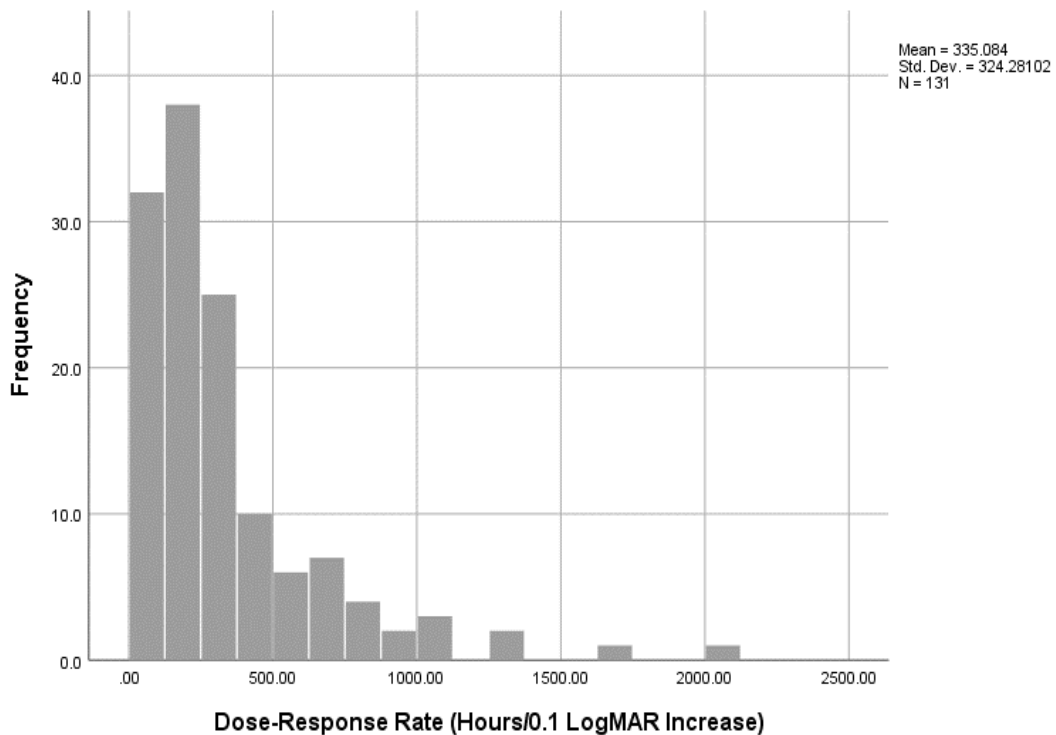
As for age, as illustrated in Table 7, the mean and median dose required for a 0.1 logMAR increase in VA became larger as age increased.

Table 7

Total Dose Response Rate to Achieve 0.1 logMAR VA Increase in the Amblyopic Eye per Age Across All Participants

Age	N	Min Dose	Max Dose	Mean	Median	Standard Deviation	Skewness	Kurtosis
2	6	65.33	336.00	204.77	175.64	109.45	0.34	-1.42
3	30	62.22	672.00	261.49	201.60	163.35	1.20	0.98
4	37	37.33	1075.20	291.38	210.00	247.64	1.47	1.91
5	26	48.00	1680.00	378.76	217.00	397.48	2.00	4.02
6	23	22.40	2016.00	493.70	336.00	478.30	1.85	3.68
7	3	124.44	882.00	402.15	200.00	417.28	1.67	
8	3	84.00	672.00	364.00	336.00	295.00	0.42	
9	2	22.40	392.00	207.20	207.00	261.35		
11	1	126.00	126.00	126.00	126.00			

Figure 3 provides a visual representation of the dose-response rate across age, showing dose-response rate to become slower with increased age.

Figure 3
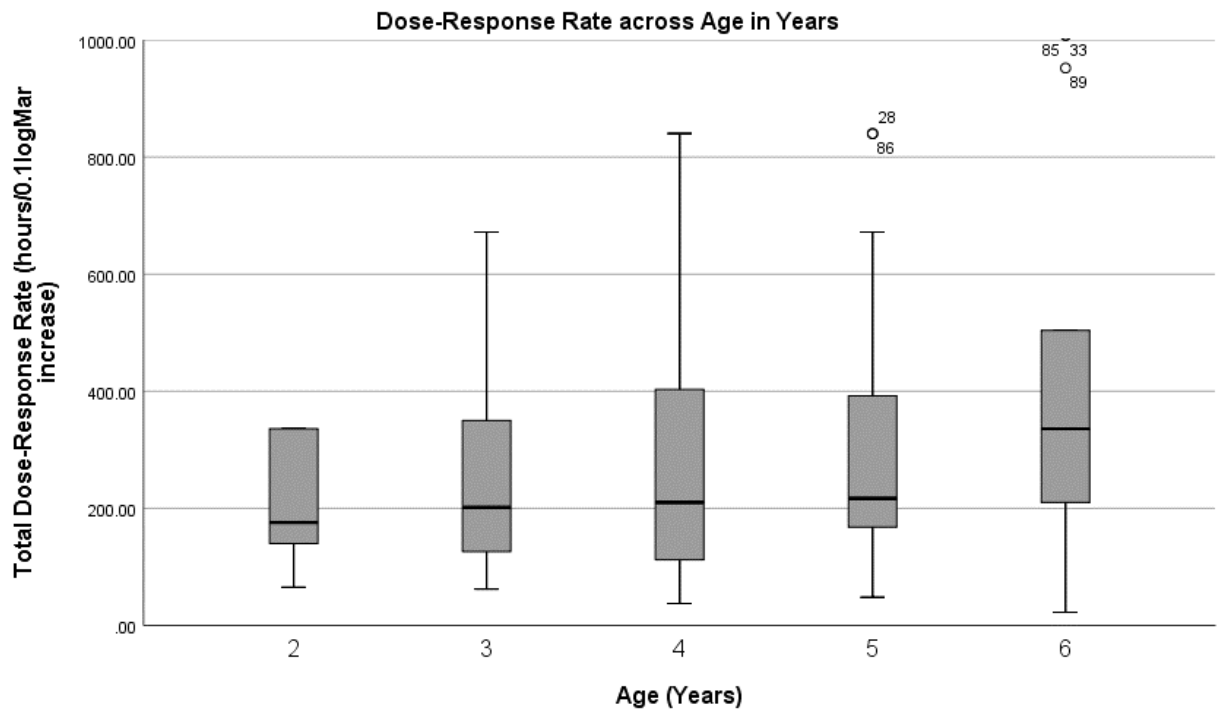
Figure 3. The circles on the graph represent outliers outside of the error bars with their study identifiers.

The present study also investigated the change in dose-response rate at each 4-week follow-up visit. Table 8 presents the dose-response rate per 0.1 logMAR increase in DVA for every 4-week treatment interval. This table illustrates that the fastest dose-response rate occurred at 4 weeks of treatment and continued to slow thereafter.

Table 8

Dose-Response Rate at Each 4 Week Interval per 0.1 logMar Increase

Weeks	N	Min	Max	Mean	Median	Standard Deviation	Skewness	Kurtosis
4	117	-140.00	336.00	138.49	112.00	108.75	0.64	-0.43
8	112	22.40	672.00	211.69	168.00	171.94	1.56	1.87
12	99	42.00	1008.00	299.06	224.00	245.50	1.66	2.32
16	76	48.00	1344.00	361.74	268.00	307.63	1.85	3.48
20	53	46.67	1680.00	406.34	280.00	395.68	2.16	4.47
24	31	46.67	2016.00	426.16	336.00	394.49	2.56	8.19
28	16	57.65	1176.00	379.12	331.00	284.59	1.60	3.29
32	10	62.22	896.00	431.08	410.00	289.47	0.62	-0.48
36	7	108.00	1512.00	671.83	504.00	479.82	0.83	0.16
40	4	120.00	1680.00	940.00	980.00	724.80	-0.18	-3.62
44	3	132.00	1232.00	711.33		552.34	-0.47	
48	2	672.00	1008.00	840.00		237.59		
52	1	1092.00	1092.00	1092.00	1092.00			

Next, the dose-response rate was calculated for each classifications of amblyopia. Table 9 shows that anisometropic and mixed amblyopic classifications have the slowest dose-response rate and strabismic the fastest.

Table 9

Total Dose Response Rate to Achieve 0.1logMar Increase in VA in the Amblyopic Eye Across Classifications of Amblyopia

Variable	N	Minimum Dose	Maximum Dose	Mean	Median	Standard Deviation	Skewness	Kurtosis
Strabismic	56	22.40	840	213	168	167.48	1.55	2.83
Anisometropic	29	22.40	1344	425	336	319.60	1.40	1.42
Mixed	46	37.33	2016	426	270	416.86	2.12	5.00

Following classification of amblyopia, the dose-response rate across the severity of amblyopia was also calculated. Results are illustrated in Table 10, with severe having the fastest dose-response rate and moderate the slowest.

Table 10

Total Dose Response Rate to Achieve 0.1logMar Increase in VA in the Amblyopic Eye Across Severity of Amblyopia

Variable	N	Minimum Dose	Maximum Dose	Mean	Median	Standard Deviation	Skewness	Kurtosis
Mild	12	28	672	316	280	208.21	0.66	-0.36
Moderate	69	56	2016	410	336	356.13	2.07	5.57
Severe	50	22.4	1680	235	177.1	273.55	3.60	16.15

Lastly, the dose-response rate was calculated across VA chart used. The results are illustrated in Table 11, showing that patients on LH have a faster dose-response rate than on ETDRS. On average, participants on the LH VA chart had a mean age of 3.53 years and on ETDRS a mean age of 5.62 years.

Table 11

Total Dose Response Rate to Achieve 0.1logMar Increase in VA in the Amblyopic Eye Across VA Chart Used

Variable	N	Minimum Dose	Maximum Dose	Mean	Median	Standard Deviation	Skewness	Kurtosis
LH	68	37.30	840	231.71	197	154.64	1.43	2.93
ETDRS	63	22.40	2016	446.66	336	412.65	1.68	3.17

4.2 Correlations

After assembling descriptive statistics, Spearman Rank correlation coefficients were completed across all continuous variables. Correlations are shown in Table 12, with significant correlations flagged (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). A positive correlation signifies that as one variable increases, the other variable also increases whereas a negative correlation signifies as one variable increases, the other variable decreases. All significant correlations for treatment success and total dose-response rate were used to perform regression analyses to explore predictors of treatment success and total dose-response rate. These variables included: initial DVA in the amblyopic eye, final DVA in the amblyopic eye, age at the initial visit, the interocular difference at distance initial, interocular difference at distance final, and occlusion for the success regression. For the regression on dose-response rate, predictive continuous variables included angle of strabismus at 1/3 and 6m, interocular VA difference at initial and outcome visits, age at the initial visit, age at treatment outcome, Rx in the amblyopic eye, Rx in the non-amblyopic eye, occlusion, and treatment. Only significantly correlated variables were included in the regression analysis to prevent overfitting a regression model with too

many predictors. Overfitting occurs when a statistical regression model contains more variables than can be justified given the sample data (Babyak, 2004). Overfitting could lead to false-negative outcomes and loss of residual variance. Limiting the number of predictors also avoids over-specification bias which increases error by including too many variables in a regression model (Babyak, 2004).

Table 12

Spearman's Rank Correlation Coefficients (ρ) for Test Variables

	Age1	Age2	Rx Amb Eye	Rx Non Amb Eye	TreatD	Treat Du	Ref A Weeks	Angle SN	Angle SD	IODDI	IODDF	Non Amb DI	Amb DI	Non Amb DF	Amb DF	Total Dose	Age in Years	Treatment Success	Occlusion	Total DRR
Age1	-																			
Age2	.978**	-																		
RxAmbEye	0.00	0.04	-																	
RxNonAmbEye	-0.11	-0.09	.747**	-																
TreatD	0.02	-0.03	0.05	0.01	-															
TreatDu	-0.07	0.08	.248**	0.13	-0.14	-														
RefAWeeks	.186*	.206*	0.13	.196*	0.05	0.10	-													
AngleSN	-.232**	-.249**	0.04	.244**	0.01	-0.14	0.12	-												
AngleSD	-0.13	-0.14	0.06	.228**	0.00	-0.04	0.16	.866**	-											
IODDI	-0.02	0.02	0.05	0.04	-0.07	0.06	-0.12	-0.16	.184*	-										
IODDF	0.14	.181*	.223**	0.01	.248**	.282**	0.03	0.14	-0.10	.205*	-									
NonAmbDI	-.602**	-.582**	0.06	.268**	0.04	0.08	-0.06	0.16	0.03	0.03	-.253**	-								
AmbDI	-.241*	-.203*	0.08	0.15	0.14	.299**	-0.12	0.17	.236**	.825**	0.06	.426**	-							
NonAmbDF	-.445**	-.478**	-0.03	0.08	-0.03	-0.11	0.00	.233**	.208*	0.02	-.307**	.632**	.296**	-						
AmbDF	-0.05	-0.03	0.14	0.10	-0.01	.190*	0.09	-0.03	-0.03	.185*	.558**	0.12	.203*	.345**	-					
Total Dose	-0.03	0.08	.231**	0.08	.472**	.755**	0.08	-0.09	-0.03	.310**	.192*	0.07	.359**	-0.13	0.16	-				
Age in Years	.976**	.957**	0.01	-0.10	-0.01	0.14	0.15	-.249**	-0.13	-0.02	0.15	-.578**	-.234**	-.452**	-0.06	-0.05	-			
Treatment Success	0.10	0.11	0.04	-0.04	0.06	0.14	0.03	-0.11	-0.06	.293**	.499**	0.00	.217*	-0.02	.540**	0.17	0.09	-		
Occlusion	0.01	0.05	-0.05	0.01	-.880**	0.05	0.01	0.00	-0.02	-0.15	0.01	-0.04	-.237**	-0.02	-0.07	-.510**	0.04	-0.11	-	
Total DRR	0.15	.229**	.194*	-0.03	-.295**	.483**	0.17	-.266**	-.245**	-.298**	-.298**	-.232**	-.373**	-.269**	.266**	.617**	0.13	.188*	-.285**	-

Note. Significant correlations are flagged (*p < 0.05, **p < 0.01, ***p < 0.001). Variable labels are the following: Age1-Age at Initial Visit; Age2-Age at Treatment Outcome; RxAmbEye-Rx in the Amblyopic Eye; RxNonAmbEye-Rx in the Non-Amblyopic Eye; SterI-Initial Stereoacuity; SterF-Final Stereoacuity; TreatD-Treatment Dose; TreatDu-Treatment Duration; RefAWeeks-Weeks of Refractive Adaptation; AngleSN-Angle of Strabismus at 1/3m; AngleSD-Angle of Strabismus at 6m; IODDI-Intra-ocular Difference Distance Vision Initial; IODDF-Intra-ocular Difference Distance Vision Final; NonAmbDI-Initial Distance VA in the Non-Amblyopic Eye; AmbDI-Initial Distance VA in the Amblyopic Eye; NonAmbDF-Final Distance VA in the Non-Amblyopic Eye; AmbDF-Final Distance VA in the Amblyopic Eye; Total Dose-Total Dose of Occlusion Therapy; Age in Years-Age in Years; Treatment Success-Treatment Success Yes/No; Occlusion-Fulltime/Parttime Occlusion; Total DRR-Total Dose Response Rate

4.3 Group Comparison Statistical Tests

Following the calculations of descriptive statistics, group comparison tests were performed on variables that seemed to have meaningful differences in the statistics reported above. These analyses included dose-response rate for PTO and FTO, severity of amblyopia, classification of amblyopia, visual acuity chart used, and follow-up. Non-parametric group comparison analyses were used because of the skewed nature of the data violating the assumption of normality required for traditional parametric analyses.

First, the total dose-response rate was calculated for severity of amblyopia, as results differed across severity of amblyopia in the previous section (Table 13). When performing an independent samples Kruskal-Wallace test, severe versus mild and severe versus moderate amblyopia were significantly different across dose-response rate (23.24, $p < 0.05$). However, no statistically significant difference between mild and moderate amblyopia was found (27.81, $p > 0.05$). This signifies that mild amblyopia was statistically slower in dose-response rate of VA improvement compared to severe amblyopia. Severe amblyopia also had a significantly faster dose-response rate than moderate amblyopia (-4.58, $p < .05$). Figure 4 illustrates boxplots of dose-response rate across severity of amblyopia showing severe amblyopia to have the fastest dose-response rate and mild amblyopia the slowest. Figure 5 shows a scatterplot of dose-response rate across severity of amblyopia showing severe amblyopia to have the fastest dose-response rate and mild amblyopia the slowest.

Table 13

Independent Samples Kruskal-Wallace Test of Severity of Amblyopia Against Total Dose Response Rate

Variable	N	Test Statistic	Standard Error	Standardized Test Statistic	Significance	Adj. Significance	Kruskal Wallace	Degree of Freedom	Effect Size	Eta Squared
Severe-Mild	50,14	23.24	12.20	1.91	0.047	0.17				
Severe-Moderate	50,70	27.82	7.05	3.95	0.00	0.00	15.96	2.00	0.72	0.12
Mild-Moderate	14,50	-4.58	11.87	-0.39	0.70	1.00				

Note. Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed. The significance level is .05. Significance values have been adjusted by the Bonferroni correction for multiple tests. Small effect size = 0.2, medium effect size = 0.5, and large effect size = 0.8 using Cohen's d.

Figure 4

Boxplot of Total Dose-Response Rate across Severity of Amblyopia

Figure 5
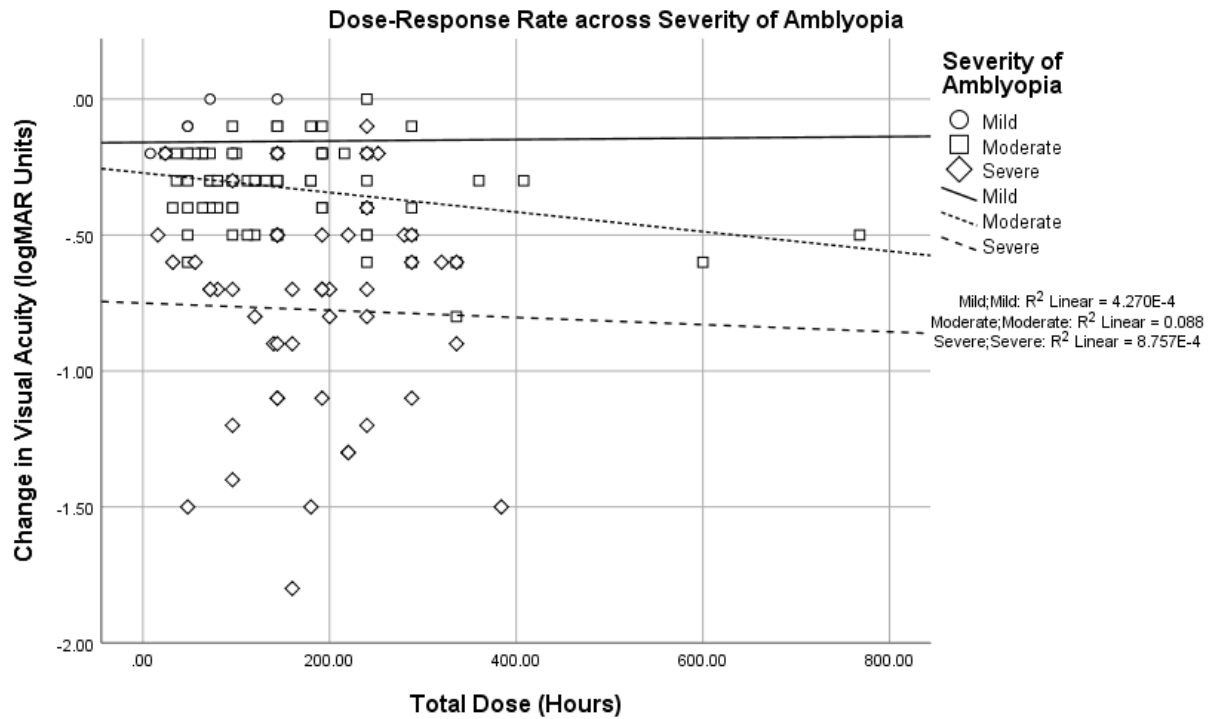
Next, dose-response rate group differences were explored across classification of amblyopia. Using an independent samples Kruskal Wallace Test, dose-response rate was significantly different (-25.60, -31.94, $p < 0.05$) between strabismic amblyopia and mixed compared to anisometropic amblyopia. Results are shown in Table 14. Therefore, strabismic amblyopia has a faster dose-response rate than both anisometropic and mixed amblyopia. However, no statistically different dose-response rate was found between anisometropic and mixed amblyopia (6.34, $p > .05$). Figure 6 presents boxplots of dose-response rate across classifications of amblyopia. Figure 7 shows scatterplots of dose-response rate across classification of amblyopia. Both figures illustrate that strabismic amblyopia has the fastest dose-response rate and anisometropic the slowest.

Table 14

Independent Samples Kruskal-Wallace Test of Classification of Amblyopia Against Total Dose Response Rate

Variable	N	Test Statistic	Standard Error	Standardized Test Statistic	Significance	Adj. Significance	Kruskal Wallace	Degree of Freedom	Effect Size	Eta Squared
Strabismic-Mixed	57,47	-25.61	7.55	-3.39	0.00	0.00				
Strabismic-Anisometropic	57,30	-31.94	8.68	-3.68	0.00	0.00	18.02	2.00	0.80	0.13
Mixed-Anisometropic	47,30	6.34	9.00	0.70	0.48	1.00				

Note. Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed. The significance level is .05. Significance values have been adjusted by the Bonferroni correction for multiple tests. Small effect size = 0.2, medium effect size = 0.5, and large effect size = 0.8 using Cohen's d.
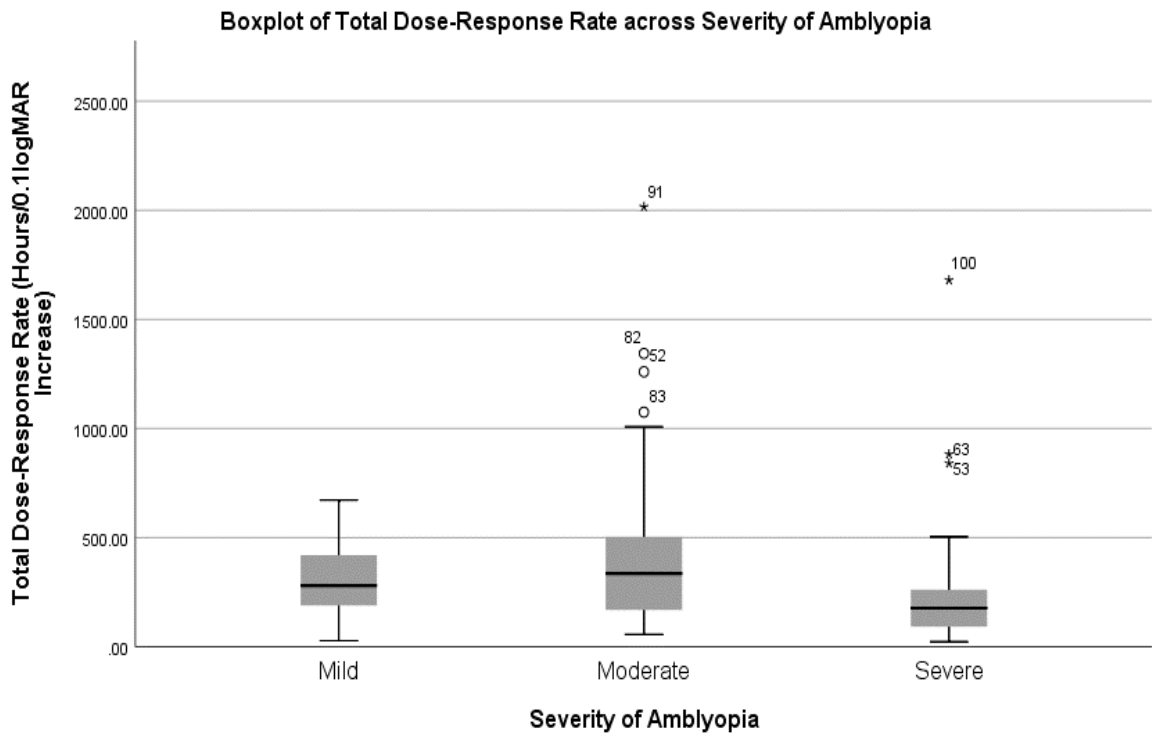
Figure 6

Boxplot of Total Dose-Response Rate across Classifications of Amblyopia

Figure 7

Dose-Response Rate across Classification of Amblyopia
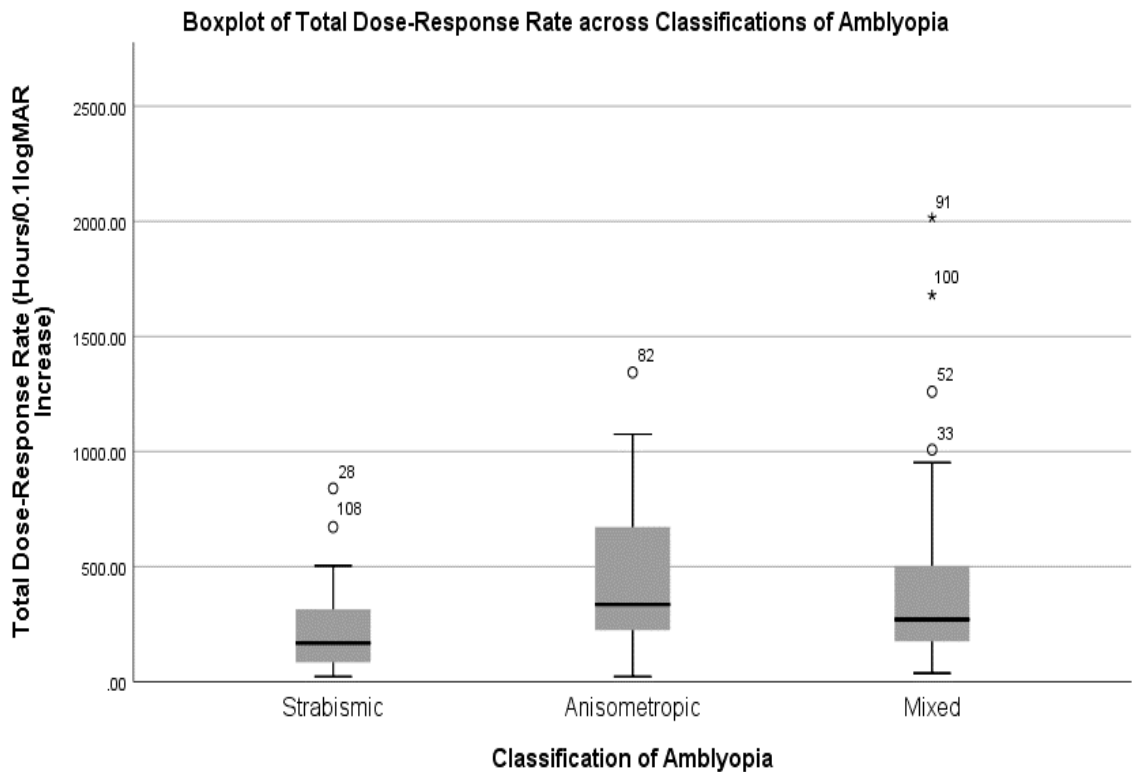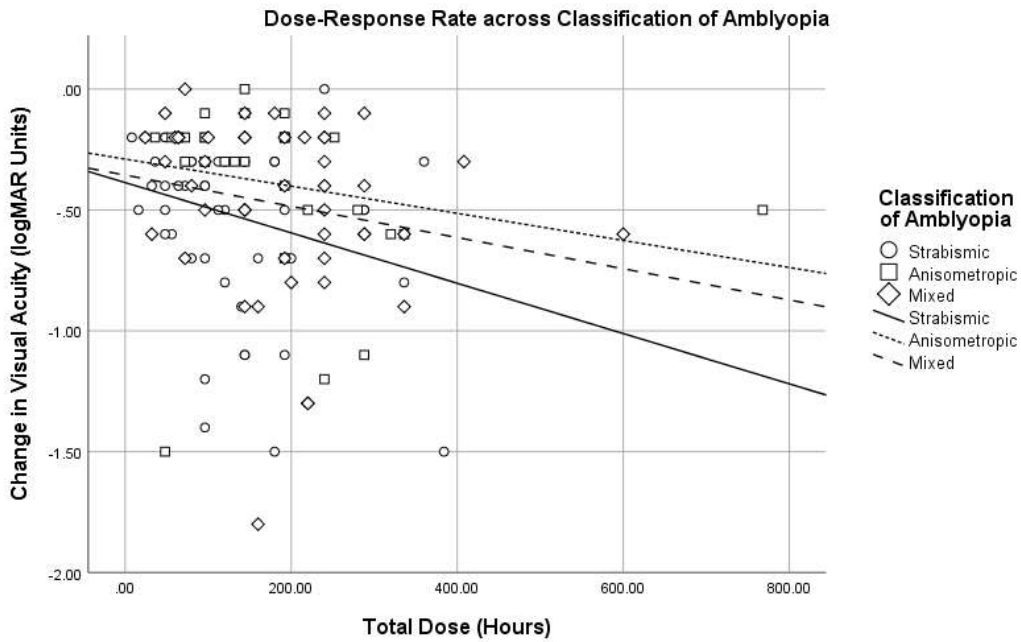
Following analyses for classification of amblyopia, the dose-response rate was

compared between FTO and PTO. Table 15 illustrates that dose-response rate is

significantly faster for patients doing PTO over FTO (52.52-74.60, p < .05). Figure 8

illustrates the scatterplot of dose-response rate across occlusion dose with FTO having a

slower dose-response rate and PTO faster.

Table 15

Independent Samples Mann-Whittney U Test of Occlusion Against Total Dose Response Rate

Variable	N	Mean Rank	Man-Whitney U	Standard Error	Standardized Test Statistic	Significance	Effect Size	Eta Squared
FTO	82	74.6	1352.00	211.81	-3.25	0.00	0.65	0.10
PTO	52	52.52						

Note. Small effect size = 0.2, medium effect size = 0.5, and large effect size = 0.8 using Cohen's d.

Figure 8
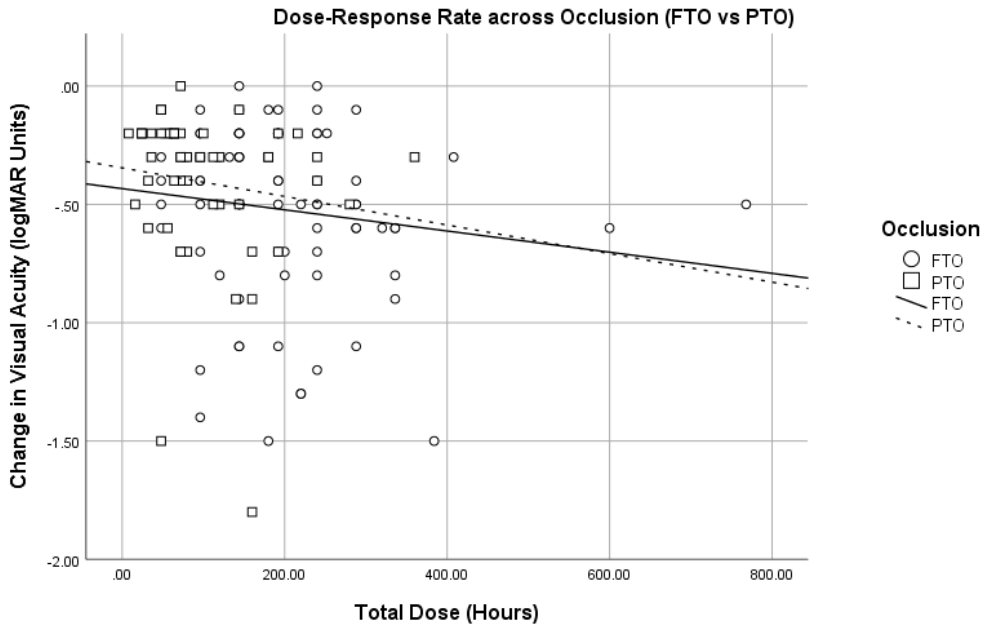
After performing tests of group comparisons on dose-response rate, a group

comparison was also performed on treatment duration between PTO and FTO. A Mann-

Whitney U Test was again used to analyze these group differences. As illustrated in Table

18, FTO had a statistically significantly shorter treatment duration compared to PTO

(2263, $p < .05$). Therefore, although PTO has a faster dose-response rate compared to

FTO, FTO has a shorter treatment duration.

Table 16
Independent Samples Mann-Whittney U Test of Duration of Treatment Against Occlusion

Variable	N	Mean Rank	Man-Whitney U	Standard Error	Standardized Test Statistic	Significance	Effect Size	Eta Squared
FTO	82	65.9	2263.00	216.62	0.61	0.049	0.20	0.00
PTO	52	70.02						

Note . Small effect size = 0.2, medium effect size = 0.5, and large effect size = 0.8 using Cohen's d.

Next, dose-response rate was compared between VA charts using an independent

samples Mann-Whitney U test. Table 17 provides results that found that a statistically

significant difference (75.88-56.85, p < 0.05) exists between VA charts used, with

patients on LH having a faster dose-response rate than on ETDRS. Figure 8 illustrates the

scatterplot of dose-response rate across VA chart used. Figure 9 shows a boxplot of dose-

response rate across VA chart used. Both figures illustrate patients on LH having a faster

dose-response rate than on ETDRS.

Table 17
Independent Samples Mann-Whittney U Test of VA Chart Used Against Total Dose Response Rate

Variable	N	Mean Rank	Man-Whitney U	Standard Error	Standardized Test Statistic	Significance	Effect Size	Eta Squared
ETDRS	64	75.88	1519.50	217.04	-2.87	0.00	0.52	0.06
LH	70	56.85						

Note . Small effect size = 0.2, medium effect size = 0.5, and large effect size = 0.8 using Cohen's d.
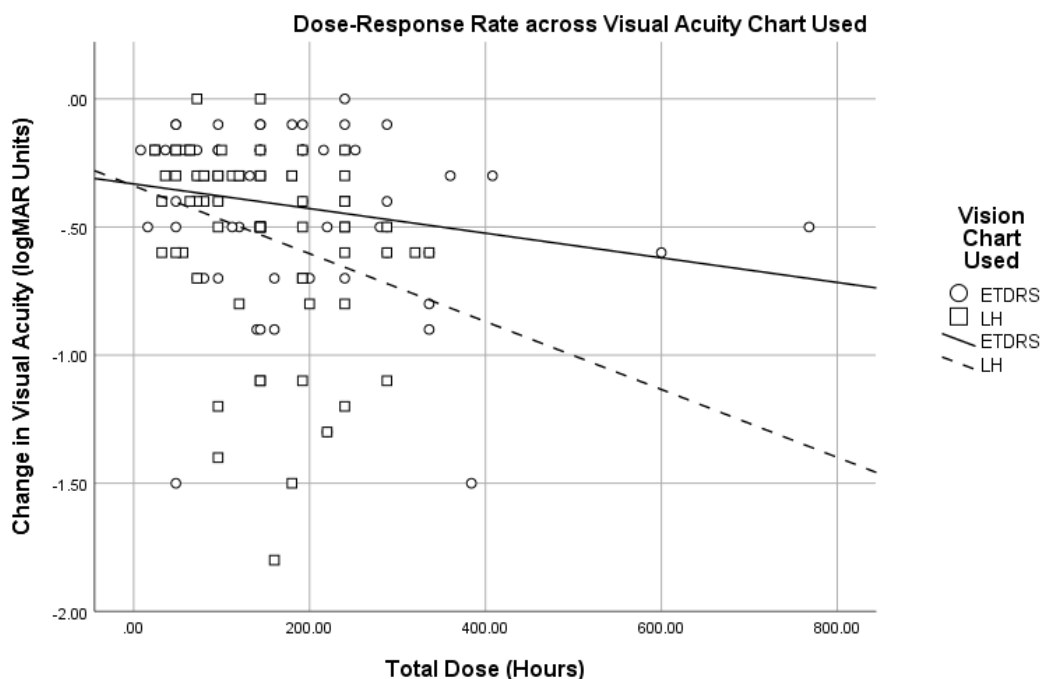
Figure 8

Figure 9
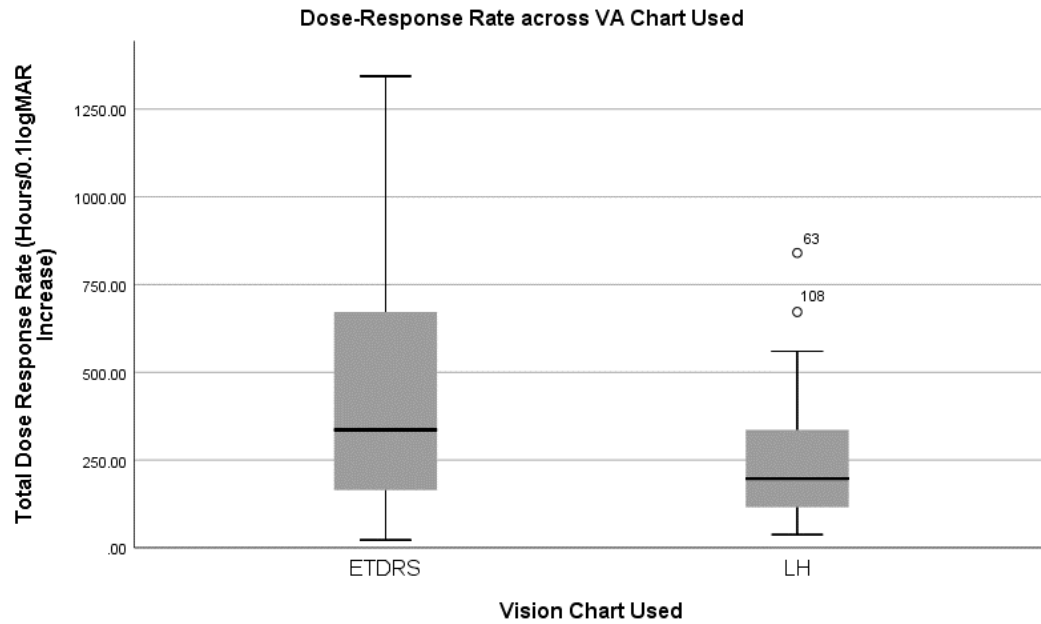
Lastly, group differences were compared at the follow-up dates of 4 and 16 weeks using a related samples Wilcoxon signed-rank test. Results are presented in Table 17. There was a statistically significant difference in dose-response rate between weeks 4 and 16 of treatment (138.50-361.75, $p < 0.05$). Thus, the dose-response rate in the first 4 weeks of treatment is significantly faster compared to week 16 of treatment.

Table 18

Related Samples Wilxoxon Signed Ranks Tests of Dose-Response Rate at 4 and 16 weeks

Weeks	N	Mean Rank	Test Statistic	Standard Error	Standardized Test Statistic	Significance	Effect Size	Eta Squared
4	76	138.5	997.00	185.59	-2.87	0.03	0.97	8.31
16	76	361.75						

Note. Small effect size = 0.2, medium effect size = 0.5, and large effect size = 0.8 using Cohen's d.

4.4 Regression and General Linear Model Statistical Analyses for Dependent Outcome Variables

Following the correlation analysis, continuous variables with a significant correlation with the relevant outcomes of total dose-response rate, final DVA in the amblyopic eye, and success were selected to explore potential predictors of these relevant outcomes using iterative exploratory multiple regression. Significant variables from the regression and group comparison analyses and were then used in GLM to control for the unique effect of each variable and determine which variables had the largest effect on outcomes overall. Additionally, GLM provides robust methods of estimation which are more appropriate than traditional regression given the skewed nature of the data.

4.4.1 Dose-Response Rate

First, an exploration of potential predictive variables was performed on dose-response rate using multiple regression. Predictive continuous variables used in the regression included angle of strabismus at 1/3 and 6m, interocular VA difference at initial and outcome visits, age at the initial visit, age at treatment outcome, Rx in the amblyopic eye, Rx in the non-amblyopic eye, occlusion, and treatment duration. Of these variables, initial DVA in the amblyopic eye, final DVA in the amblyopic eye, age in years at initial visit, age in months at initial visit, treatment duration, and occlusion were significant ($p < 0.05$).

Following this initial exploration of continuous variables, a second exploratory regression was performed on the significant predictors from the first regression as mentioned previously. This reduced set of predictors found that only initial DVA in the

amblyopic eye, final DVA in the amblyopic eye, treatment duration, and occlusion were significant ($p < 0.05$) when used together.

Finally, with all non-predictive variables excluded, a third and final regression analysis was run on the significant variables mentioned previously. All variables in this third iteration were found to be significant ($p < 0.05$). Predictive variables included initial DVA in the amblyopic eye, final DVA in the amblyopic eye, age at initial visit, occlusion amount, and treatment duration. The final regression model had an R^2 of 0.607 which signifies 60.7% of the statistical variance is accounted for within the model.

Table 19
Multiple Regression Analysis of Continuous Predictor Variables Against Total Dose Response Rate

Variable	Unstandardized Coefficients		Standardized Coefficients	Statistical Test		95.0% Confidence Interval for B	
	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
Constant	-322.17	99.01		-3.25	0.00	-518.12	-126.21
Visual Acuity in the Amblyopic Eye Distance Initial	-473.87	54.88	-0.52	-8.63	0.00	-582.49	-365.26
Visual Acuity in the Amblyopic Eye Distance Final	942.16	122.35	0.45	7.70	0.00	700.01	1184.31
Age at first visit	3.09	1.02	0.17	3.01	0.00	1.06	5.11
Treatment Dose	38.90	5.53	0.41	7.03	0.00	27.95	49.85
Treatment Duration	13.78	1.64	0.49	8.42	0.00	10.54	17.02

Note. All values with significance of $p < 0.05$ are considered statistically significant. In model summary: R=0.779, R squared=0.607, Adjusted R Square=0.591, and std. Error of Estimate=207.28.

Following regression analyses, general linear modeling (GLM) was performed to include both categorical and continuous in the same analysis, unlike a regression analysis which can only be run on continuous variables. As previous results indicated that both categorical and continuous variables had a significant impact on dose-response rate in the previous analyses, a GLM model was most appropriate. Significant continuous variables from previous analyses included initial DVA in the amblyopic eye, final DVA in the amblyopic eye, treatment duration, occlusion, and treatment dose were included as they were identified as important predictors in the correlation table. Lastly, all categorical

variables found to be predictive in the literature review were included: classification of amblyopia, severity of amblyopia, VA chart used, and occlusion amount. Notably, initial DVA in the amblyopic eye, final DVA in the amblyopic eye, treatment duration, and treatment dose were found to be statistically significant ($p < 0.05$).

Following this exploration, another GLM using only the significant categorical and significant continuous variables mentioned above was performed (Table 20). However, treatment dose was switched for occlusion as it is occlusion's continuous counterpart and severity of amblyopia was swapped for initial DVA. From this model, classification of amblyopia, VA chart used, initial DVA, treatment duration, and treatment dose were significant ($p < 0.05$). This GLM was labeled "theoretical" because treatment duration is an outcome variable that is not available upon initial examination.

Table 20

Theoretical General Linear Model Results for Total Dose-Response Rate Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Model	6460825	6	1076804.20	18.52	0.00	0.47
Intercept	20359	1	20359.26	0.35	0.56	0.00
ClassA	515216	2	257607.84	4.43	0.01	0.07
VAChart	544810	1	544810.25	9.37	0.00	0.07
AmbDI	1690457	1	1690456.63	29.07	0.00	0.19
TreatmentDu	2077250	1	2077250.46	35.73	0.00	0.22
TreatmentD	1654303	1	1654302.79	28.45	0.00	0.19
Total	28379413	131				
Corrected Total	13670563	130				
Error	7209738	124	58143.05			

Note. R Squared = .473 (Adjusted R Squared = .447)

The theoretical GLM had a partial Eta Squared (η^2) of 0.48, signifying that 48% of the variance of the outcome dependent variable is accounted for in this predictive model (Model: Intercept + ClassA + VAChart + AmbDI + TreatmentDu + TreatmentD). Partial eta squared is the calculated ratio of between-groups sum of squares and the error sum of squares (Jacob Cohen, 1973). This is considered a large effect size partial η^2 > 0.14 and is impressive for clinical prediction (Cohen, 1992). Parameter estimates for this model are presented in Table 21.

Table 21

General Linear Theoretical Model Parameter Estimates with Robust Standard Errors
Across Total Dose Response Rate

Parameter	B	Robust Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
					Lower Bound	Upper Bound	
Intercept	56.82	51.41	1.11	0.27	-44.93	158.57	0.01
Strabismic	-145.88	48.04	-3.04	0.00	-240.96	-50.80	0.07
Anisometropia	-85.12	68.98	-1.23	0.22	-221.66	51.41	0.01
Mixed	0[b]						
ETDRS	135.18	42.25	3.20	0.00	51.55	218.81	0.08
LH	0[b]						
AmbDI	-341.61	47.13	-7.25	0.00	-434.89	-248.33	0.30
TreatmentDu	11.72	1.52	7.72	0.00	8.72	14.73	0.32
TreatmentD	34.51	5.17	6.68	0.00	24.28	44.75	0.26

Note. Pararmeter estimates were calculated using the HC0 method. Values marked with b are
set to zero because they are redundant.

However, given that treatment duration is not available upon the initial patient

visit, the theoretical model cannot be practically applied to predict total dose-response

rate in new amblyopic patients. Given this, an "applied" predictive GLM model was also

conducted that excluded treatment duration from the model estimation (Table 22). This

model has predictive formula: Model: 300 + Classification of amblyopia value + VA

Chart value + (-261.45) x initial DVA in the amblyopic eye + (26.72) x daily dose with

32% of random variance controlled for and a large effect size ($\eta^2 > 0.14$). Parameter

estimates for this model are presented in Table 23. Therefore, the variables that best

accounted for the outcome variable of dose-response rate included classification of

amblyopia, VA chart, initial DVA in the amblyopic eye, treatment dose, and age at initial

visit.

Table 22

Applied General Linear Model Results for Total Dose-Response Rate Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Model	4383574.77	5.00	876714.95	11.80	0.00	0.32
Intercept	987189.34	1.00	987189.34	13.29	0.00	0.10
ClassA	1052884.05	2.00	526442.03	7.09	0.00	0.10
VAChart	786210.62	1.00	786210.62	10.58	0.00	0.08
AmbDI	1036663.79	1.00	1036663.79	13.95	0.00	0.10
TreatmentD	1033725.37	1.00	1033725.37	13.91	0.00	0.10
Total	28379413.29	131.00				
Corrected Total	13670563.41	130.00				
Error	9286988.64	125.00	74295.91			

Note. R Squared = .321 (Adjusted R Squared = .293)

Table 23

General Linear Applied Model Parameter Estimates with Robust Standard Errors Across Total Dose Response Rate

Parameter	B	Robust Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
					Lower Bound	Upper Bound	
Intercept	299.76	61.73	4.86	0.00	177.60	421.92	0.16
Strabismic	-203.08	54.95	-3.70	0.00	-311.84	-94.32	0.10
Anisometropic	-80.06	74.82	-1.07	0.29	-228.13	68.01	0.01
Mixed	0[b]						
ETDRS	161.57	48.04	3.36	0.00	66.50	256.65	0.08
LH	0[b]						
AmbDI	-261.45	49.36	-5.30	0.00	-359.15	-163.76	0.18
TreatmentD	26.72	5.94	4.50	0.00	14.97	38.47	0.14

Note. Pararmeter estimates were calculated using the HC0 method. Values marked with b are set to zero because they are redundant.

4.1.2 Treatment Success

Following the regression analysis for the dose-response rate, an exploration of predictive variables was also performed on the second dependent variable of success of treatment. Treatment success was analyzed using the same analytic strategy as dose-response rate.

Variables for the regression analysis were selected using predictive variables from the literature and significant variables from the correlation. For the initial regression analysis, initial DVA in the amblyopic eye, final DVA in the amblyopic eye, age at initial visit, interocular difference at distance initial, interocular difference at distance final, occlusion, and treatment duration were included. Of these variables, initial DVA in the amblyopic eye, final DVA in the amblyopic eye, and interocular difference at distance final were significant ($p < 0.05$).

Following the primary regression analysis, a final regression analysis was performed on only significant variables from the initial regression (Table 24). All variables were significant when used together in this regression model. The model had an R^2 of 0.593, which signifies 59.3% of the statistical variance is accounted for within the model. The model formula for success prediction is: $0.80 + (-0.23)$ x initial distance VA in the amblyopic eye $+ (1.44)$ x final distance VA in the amblyopic eye $+$ initial interocular visual optotype difference at distance.

Table 24

Regression Analysis of Continuous Predictor Variables Against Success

Variable	Unstandardized Coefficients		Standardized Coefficients	Statistical Test		95.0% Confidence Interval for B	
	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
(Constant)	0.80	0.04		20.48	0.00	0.72	0.88
Visual Acuity in the Amblyopic Eye Distance Initial	-0.23	0.09	-0.27	-2.38	0.02	-0.41	-0.04
Visual Acuity in the Amblyopic Eye Distance Final	1.44	0.11	0.74	12.87	0.00	1.21	1.66
Initial Intraocular Visual Optotype Difference at Distance	0.01	0.00	0.32	2.79	0.01	0.00	0.01

Note. All values with significance of $p < 0.05$ are considered statistically significant. In model summary: R=0.770, R squared=0.593, Adjusted R Square=0.584, and std. Error of Estimate=0.19173.

After the regression analysis, an initial exploratory GLM was performed for the dependent variable success. Significant variables from the regression were included. Age at the initial visit in months was also included as this had previously been found to be predictive in the literature. Lastly, all categorical variables found to be predictive in the literature review were included: classification of amblyopia, severity of amblyopia, VA chart used, and occlusion amount. However, with this combination of variables, initial interocular optotype difference at distance was the only variable found to be significant ($p < 0.05$). Therefore, unlike for dose-response rate, categorical variables seemingly did not influence success and the regression model presented above is the most appropriate for exploring key effects on success.

4.4.3 Outcome Visual Acuity in the Amblyopic Eye

Finally, outcome DVA in the amblyopic eye was analyzed using the same approach as dose-response rate and success.

Variables that were correlated with outcome DVA were used in the regression. Predictive continuous variables included treatment duration, interocular VA difference at initial and outcome visits, and initial DVA of the amblyopic eye. Treatment dose, age at initial visit in months, and Rx in the amblyopic eye were added due to significance in the literature. After running regression analyses and removing non-significant variables on each iteration, the final regression of statistically significant predictors ($p < 0.05$) was established (Table 25). Table 25 depicts that initial DVA in the amblyopic eye, interocular visual optotype difference at the initial visit, and interocular visual optotype difference at the outcome visit have an effect on final VA following occlusion therapy. The model has an R^2 of 0.764 which signifies 76.4% of the statistical variance is accounted for within the model. The model formula for final VA prediction is: 0.09 + (0.18) + (0.02) x final interocular visual optotype difference at distance.

Table 25

Regression Analysis of Continuous Predictor Variables Against Final Distance VA in the Amblyopic Eye

Variable	Unstandardized Coefficients		Standardized Coefficients	Statistical Test		95.0% Confidence Interval for B	
	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
(Constant)	0.09	0.01		5.89	< 0.05	0.06	0.11
Visual Acuity in the Amblyopic Eye Distance Initial	0.18	0.04	0.43	4.85	< 0.05	0.11	0.26
Intraocular Visual Optotype difference at distance VA inital visit	0.00	0.00	-0.35	-3.86	< 0.05	-0.01	0.00
Intraocular Visual Optotype difference at distance VA Final Visit	0.02	0.00	0.87	19.42	< 0.05	0.02	0.02

Note. All values with significance of $p < 0.05$ are considered statistically significant. In model summary: R=0.874, R squared=0.764, Adjusted R Square=0.757, and std. Error of Estimate=0.0761.

An initial exploratory GLM was then performed for the dependent variable outcome DVA in the amblyopic eye. Significant variables from the regression were included. Age at the initial visit in months was also included as this had previously been found to be predictive in the literature. Lastly, all categorical variables found to be

predictive in the literature review were included: classification of amblyopia, severity of amblyopia, VA chart used, and occlusion amount. None of the categorical variables were found to be predictive in the non-parametric GLM model ($p > 0.05$). Age was also non-significant. Therefore, like the model for success, the multiple regression model is the most appropriate for describing the prediction of outcome distance VA.

4.4.4 Summary of Hypothesis Results

Hypothesis 1 stated dose and total dose of occlusion therapy do significantly predict the success of amblyopia occlusion therapy. This hypothesis was tested using regression and GLM. Hypothesis 1 was not supported by the analyses given that daily dose and total dose were not significant across the analyses.

Hypothesis 2 stated that dose and total dose of occlusion therapy significantly predict the dose-response rate of visual acuity improvement. Hypothesis 2 was supported by the analyses finding that treatment dose is statistically significant ($p < 0.05$) in predicting dose-response rate across both the regression and GLM.

Hypotheses 2 and 3 stated that key predictors identified in the literature will have an effect on the outcome variables of amblyopia treatment success and dose-response relation of visual acuity. These hypotheses were tested using group comparisons, regression, and non-parametric robust GLM.

Hypothesis 3 was partially supported by the analyses, with some of the hypothesized predictors being statistically significant ($p < 0.05$). In analyzing the dose-response rate in the regression analysis, age at initial treatment, sex, angle of strabismus, and refractive error were not significant. Initial DVA in the amblyopic eye, final DVA in the amblyopic eye, age at initial visit, occlusion amount, and treatment duration were all

significant predictors of dose-response rate. However, some of these predictors were no longer significant in the GLM, which found that only classification of amblyopia, VA chart used, initial DVA in the amblyopic eye, and treatment dose were significant when analyzed together. In analyzing treatment success and outcome VA in the amblyopic eye, in the regression analysis, initial distance VA in the amblyopic eye and initial interocular optotype difference at distance were found to predict treatment success. However, none of the categorical or other continuous variables mentioned in the research hypothesis were statistically significant in predicting success based on the analyses.

5.0 Chapter 5: Discussion

Amblyopia treatment and its success predictors have been widely studied. However, to date, there have been few studies exploring the dose-response rate of amblyopia treatment as a treatment success outcome. The present study aimed to expand the empirical findings on the dose-response rate of occlusion therapy and address the limitations found in previous literature. To achieve the aforementioned goals, four research questions were proposed. These included:

1. What is the dose-response rate of occlusion therapy and outcome visual acuity in patients with strabismic, anisometropic, and mixed type amblyopia?

2. What 'dose' and 'total dose' of occlusion therapy are required to achieve outcome visual acuity in patients with amblyopia?

3. What combination of variables predicts the dose-response rate of visual acuity to occlusion therapy?

4. Which combination of variables predicts the outcome of achieving at least 0.3 LogMAR visual acuity and final visual acuity in the amblyopic eye following occlusion therapy?

To answer these research questions, a retrospective chart review of approximately 1900 patients from the IWK Health Centre Eye Clinic in Halifax, Nova Scotia was conducted. 134 amblyopic patients, 68 males and 66 females, met the established inclusion criteria. Of these participants, hyperopia was the most common refractive error and esotropia the most common form of strabismus. Following data collection, a range of statistical analyses were run to answer the research questions including descriptive statistics, analyses of variance, Mann-Whitney U, Chi-square, Wilcoxon Signed Ranks, Kruskal-Wallis Test, correlations, regressions, and GLMs.

5.1 Dose-Response Rate

Dose-response rate was investigated to answer research questions 1 and 3. The results of the present study found the fastest dose-response rate with younger age at treatment initiation (Table 23), during the first 4 weeks of treatment (Table 18), and in patients with strabismic and/or severe amblyopia (Tables 13 and 14). Variables that best accounted for dose-response rate included classification of amblyopia, VA chart, initial DVA in the amblyopic eye, treatment dose, and age at initial visit using the GLM predictive model illustrated in Tables 22 and 23.

In alignment with previous literature, the present study results suggest that dose-response rate becomes slower with age with children <2 years of age having the fastest dose-response rate and >6 years slowest as shown in Table 7 (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a). This significance of age may be due to the fact that in previous studies older patients had milder amblyopia compared to younger patients, allowing a greater improvement of VA in younger patients (Fronius et al., 2014; Stewart et al., 2004, 2007a). In relation to age, the present study also investigated dose-response rate across VA chart used as LH is typically used for younger participants >5 years and ETDRS for older <4 years of age. In this study, the VA chart used appeared to correlate with a faster treatment dose-response. Patients tested using the LH VA chart had a statistically significant better dose-response rate (Table 17). This difference may have occurred because in general younger children used the LH VA chart and older children were tested using the ETDRS VA chart. Thus, the results may not have been due to the VA chart itself. Additionally, LH is an easier VA chart, possibly also accounting for this difference. The dose-response rate across VA chart used has not specifically been

analyzed in the literature thus we are not able to make any comparisons with the current study.

This study found the highest rate of DVA improvement at 4 weeks of treatment consisting of median 112hours/0.1 logMAR increase (Table 8). This finding was similar to previous studies that found the highest rates of VA improvement at 4-6 weeks of treatment (Fronius et al., 2009; Stewart et al., 2004, 2007a). The present study's dose-response rate is slightly slower than previous studies at 4 weeks of treatment and similar to previous findings at 4 months. It is important to note that previous studies on dose-response rate used only PTO (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a), whereas the present study also included higher intensity occlusion amounts. As the present study used larger daily occlusion amounts and occlusion method (FTO versus PTO) is not significant in predicting outcome level of VA, it would be expected that our sample has a higher dose-response rate as more dose was given over the same period of time compared to PTO previous studies.

Next, dose-response rate was compared across classification of amblyopia. Results suggested that strabismic amblyopia had a faster dose-response rate than both anisometropic and mixed amblyopia, with no significant difference between anisometropic and mixed amblyopia. This analysis was unique to this study, so viable comparisons with preexisting research are limited. Although mean VA improvement was not statistically different across classifications of amblyopia in the previous literature (Fronius et al., 2014; Stewart et al., 2004, 2007a). This difference between classifications of amblyopia may be due to the fact that anisometropic amblyopia may be treated later than strabismic and mixed since it is not visible to parents and may take a school vision screening to be detected.

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Dose-response rate was then compared across severity of amblyopia. Through this analysis, it was noted that mild amblyopia had a statistically slower dose-response rate compared to severe amblyopia. Severe amblyopia also has a significantly faster dose-response rate than moderate amblyopia. This finding is likely due to the fact that severe amblyopia has lower initial VA, allowing a greater rise in VA and thus greater dose-response rate.

Lastly, the regressions and GLM provided insight into how to predict treatment success. This model is illustrated in Tables 22 and 23 finding classification of amblyopia, VA chart used, initial DVA in the amblyopic eye, and treatment dose to significantly predict dose-response rate of DVA to occlusion therapy. This model agrees with and expands on previous studies on dose-response rate that found classification of amblyopia to be a significant predictor of dose-response rate (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a). This model will be discussed further in section *5.4 clinical significance to orthoptics.*

5.2 Relationship between 'Dose' and 'Total Dose' of Occlusion Therapy and Outcome VA

Following success calculations, treatment dose and duration were calculated to answer research question 2. Research question 2 was assessed by Hypothesis 1 which stated: dose and total dose of occlusion therapy do significantly predict the success of amblyopia occlusion therapy. This hypothesis was not supported by the analyses given that daily dose and total dose were not significant across the analyses. These results align with previous research which found no significant difference between FTO and PTO in relation to treatment success (Scott et al., n.d.; Scott et al., 2005; Scott & Dickey, 1988;

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The Pediatric Eye Disease Investigator Group, 2003c, 2003b; Yazdani et al., 2017).

However, a persistent limitation existed across these studies in that compliance variations

lead to a lack of difference in hours patched between groups. Given that compliance was

measured subjectively in the present study, similar limitations exist, possibly accounting

for the lack of difference between patching groups. Additionally, given that the daily dose

was not significant in predicting outcome VA, it makes sense that the total dose to

outcome VA for PTO is about half the dose of FTO as PTO patients patched about half

the number of hours of FTO patients. Compared to the previous literature, the total dose

has yet to be investigated. Additionally, all previous studies only analyzed PTO having

daily doses ranging from 2.8-4.19 hours per day (Fronius et al., 2009, 2014; Stewart et al.,

2004, 2007a). Therefore, this is likely one of the first studies to analyze FTO in relation to

the total dose of occlusion therapy.

     Although PTO versus FTO was not statistically significant in predicting treatment

success, treatment duration in the present study was shorter than the duration reported in

previous studies. Previous research reported treatment durations ranging from 19.8-20.2

weeks (Cleary, 2000; Hug, 2004), compared to the present studies duration of 16 weeks.

This difference could be because more FTO patients were included, whereas PTO was

used in the studies cited. As FTO had shorter treatment durations than PTO, this could

account for the difference in the literature. Results found FTO treatment was on average 5

weeks shorter than PTO treatment (Table 16). Thus, although the intensity of occlusion

does not appear to improve VA outcomes, it decreases the length of treatment. This is

significant as studies on occlusion therapy compliance for amblyopia found that

compliance to treatment significantly increased with shorter treatment duration (Wallace

et al., 2013). These results align with previous findings that suggested dose-response rate

of VA was linear and monotonic, with patching over 2 hours increasing dose-rate response but not final VA outcome (Stewart et al., 2004). This result has the clinical implication that FTO should be used to promote shorter treatment duration, and thereby could reducing expenditure on healthcare resources provided the follow-up is the same for FTO and PTO, and improve treatment compliance.

5.3 Predictor Variables and Final Outcome VA

This section will discuss success and final outcome VA. The results of the present study found that VA improved in the amblyopic eye following occlusion therapy in 90.3% of participants (Table 1). In this study, to achieve outcome VA, 1344 hours (FTO) and 504 hours (PTO) total dose and median treatment duration of 16 weeks were required. The refractive error distribution was similar to previous literature, finding the development of amblyopia more common in patients with hyperopia than myopia (DeSantis, 2014; Raab et al., 2010; Von Noorden, 1996). Furthermore, as more esodeviations than exodeviations were present in the sample, this suggests that esodeviations are more likely to develop amblyopia compared to exodeviations, confirming findings in the previous literature (DeSantis, 2014; Raab et al., 2010).

Initial and final DVA in the amblyopic eye and final interocular difference predicted treatment success. With a 90.3% success rate, this finding is higher than previous studies, which reported treatment success between 58-76% (Hoscox et al. 1992; Hug 2004). This difference may be due to the fact that only compliant children were included in the present study. When controlling for compliance, Mintz-Hittner et al. (2000) found 100% of participants achieved VA between 6/9.6 and 6/6 (Mintz-Hittner & Fernandez, 2000). Additionally, most patients in our sample had consistent close follow-

up visits, between 4-6 weeks, with previous literature showing that more frequent follow-up in amblyopia treatment increases compliance (Wallace et al., 2013).

The result of 69% equal vision is similar to previous studies that reported equal final VA ranging from 60-73% (Scott et al., 2005; Stein et al., 2014). Although similar to previous findings, these findings do not necessarily match what is observed clinically at the IWK Eye Clinic. Anecdotally, most clinicians would agree that treatment cessation due to a finding of equal visual acuity is not common in our current patient population. Until the current study, this belief had not been explored. This disparity in study results and clinical observation may be due to the cut-off for final DVA in the present study. Most of our participants were median age 4 years. With most participants under age 5 years, their best achievable vision was statistically limited to 6/12 for ages 2-4 years, 6/9.6 for ages 4-5 years, and 6/6 for school-age children based on findings in previous literature (Iannelli, 2020). Following the time-frames included in our study, visual acuity may have improved in the non-amblyopic or both eyes leading to the clinical observation that is in contrast to the results found in the current study.

Success in amblyopia treatment cannot be discussed without considering initial and final DVA in the amblyopic eye, and final interocular difference at distance, as they all predicted treatment success. These results agree with previous findings that suggest the severity of amblyopia impacts treatment success. Previous studies concluded that lower initial VA correlated to lower final VA after treatment (Scott et al., 2005; Scott & Dickey, 1988). However, these results differ from previous literature that found variables such as age (Fronius et al., 2014; Holmes, Lazar, Melia, Astle, Dagi, Donahue, Frazier, Hertle, Repka, Quinn, Weise, et al., 2011; The Pediatric Eye Disease Investigator Group, 2005) and classification of amblyopia (Cleary, 2000; Hiscox et al., 1992; Woodruff et al.,

1994) predicted success. Children under age 7 typically have higher rates of success (Fronius et al., 2014; Holmes, Lazar, Melia, Astle, Dagi, Donahue, Frazier, Hertle, Repka, Quinn, Weise, et al., 2011; The Pediatric Eye Disease Investigator Group, 2005), while mixed amblyopia typically has the worst success outcomes compared to other amblyogenic factors (Cleary, 2000; Hiscox et al., 1992; Woodruff et al., 1994). This difference in results could be since 90% of our participants were successful, leading to a lack of statistical power to calculate differences in the unsuccessful treatment group.

On the topic of success, it is also important to address final VA outcomes across participants. Final VA results of median 0.40 logMAR units are higher than in previous studies having found a total VA gain of -0.1-0.4 logMAR units on crowded optotypes (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a). A mean of 0.43 logMAR units was only found by Stewart et al. (2007) for children under 4 years of age, but given the skewed nature of these outcomes, the mean might not be the best measure of central tendency for this variable. This difference may be due to high compliance as median values for initial DVA of the amblyopic eye were similar in the present study to previous studies (mean=0.58) (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a). Additionally, all previous studies stopped recording VA at 4 months of treatment while the present study continued follow-up until outcome VA was obtained (as defined in Chapter 3). As final VA outcomes are higher in the present study, occlusion therapy should be continued past 4 months if VA is not equal or stable over 3 consecutive cycles.

5.4 Clinical Significance to Orthoptists

The results of the present study illustrate that occlusion therapy, in this clinical environment, is successful in the management of amblyopia. Ninety percent of our study

patients were able to obtain driving level VA in the amblyopic eye, with good treatment compliance. Additionally, the predictive GLM of dose-response rate can be used to calculate dose-response rate per patient performing occlusion therapy by imputing lower, and upper bound values to calculate the expected dose-response rate range. In particular, the study results present amblyogenic risk factors, amblyopia treatment success calculations, and dose-response rate predictors. By understanding predictors of faster or slower dose-response rate, appropriate therapeutic plans can be designed.

In relation to amblyopia treatment, treatment efficacy is an important outcome. The current study found high treatment success and improved DVA for the sample following occlusion therapy. These results support the conclusion that occlusion therapy, both PTO and FTO, can be effective in treating amblyopia when good compliance is maintained. Despite the positive impact of these treatments, as VA gain in the present study was higher than previous literature on dose-response rate, it is important to continue treatment until VA is equal or 3 consecutive cycles of stable VA in the amblyopia eye has been obtained to ensure maximum VA improvement. One additional consideration of practical importance is the fact that improved VA outcomes may lead to more predictable and desirable surgical results (Repka et al., 2005; The Pediatric Eye Disease Investigator Group, 2017).

When analyzing amblyopia treatment success outcomes, dose-response rate is an integral factor. From study results, it is important to be aware that with older age, longer treatment duration, and less severe amblyopia, the dose-response rate of VA may slow down. Therefore, longer treatment durations can be explained to children and their families to prepare them for the time it will take to improve vision in their amblyopic eye. Conversely, as dose-response rate of VA improvement slows with age, treatment should

be started at younger ages to ensure a faster dose-response rate of VA to maximize the effectiveness of treatment. Additionally, doses over 8 hours per day significantly reduced treatment duration, possibly increasing treatment compliance and reducing expenditure on healthcare resources as noted in previous literature (Cleary, 2000; Dorey et al., 2001). This is significant as compliance is often an obstacle in amblyopia treatment (Mintz-Hittner & Fernandez, 2000; Stewart et al., 2004, 2007a). The importance of the first month of treatment should be specifically emphasized as the most important treatment period for achieving outcome VA. Previous studies using ODM found compliance to occlusion therapy to drop across all ages after the first month of treatment (Fronius et al., 2009; Stewart et al., 2004, 2007a). Fronius et al. (2009) even found compliance was measured as 85% at 1 month and 56% at 3 months of treatment, with 2 patients not patching at all after the first month of treatment. Therefore, as both dose-response rate and treatment compliance decrease after the first 4 weeks of treatment, treatment importance should be emphasized in the first month. In summary, these findings have the clinical implication that amblyopia treatment should be started at younger ages to ensure a faster dose-response rate of VA and thereby increasing the effectiveness and compliance of treatment.

In terms of the study findings, demographic statistics revealed that more participants in the sample had hyperopia and esodeviations versus myopia and exodeviations, confirming previous literature findings that these factors are the most prevalent in amblyopia. These results suggest that both children with myopic and hyperopic refractive errors can develop amblyopia, with those with hyperopia at greater risk of amblyopia. From a practical point of view, clinicians should consider monitoring

children with these characteristics during visual immaturity to detect and treat any developing amblyopia given the potential negative impact of these amblyogenic factors.

Finally, by creating a GLM model of dose-response rate, it allows clinicians to calculate dose-response rate of amblyopic patients initiating occlusion therapy. To apply this formula:

1. Strabismic amblyopia on ETDRS chart dose-response rate = 258.49 + (-261.45) x initial logMAR distance vision in the amblyopic eye + (26.72) x daily dose in hours

2. Strabismic amblyopia on LH chart dose-response rate = 96.92 + (-261.45) x initial logMAR distance vision in the amblyopic eye + (26.72) x daily dose in hours

3. Anisometropic amblyopia on ETDRS chart dose-response rate = 381.51 + (-261.45) x initial logMAR distance vision in the amblyopic eye + (26.72) x daily dose in hours

4. Anisometropic amblyopia on LH chart dose-response rate = 219.94 + (-261.45) x initial logMAR distance vision in the amblyopic eye + (26.72) x daily dose in hours

5. Mixed amblyopia on ETDRS chart dose-response rate = 461.57 + (-261.45) x initial logMAR distance vision in the amblyopic eye + (26.72) x daily dose in hours

6. Mixed amblyopia on LH chart dose-response rate = 219.94 + (0) x initial logMAR distance vision in the amblyopic eye + (26.72) x daily dose in hours

Additionally, parameter estimates in Table 23 can be applied to estimate the range of dose-response rates for a patient within a 95% confidence interval.

1. Strabismic amblyopia on ETDRS chart dose-response rate range

a. Lower Bound Range= (-67.74) + (-359.15) x initial logMAR distance vision in the amblyopic eye + (14.97) x daily dose in hours

b. Upper Bound Range = 584.25 + (-163.76) x initial logMAR distance vision in the amblyopic eye + (38.47) x daily dose in hours

2. Strabismic amblyopia on LH chart dose-response range:

a. Lower Bound Range= (-134.24) + (-359.15) x initial logMAR distance vision in the amblyopic eye + (14.97) x daily dose in hours

b. Upper Bound Range = 327.60 + (-163.76) x initial logMAR distance vision in the amblyopic eye + (38.47) x daily dose in hours

3. Anisometropic amblyopia on ETDRS chart dose-response rate range:

a. Lower Bound Range= 15.97 + (-359.15) x initial logMAR distance vision in the amblyopic eye + (14.97) x daily dose in hours

b. Upper Bound Range = 746.58 + (-163.76) x initial logMAR distance vision in the amblyopic eye + (38.47) x daily dose in hours

4. Anisometropic amblyopia on LH chart dose-response rate range:

a. Lower Bound Range= (-50.53) + (-359.15) x initial logMAR distance vision in the amblyopic eye + (14.97) x daily dose in hours

b. Upper Bound Range = 489.93 + (-163.76) x initial logMAR distance vision in the amblyopic eye + (38.47) x daily dose in hours

5. Mixed amblyopia on ETDRS chart dose-response rate range:

a. Lower Bound Range= 244.10 + (-359.15) x initial logMAR distance vision in the amblyopic eye + (14.97) x daily dose in hours

b. Upper Bound Range = 678.57 + (-163.76) x initial logMAR distance vision in the amblyopic eye + (38.47) x daily dose in hours

6. Mixed amblyopia on LH chart dose-response rate range:

   a. Lower Bound Range= 177.60 + (-359.15) x initial logMAR distance vision in the amblyopic eye + (14.97) x daily dose in hours

   b. Upper Bound Range = 421.92 + (-163.76) x initial logMAR distance vision in the amblyopic eye + (38.47) x daily dose in hours

As discussed, results related to dose-response rate have the clinical implication of illustrating the total dose required across patients to obtain treatment outcome to allocate resources and time. Providing additional information to patients in relation to what they can expect for overall treatment duration has been shown to increase treatment compliance (Stewart et al., 2004, 2007b). Dose-response rate calculations can be performed to estimate the rate of VA improvement based on known predictors. Therefore, an estimated timeline can be developed to allow allocation of clinical resources and to prepare the patient for the treatment duration required, and improve treatment compliance.

In summary, study results presented amblyogenic risk factors, amblyopia treatment success outcomes, dose-response rate predictors, and prediction calculations. By understanding predictors of faster or slower dose-response rate, rates can be presented to amblyopia patients and families, inform clinical practice, and improve treatment outcomes and compliance.

5.5 Limitations

The present study had the largest sample size and most representative distribution of participants across classifications of amblyopia compared to previous literature on dose-response rate (Fronius et al., 2009, 2014; Stewart et al., 2004, 2007a). Despite

providing a series of novel results which could shape future amblyopia research and practice patterns, the present study has several key limitations. The first limitation is that the study is retrospective. With any retrospective sample, variables are assessed and reported prior to study initiation, limiting the precision of the data entry process, and posing possible recall bias. Additionally, possible confounding variables such as near visual acuity, birth weight, and gestational age were unable to be included due to missing data. To address this limitation, stringent inclusion/exclusion criteria attempted to reduce both lack of variables due to missing data and sampling bias. These criteria included only amblyopic patients with ≥2 line interocular difference, with outcome VA established by equal vision or 3 consecutive cycles with no VA improvement and good reported compliance. Additionally, after sampling, every 3rd patient that met inclusion/exclusion criteria was selected for the study, in an attempt to limit sampling bias. Despite the limitations, retrospective studies can provide invaluable information necessary to evaluate current practice patterns and individual standards of care. Retrospective studies also have the advantage of being inexpensive and quicker with no participant attrition due to the need for ongoing follow-up.

The next limitation of this study is that no objective method was used to measure treatment compliance measurement. This limitation is widespread and is commonly cited as a key limitation to the current research paradigm within amblyopia treatment literature. Compliance issues were addressed in this study by using subjective methods of recording reported patching hours versus the prescribed patching hours. Despite the development and use of ODM, minimal progress has been made towards effectively controlling for compliance in amblyopia research designs. Therefore, the results could have some degree of error resulting from a patient's inaccurate reporting of actual patching amounts. This

error could account for the lack of success differences between PTO and FTO as discussed in Chapter 2.

Another limitation of this study is that long-term, post-treatment cessation, follow-up was not analyzed. Amblyopia recurrence and vision stability were not addressed in this study, making any possible correlations with amblyopia regression and occlusion dose impossible. Another limitation of this study is that follow-up post initial treatment endpoint was reached, further treatment regimens were not analyzed. In the visually immature population, VA naturally increases, reaching 6/6 by age 5. As most of our sample was age 3-4, this limited best VA to 6/12 (the success outcome). However, if tracked past "successful" treatment, VA in the non-amblyopic eye may increase, thus possibly decreasing our treatment success rates. Additionally, in relation to age, most of the sample was age 3-5 years, with few participants under age 3 and over age 6 years. This limitation prevented the analysis of age effects on dose-response rate on participants over the age of 6 and under the age of 3. This prevented comparisons to previous studies which included participants over the age of 7. These limitations could be addressed by a longitudinal follow-up and larger sampling of older age groups.

A further limitation of the study was smaller sample size in PTO, anisometropic amblyopia, and mild amblyopia groups compared to FTO, strabismic/mixed amblyopia, and moderate/severe amblyopia groups. This smaller group size may have led to Type II error by limiting the statistical power of those variables across the various analyses, leading to a higher probability of false non-significant results. This limitation could be addressed by including multicenter data to expand the sample size. Due to the small number of participants wearing less than 8 hours/day of occlusion, FTO had to be defined as >8 for statistical purposes only. This is not the classic definition used in this

institution's current standardized amblyopia treatment protocol. Referring to >8 hours per day as FTO could possibly mislead the reader, as anything less than all waking hours could be considered by some as PTO. In order to have transparency in the study results, as clarified in terminology, clear definitions of FTO vs PTO were included in this research.

An additional limitation is that the IWK Eye Clinic does not have a standard protocol for visual acuity measurement across clinicians. Therefore, clinician variability is a limitation of the present study.

One final limitation of the current study is that only one type of amblyopia therapy was included for analysis. Other forms of amblyopia treatment, such as atropine and/or optical penalization, were not investigated. This reduced scope limits application of the current study results to only patients who perform occlusion therapy. This limitation could be addressed by performing future research including other forms of amblyopia management.

5.6 Future Directions

Given the limitations of the present study, a range of research could be performed. As this study was retrospective in nature, future research could be performed on a prospective sample, and a more inclusive range of participants across age and predictive variables, such as classification and severity of amblyopia. By performing a prospective study, data collection could be standardized to collect a wider range of covariates which may be predictive of treatment success and dose-response rate. Additionally, a more evenly distributed sample across predictors such as PTO, FTO, severity, and classification of amblyopia could be obtained. This would resolve limitations regarding Type II error

and lack of participants, limiting statistical power for certain analyses. Future research could also analyze the impact of providing an estimated dose-response rate, faster dose-response rates, and shorter treatment duration on patient compliance to occlusion therapy.

When considering the present study's lack of long-term post-treatment follow-up analysis, future research is needed to investigate VA following initial treatment outcome. As mentioned, although our success rates are similar to previous findings, these findings do not necessarily match what we observe clinically. Following the time frames included in our study, vision may have improved in the non-amblyopic or both eyes leading to the clinical observation contradiction to the current study results. Therefore, future research could investigate VA regression and improvement in the amblyopic eye following initial treatment outcomes and associated treatment success and dose-response rates.

Finally, future research is needed to calculate dose-response rates across other amblyopia treatments such as Bangerter foils, optical penalization, and atropine penalization. Although occlusion therapy is the gold standard of amblyopia treatment, other treatment modalities are used clinically and are thus important to investigate. Both retrospective and prospective studies could investigate dose-response rates across amblyopia treatment modalities to determine if predictors and treatment success are different.

5.7 Conclusions

In conclusion, the present study analyzed success and dose-response rate outcomes of VA across predictors using a sample of patients from the IWK Eye Clinic. Dose-response rate was faster in younger participants, in participants with strabismic and severe amblyopia, and during the first month of occlusion. Therefore, the main outcomes

of this study found that with good compliance, occlusion therapy is successful and effective in treating amblyopia. Therefore, amblyopia occlusion therapy should be initiated at the youngest age possible, and good compliance should be emphasized, especially during the first month of treatment, to ensure good short-term treatment outcomes. Lastly, occlusion therapy should be continued until equal vision or 3 consecutive cycles or stable vision are obtained to ensure best outcome VA.

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Appendix A: IWK Research Ethics Board Approval

IWK Health
Research
5850/5980 University Avenue
PO Box 9700, Halifax
Nova Scotia B3K 6R8
Canada
Tel: 902.470.8888
www.iwk.nshealth.ca

Approval – Delegated Review
October 15, 2020

Principal Investigator: Miss. Emily White
Supervisors: Leah Walsh, Erik Hahn
Title: The impact of occlusion therapy and demographics on amblyopia dose-response relationship and success outcomes
Project #: 1026038

On behalf of the IWK Research Ethics Board (IWK-REB), I have reviewed the documents included in this study. I am pleased to confirm the Board's full approval for this research study, effective today.

Please ensure that any agreements, contracts and funding (where applicable) are in place prior to commencing this research.

Best wishes for a successful study.

Yours truly,

Co-Chair, Research Ethics Board

This approval includes the following study documents:

Document Name	Version Date
Protocol	2020/10/08
Data Collection Form - Variable List	2020/09/30
Data Collection Form - Patient Identification	2020/07/18

The Board's approval for this study will expire one year from the date of this letter (October 15, 2021). To ensure continuing approval, submit a Request for Continuing Review to the Board 2 - 4 weeks prior to the renewal date. If approval is not renewed prior to the anniversary date, the Board will close your file and you must cease all study activities immediately. To reactivate a study, you must submit a new Initial Submission (together with the usual fee, if applicable) to the IWK-REB and await notice of re-approval.

Please be sure to notify the Board of any of the following:

- Proposed changes to the initial submission (i.e. new or amended study documents)
- Additional information to be provided to study participants
- Material designed for advertisement or publication with a view to attracting participants
- Serious adverse events experience by local participants
- Unanticipated problems involving risks to participants or others
- Sponsor-provided safety information
- Additional Compensation available to participants
- Upcoming audits/inspections by a sponsor or regulatory authority
- Closure of the study (within 90 days of the event)

Approved studies may be subject to internal audit. Should your research be selected for audit, the Board will advise you and indicate any other requests at that time.

Important Instructions and Reminders

Submit all correspondence to Ethics Coordinator, Joanne Street at the address listed at the top of this letter (do not send your response to the IWK-REB Chair or Co-Chair)

Be sure to reference the Board's assigned file number, 1026038 on all communications.

Highlight all changes on revised documents and remember to update version numbers and version dates, include a clean copy of all revised documents.

Research Ethics Board Committee Members		
Victoria	Allen	Obstetrics and Gynecology (Clinical Researcher)
Christopher	Blackmore	Surgery (Clinical Researcher)
Carol	Digout	APPHON (Clinical Researcher)
Jon	Dorling	Pediatric Neonatology (Clinical Researcher)
Tricia	Beattie	Pediatric Psychology (Clinical Researcher)
Kimberly	Brewer	BIOTIC (Clinical Researcher)
Janet	Curran	Nursing (Clinical Researcher)
Bryan	Fader	Lay Representative
Eleanor	Fitzpatrick	Nursing (Clinical Researcher), Co-Chair
Isabelle	French	Legal Representative
Adam	Huber	Pediatric Rheumatology (Clinical Researcher), Co-Chair
Daddy	Mata-Mbemba	Diagnostic Radiology (Clinical Researcher)
Francois	Tremblay	Pediatric Ophthalmology (Clinical Researcher)

* REB members are not in attendance during the review of their own proposed research involving human subjects or where there is a conflict of interest with the proposed research

This statement is in lieu of Health Canada's Research Ethics Board Attestation: *The Research Ethics Board for the IWK Health Centre operates in accordance with:*

- *Food and Drug Regulations, Division 5 "Drugs for Clinical Trials Involving Human Subjects"*
- *The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans - TCPS(2)*
- *International Conference on Harmonization - Good Clinical Practice Guidelines - ICH-GCP*
- *FWA #: FWA00005630 / IORG #: IORG0003102 / IRB00003719*

Appendix B: Data Collection Example & Variables of Interest

Study patient identifier	Variables of Interest			
	Age		OS 20 weeks	
	Sex (1,2)		OD 24 weeks	
	Treatment Dose (Hours per day)		OS 24 weeks	
	Refractive Adaptation (In weeks)		OD 28 weeks	
	OD (near) initial		OS 28 weeks	
	OS near initial		OD 32 weeks	
	OD distance initial		OS 32 weeks	
	OS distance initial		OD continued	
	Intraocular difference in initial distance		OS continued	
	OD 4 weeks		OD Final	
	OS 4 weeks		OS Final	
	OD 6 weeks		Classification of amblyopia (1,2,3)	
	OS 6 weeks		Treatment duration (Weeks)	
	OD 8 weeks		Severity of amblyopia (1,2,3)	
	OS 8 weeks		Refractive error OD	
	OD 12 weeks		Refractive error OS	
	OS 12 weeks		Angle of strabismus at 1/3m	
	OD 16 weeks		Angle of strabismus at 6m	
	OS 16 weeks		Follow-up schedule (Weeks)	
	OD 20 weeks		Dose-response rate	

Appendix C: Vision Progress Chart Template

Vision Progress Chart

IWK Health Centre

	Visual Acuity Test				Method of Treatment			
LEGEND	1. = ETDRS letters	5. = OTHER		A = Atropine	EZ = EZE Patch			
	2. = LH pictures	X = right eye		O = Optical Penalization	G = Glasses Only			
	3. = HOTV letters	O = left eye		B = Bangerter Foil	P = Patching (Adhesive)			
	4. = ALLEN pictures			❑ ERG ❑ VEP				

Rows (visual acuity levels):
- 6/4.8
- 6/6
- 6/7.5
- 6/9.6
- 6/12
- 6/15
- 6/18.9
- 6/24
- 6/30
- 6/37.5
- 6/48
- 6/60
- 6/120
- less than 6/120

Additional rows:
- Date of Visit (dd/mm/yyyy)
- VA Test Used
- Occlusion Method
- Hours Occluded
- Initials

PERMANENT RECORD Page 1 of 2   03/16

IWKVIPR

Vision Progress Chart

IWK Health Centre

Signature	Initials	Signature	Initials

IWKVIPR

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Appendix D: Patient Age Frequencies

Simple Histogram of Age in Months at Initial Visit

Mean = 59.49
Std. Dev. = 18.194
N = 134