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### Analyzing Trends In Intermittent Exotropia With Adhd Medication Use

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**Analyzing Trends in Intermittent Exotropia with ADHD Medication Use**

A Thesis Submitted to the Yale University School of Medicine

In Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Kevin K. Wang

2022

## ABSTRACT

### **ANALYZING TRENDS IN INTERMITTENT EXOTROPIA WITH ADHD MEDICATION USE.**

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**Objective:** This study aims to examine whether ADHD medication usage is associated with changes in intermittent exotropia in children, and whether such ADHD medication use is associated with prevention of strabismus surgery.

**Design/Participants:** We conducted a retrospective cohort study of children with both ADHD and intermittent exotropia seen at the Yale Eye Center between 2005 and 2020 who were taking medications for ADHD.

**Methods:** A list of eligible patients was identified by the Joint Data Analytics Team at Yale University based on presence of ADHD and intermittent exotropia ICD10 code diagnoses. For each patient, the following variables were collected: age, sex, ADHD medications used, dosage of medication, medication start and end dates, date of ADHD diagnosis, date of X(T) diagnosis, dates of strabismus surgeries, and presence of comorbid developmental disorders. For each strabismus appointment recorded for a patient, the following variables were collected: date of appointment, strabismus measurements at near and distance, visual acuity, stereoacuity, presence or absence of amblyopia, grade of X(T) control, presence or absence of symptomatic diplopia, strabismus treatments being used at time of appointment, and presence or absence of

refractive correction. The resulting data was qualitatively analyzed for trends in X(T) deviation, stereo-acuity, grade of control, and amblyopia off versus on ADHD medications. Criteria for defining what qualified as a change were: X(T) deviation change of  $\geq 10$  prism diopters (PD), stereo-acuity change of at least two octaves, and grade of control change from 0-2 to 3-5 or vice versa.

**Results:** Eight patients (5 male, 3 female; ages 7-19 years) were included for analysis.

Intermittent exotropia at near remained stable in seven patients following ADHD medication use and worsened in one patient. X(T) at distance remained stable following ADHD medication use in six patients, worsened in one patient, and improved in one patient. Stereo-acuity worsened in two patients and remained stable in five patients who had stereo-acuity data available. Of the four patients with data on grade of control, control remained stable in two and worsened in two patients. One patient had worsening amblyopia while taking ADHD medications. Five of the eight patients required strabismus surgery to correct their intermittent exotropia; three of these patients required surgery while taking medication, and two patients after they had discontinued their ADHD medication.

**Conclusions:** Our study shows that patients remained predominantly stable in exotropic deviation, stereoacuity, and grade of control when taking ADHD medications. However, three patients required surgical correction of X(T) while taking ADHD medications due to worsening stereoacuity, control, or alignment. Our results show that ADHD medications do not seem to have any consistent effect on preventing strabismus surgery.

## ACKNOWLEDGEMENTS

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## INTRODUCTION

Exotropia is an ocular misalignment that causes an outward turn of an eye. Intermittent exotropia (X(T)) is an ocular misalignment condition that is characterized by an intermittent outward eye turn. Intermittent exotropia is typically seen under conditions such as fatigue, illness, and inattention.<sup>1</sup> Several theories have been proposed to explain the cause of X(T). These include mechanical and neurological causes;<sup>2</sup> however, the etiology of this condition is unknown. Intermittent exotropia usually manifests before the age of five years and presents at birth in around 43% of X(T) patients.<sup>2</sup> It can progress to symptomatic diplopia (double vision) or amblyopia (decreased visual acuity in one eye) due to suppression of the deviating eye. The condition can be treated with over-minused lenses that induce convergence, alternate day eye patching, prism glasses, eye convergence exercises, and, in refractory cases, surgical correction.<sup>2</sup>

There are several theories that have been proposed to explain the etiology of intermittent exotropia. Given that the condition often has a positive family history, there is likely a genetic component to X(T).<sup>2</sup> For example, exotropia has been noted to be a feature of a group of genetic disorders linked to the *RERE* gene, which codes for a protein that modulates the activity of transcription factors involved in apoptosis in several different organs.<sup>3</sup> There are also in utero environmental factors that may be involved with the development of exotropia, as maternal cigarette smoking, paternal lead exposure, and low socioeconomic index have all been found to be significant risk factors.<sup>4</sup> Neurological theories that have been proposed

include an innervational imbalance within the divergence centers located in the brainstem, specifically the tegmentum and mesencephalic reticular formation.<sup>5</sup> An intermittent exotropia can also develop in patients with uncorrected myopia, as these patients experience less accommodative effort, and an exotropia can develop as a result of under-stimulation of the convergence neural pathways.<sup>2</sup>

### ***To Operate or Not?***

Surgical correction is the definitive treatment of intermittent exotropia but is not always successful. Surgical correction can be achieved by tightening the extraocular muscles (resection) opposite from the direction of the eye deviation and loosening the extraocular muscles on the same side as the direction of eye deviation (recession), or both. Surgical correction is reported to have a success rate of around 60-70% in intermittent exotropia.<sup>2</sup> Zou et al. found that factors that can predict a higher chance of success with strabismus surgery include having a smaller angle of deviation and a greater myopic refractive error, while having larger angles of exotropic deviation and more hypertropia (upward eye turn) were associated with a lower chance of surgical success.<sup>6</sup> In another study, a greater age at the time of surgery was found to be associated with a higher chance of exotropia recurrence.<sup>7</sup> A study investigating the association of post-operative diplopia with surgical outcomes showed that as many as 44% of patients can experience diplopia on post-operative day one, but all patients in this study reported resolution of diplopia by two weeks following surgery.<sup>8</sup> Interestingly, the presence of diplopia on post-operative day one, often a result of overcorrection and consequent esotropia,



was associated with a higher rate of surgical success at post-operative month one in this study.<sup>8</sup> Although the rate of surgical success in the few weeks or months following surgery has been reported to be around 60%, the rate of long-term surgical success years after surgery is less impressive. The rate of successful surgical correction of X(T) at five years following surgery is reported to be 30%, with no statistically significant difference with the rate of X(T) resolution using non-surgical interventions alone (12%).<sup>9</sup> However, surgical correction is associated with statistically significant improvement in stereoacuity compared to no surgical correction.<sup>9</sup> The variable and unpredictable response of X(T) to strabismus surgery has led to growing interest in the development of non-surgical treatments for intermittent exotropia patients.

If left untreated with surgical correction, intermittent exotropic deviation is expected to worsen in 15% of patients over the course of three years, 29% over the course of 10 years, and 53% over the course of 20 years.<sup>10,11</sup> It is possible for intermittent exotropia to resolve spontaneously in a very small minority of patients (4%) over the course of nine years.<sup>10</sup> Approximately 74% of patients will undergo surgical correction over the course of 20 years.<sup>10</sup> Stereoacuity and control of exotropia, on the other hand, have been reported to improve without any treatment for intermittent exotropia, as reported in one study tracking these outcomes over the course of three years in 132 patients.<sup>11</sup> Other studies, however, have reported different results. Intermittent exotropia deviation was found in one study by von Noorden et al. to worsen in 75% of patients over the course of three years, remain stable in 9%, and improve in 16%, while another study by Hiles et al. reported X(T) deviation remained stable

in 81% of patients.<sup>12,13</sup> Thus, the natural course of patients with intermittent exotropia remains difficult to define.

### ***Neurobiology of X(T)***

Studies have found associations between X(T) and neurodevelopmental disorders like attention deficit hyperactivity disorder (ADHD).<sup>14</sup> One study by Chung et al. found that children with ADHD showed statistically significant improvement of inattention and hyperactivity symptoms following surgical correction of X(T), suggesting that the presence of exotropia may contribute to symptoms of ADHD.<sup>15</sup> The impact of surgical correction of intermittent exotropia for other childhood psychiatric disorders, however, is not as marked, as suggested by a study by Kilgore et al. that found no significant difference in the rate of developing mental illness between X(T) patients who did and did not undergo surgical correction.<sup>16</sup>

Supporting the neurological basis of X(T) are neuroimaging studies that have found that X(T) patients show differences in brain activity compared to control subjects.<sup>17,18</sup> Specifically, lower baseline functional connectivity was seen between the right visual cortex and the right calcarine sulcus and superior occipital gyrus, and also between the left visual cortex and the right cuneus and postcentral gyrus in patients with intermittent exotropia compared to healthy patients.<sup>18</sup> In a study analyzing cortical activity of intermittent exotropia patients when presented with visual stimuli, X(T) patients showed increased activation of bilateral parietal lobes compared to controls.<sup>17</sup> Given that the parietal lobe is involved with spatial attention and

shifting attention between objects, increased activity in this area in intermittent exotropia patients may reflect an attempt of these patients to compensate for a dysfunction in binocular fusion ability.<sup>17</sup>

### ***Stimulants and the Eye***

Medications are generally not used to treat intermittent exotropia, with the exception of botulinum toxin type A, which has been used to paralyze over-acting extraocular muscles.<sup>19</sup> However, the variability of success with surgical correction of X(T) warrants exploration of novel non-surgical treatment options for X(T) patients. One area that has not been as closely investigated is the relationship between X(T) and the medications that are used for ADHD treatment, which have historically been central nervous system stimulants like amphetamines and methylphenidate. Amphetamine acts mainly as an inhibitor of dopamine and norepinephrine reuptake transporters (DAT and NET, respectively) to increase the levels of these neurotransmitters in neuronal synapses.<sup>20</sup> Amphetamine exerts this effect mainly in the striatum and the ventral tegmental area.<sup>20</sup> Methylphenidate also has DAT and NET blocking activity, specifically in the thalamus, parietal cortex, and prefrontal cortex.<sup>20</sup> Patients with ADHD have shown functional deficits in the inferior prefrontal, parietal, and cerebellar regions of the brain.<sup>20</sup> Given that functional changes in the parietal cortex are involved in not only ADHD and methylphenidate site of action, but also intermittent exotropia, this area may be a potential link connecting X(T) and stimulants used for ADHD treatment.

Case reports of patients showing improvement in stereopsis and exotropic deviation with stimulant medications have been published. In one case, a patient with rod-cone dystrophy, exotropia, and congenital nystagmus showed significant improvement in deviation and stereoacuity after taking dextroamphetamine, a stimulant medication used for ADHD treatment.<sup>21</sup> In another case, a patient with congenital nystagmus showed improvement in eye deviation and stereoacuity after taking diethylpropionate, a central nervous system stimulant that is used not for ADHD treatment but for appetite suppression.<sup>22</sup> Bemegride, another stimulant medication, has also been associated with improvement in exotropia patients.<sup>23,24</sup>

Other studies have examined the effect of stimulant medications on other visual function parameters. One study evaluating ophthalmologic differences between patients with and without ADHD found that ADHD patients had significantly worse visual acuity, heterophoria, and near point of convergence than patients without ADHD at baseline in the absence of medication.<sup>25</sup> The difference between the two groups was not significant an hour after the study subjects took stimulant medication, suggesting that stimulant medication had improved these visual parameters in the ADHD patients. Treatment with stimulants, however, did not cause any statistically significant difference in these visual function measures compared to measurements without stimulants. A follow-up study by the same research group found that the performance of ADHD patients on Rarebit perimetry visual field testing significantly improved two hours following stimulant medication use.<sup>26</sup> In contrast to these results, one study by a different research group found that the visual accommodative response in children with ADHD was not affected by the administration of stimulant medication.<sup>27</sup> A case has also

been reported of a child experiencing a significant decrease in visual acuity after being treated with the ADHD medications methylphenidate and lisdexmafetamine.<sup>28</sup>

Given the published cases suggesting a potential effect of ADHD medication on X(T) as well as the growing interest in developing non-surgical treatment options for X(T) patients, we were interested in a systematic review of patients with ADHD and X(T) seen at Yale Eye Center to evaluate for any potential association of ADHD medications with X(T).

## STATEMENT OF PURPOSE

The aim of this study was to determine if there is an association between ADHD medication usage and changes in intermittent exotropia among children with dual diagnoses of ADHD and intermittent exotropia. On the one hand, published case reports have demonstrated an improvement in exotropia with stimulant medication administration. On the other hand, there exist no systematic, larger scale studies on this topic. We thus considered it a worthwhile contribution to the fields of pediatric ophthalmology and child psychiatry to investigate if any such association between ADHD medications and intermittent exotropia exists.

We aimed specifically to:

- 1) Investigate the changes in exotropic deviation, stereoacuity, and control that occur in intermittent exotropia patients taking ADHD medications.
- 2) Characterize the individual trends of specific ADHD stimulant and non-stimulant medications with changes in intermittent exotropia.
- 3) Determine if there is any association between ADHD medication use and prevention of patients from requiring strabismus surgery.

## METHODS

*Student Contributions:* The idea for the study was originally conceived by Dr. Martha Howard. Dr. Martha Howard and Dr. Marez Megalla submitted the study protocol to the Institutional Review Board. I was responsible for the initial patient screening process, data collection, data analysis, review of literature, and writing of the manuscript. Dr. Martha Howard and Dr. Marez Megalla both contributed to editing of the manuscript and general guidance of the study.

*Human Subjects Research:* The study, along with a waiver of consent, was approved by the Institutional Review Board of the Yale University School of Medicine. The identities of patients in the study were protected in a secure encrypted Yale Box folder throughout the duration of the study. Pregnant women and prisoners were excluded from this study.

### *Methods Description:*

The Joint Data Analytics Team (JDAT) at Yale University compiled a list of all patients in the Yale electronic medical record (EMR) from 2005 to 2020 who carried diagnoses of both X(T) and ADHD based on ICD 10 codes. Patients with the following conditions were excluded: pregnancy, thyroid disease, cranial nerve palsies, sensory exotropia, and incarceration.

For each patient, the following variables were collected if available in the EMR: age, sex, ADHD medications used, dosage of medication, medication start and end dates, date of ADHD

diagnosis, date of X(T) diagnosis, dates of strabismus surgeries, and presence of developmental disorders.

For each strabismus appointment recorded for a patient, the following variables were collected: date of appointment, strabismus measurements at near and distance, visual acuity, stereoacuity with the Stereo Fly Test, presence or absence of amblyopia, grade of X(T) control according to the Mohny and Holmes scale, presence or absence of symptomatic diplopia, strabismus treatments being used at the time of appointment, and the presence or absence of refractive correction.<sup>29</sup>

The following comprehensive list of ADHD medications was used to search the electronic medical records of the cohort to establish what was prescribed for each patient:

methylphenidate, dexamethylphenidate, amphetamine, dextroamphetamine, methamphetamine, lisdexamfetamine, atomoxetine, clonidine, guanfacine, bupropion, and viloxazine. The different brand names of each of these medications were also included in the search.

The data collected for each patient was qualitatively analyzed for trends in X(T) deviation, stereoacuity, grade of control, and amblyopia during active use of ADHD medications compared to when they were on no treatment. Intermittent exotropia deviations were also averaged and compared across all measurements taken while on and off ADHD medication. Criteria for defining what qualified as a change were: X(T) deviation change of  $\geq 10$  prism diopters (PD),



stereoacuity change of at least two octaves as suggested by Adams et al., and grade of control change from 0-2 to 3-5 or vice versa.<sup>30</sup> The timing of strabismus appointments was also considered in relation to the duration of action of the medications patients were taking, and only strabismus appointments taken within the window of biologic activity of a medication were included for analysis.

A comprehensive literature search was also conducted to find all published research articles studying and reporting associations between ADHD medication use and intermittent exotropia. From PubMed, the MeSH search of “(‘Attention Deficit Disorder with Hyperactivity’[MeSH] OR ADHD OR ‘Central Nervous System Stimulants’[MeSH]) AND (‘Visual Acuity’[MeSH] OR ‘Strabismus’[MeSH])” yielded 45 results, of which five were articles were deemed relevant and included in this thesis. On SCOPUS, the search (“ADHD” OR “Stimulant”) AND (“Exotropia” OR “Strabismus” OR “Visual Acuity”)) yielded 138 results, of which eight were relevant articles. On Web of Science, the search (“ADHD” OR “Stimulant”) AND (“Exotropia” OR “Strabismus” OR “Visual Acuity”)) yielded 44 results, of which four were relevant articles. The eight relevant results from SCOPUS included all the articles from the searches on the other databases.

## RESULTS

JDAT originally identified 167 patients according to the defined eligibility criteria. Of the total, 159 were ineligible for the study due to lack of follow-up appointments, absence of recorded ADHD medication use, presence of sensory exotropia/esotropia/cranial nerve palsies, and/or lack of strabismus measurements while off medications. Eight patients (5 male, 3 female; ages 7-19 years) were included for analysis. Three of these eight patients had comorbid developmental delay or autism. Five patients had sufficient information regarding the date of diagnosis of ADHD to compare the timing of ADHD and X(T) diagnoses. In three of these patients, X(T) was diagnosed first. In two of these patients, ADHD was diagnosed first.

Intermittent exotropia at near remained stable in seven patients following ADHD medication use and worsened in one patient. X(T) at distance remained stable following ADHD medication use in six patients, worsened in one patient, and improved in one patient. When X(T) deviations were averaged across all subjects, deviation at near and distance remained stable with medication use. At near, average deviation was 11.9 PD off medication and 17.1 PD on medication. Average X(T) deviation at distance was 18.7 PD off medication and 13.5 PD on medication.

Stereoacuity worsened by  $\geq$  two octaves in two patients and remained stable in five patients who had stereoacuity data available. Of the four patients with data on grade of control, control remained stable in two and worsened in two patients. One patient had worsening amblyopia

while taking ADHD medications. Five of the eight patients required strabismus surgery to correct their intermittent exotropia; three of these patients required surgery while taking medication, and two patients after they had discontinued their ADHD medication.

Most ADHD medications had no effect on X(T). Atomoxetine was the only medication associated with improved X(T) deviation (n=1), while dexamethylphenidate was the only medication that was associated with decreased stereoacuity (n=2). A decrease in control was associated with clonidine and methylphenidate (n=2). Table 1 shows the changes in exotropia associated with the use of each individual medication or combination of medications.

**Table 1: Summary of Associations of Individual Medications with Strabismus Changes\***

<b>Medication(s) Duration of Action</b>	<b>Change in Deviation at Near (# of patients)</b>	<b>Change in Deviation at Distance (# of patients)</b>	<b>Change in Stereoacuity (# of patients)</b>	<b>Change in Grade of Control (# of patients)</b>
<b>Dexamethylphenidate 4 hours</b>	Stable: 1	Stable: 1	Worse: 1	N/A
<b>Guanfacine 6-12 hours</b>	Stable: 2	Stable: 2	Stable: 2	N/A
<b>Methylphenidate 7-12 hours</b>	Stable: 3	Stable: 3	Stable: 3	Stable: 1 Worse: 1
<b>Clonidine 12 hours</b>	Stable: 1	Stable: 1	Stable: 1	N/A
<b>Atomoxetine 24 hours</b>	Stable: 1	Improve: 1	Stable: 1	Stable: 1
<b>Dexamethylphenidate/Guanfacine ER 4 hours/8-12 hours</b>	Worse: 1	Worse: 1	Worse: 1	N/A
<b>Clonidine/Methylphenidate ER 12 hours/10-12 hours</b>	Stable: 1	Stable: 1	Stable: 1	Worse: 1
<b>Atomoxetine/Methylphenidate XR 24 hours/10-12 hours</b>	Stable: 1	Improve: 1	Stable: 1	Stable: 1
<b>Guanfacine/Methylphenidate 6-12 hours/3-4 hours</b>	Stable: 1	Stable: 1	Stable: 1	N/A

\*Data was taken from exams performed while medications are biologically active according to duration of action. Medication durations of action sourced from American Academy of Pediatrics.<sup>31</sup>

Each patient's case description is included below.

Patient 1 is a 19-year-old male with autism who had prior surgery for X(T). He began taking dexamethylphenidate (Focalin, four hours duration of action) at age 10. His first strabismus appointment while on medication was a mid-afternoon appointment, thus the Focalin was most likely not active during the appointment. His second appointment while on medication, however, was a morning appointment, and Focalin was most likely active. When taking Focalin, his exotropic deviation remained stable (12 PD off medication vs 20 PD on medication at near, 15 PD off medication vs 16 PD on medication at distance). However, his stereoacuity worsened by more than two octaves, and he developed symptomatic diplopia while taking the medication. He subsequently required strabismus surgery six months after starting dexamethylphenidate.

Patient 2 is a 10-year-old female who was diagnosed with both ADHD and X(T) at age four and began taking clonidine (12 hours duration of action) at age five. Due to its long duration of action, the patient's medication would have been active regardless of the timing of the appointment. While on clonidine, the patient's exotropic deviation remained stable (17 PD off vs 22 PD on at near, 17 PD off vs 12 PD on at distance), as did the stereoacuity. The patient then added methylphenidate (Concerta, 10-12 hours duration of action), which was also considered active at all the patient's strabismus appointments regardless of time of day of the appointment. While taking both clonidine and Concerta, the patient's exotropic deviation and

stereoacuity remained stable (17 PD off vs 19 PD on at near, 17 PD off vs 17 PD on at distance). However, her grade of control worsened from grade zero to grade four while taking dual therapy. Despite treatment with overminused glasses, she required strabismus surgery due to worsening control, 4.5 years after initial strabismus diagnosis and less than two years after beginning dual stimulant therapy for her ADHD.

Patient 3 is a nine-year-old male who was diagnosed with intermittent exotropia at age four before being diagnosed with ADHD and starting dexamethylphenidate (Focalin, four hours duration of action) and guanfacine (Intuniv ER, 8-12 hours duration of action) at age six. The patient's single strabismus appointment while taking these medications was in the morning, so both medications would have been active at the time of this appointment. Despite patching, glasses, and atropine, the patient's X(T) worsened after starting these medications (from 13 PD off to 30 PD on at near and from 20 PD off to 30 PD on at distance), and stereoacuity worsened by four octaves. The patient also developed worsening amblyopia when he was taking these medications, with OS VA changing from 20/70 to 20/200. OD VA also worsened from 20/20 to 20/50. A subsequent MRI scan of the brain and orbits was normal. The patient was subsequently lost to follow-up.

Patient 4 is a 10-year-old male who was diagnosed with intermittent exotropia at age four and with ADHD at age six, starting treatment with methylphenidate (Ritalin, 3-5 hours duration of action) shortly after ADHD diagnosis. The patient's first strabismus appointment while on Ritalin took place in the afternoon, thus the medication was most likely not active at this appointment.

Despite treatment with glasses and patching and while remaining on treatment with methylphenidate, the patient subsequently required strabismus surgery 3.5 years after initial X(T) diagnosis due to worsening deviation and grade of control. The surgery improved but did not eliminate the patient's X(T), and shortly after surgery the patient resumed patching for mild amblyopia. The patient then started methylphenidate (Ritalin LA, 7-9 hours duration of action), and while on this medication the patient's exotropic deviation, stereoacuity, and grade of control all remained stable. Because the patient's strabismus appointment while taking short-acting Ritalin fell outside the time window of the medication's duration of action, only the patient's strabismus measurements while taking Ritalin LA were included for analysis.

Patient 5 is a 14-year-old female who was diagnosed with intermittent exotropia at age five and with ADHD at age seven. She started taking atomoxetine (Strattera, 24 hours duration of action) at age eight, during which her exotropic deviation remained stable at near (12 PD off vs 4 PD on) but improved at distance (22 PD off to 4 PD on), and stereoacuity and grade of control remained stable. A few months after starting Strattera, methylphenidate (Quillivant XR, 10-12 hours duration of action) was added to the patient's medication regimen. While on Strattera and Quillivant XR combined, exotropia at near remained stable, exotropia at distance improved although to a lesser degree than while on Strattera alone (22 PD off to 12 PD on), and stereoacuity and grade of control remained stable. The patient subsequently stopped taking Strattera, and while on Quillivant XR alone, exotropia at near and distance and stereoacuity all remained stable. After discontinuing all ADHD medications at age 11, the patient's exotropia

worsened to the degree of 30 PD deviation at distance and grade four control, consequently requiring corrective surgery two years after discontinuing ADHD medications.

Patient 6 is a 14-year-old female with developmental delay who was diagnosed with ADHD at age 11 and began taking methylphenidate (Ritalin LA, duration of action 7-9 hours) at the time of diagnosis. A year later, she was diagnosed with intermittent exotropia at a morning strabismus appointment, during which she had an exotropic deviation of 16 PD at near. She subsequently stopped taking Ritalin LA, and while her X(T) remained stable at 25 PD, her grade of control worsened to the point that exotropia was manifest 50% of the time. However, X(T) at distance and stereoacuity both remained stable on vs off the medication. Despite treatment with glasses, the patient required strabismus surgery two years after stopping her ADHD medication due to poor control.

Patient 7, a 19-year-old male with Hunter's Syndrome and developmental delay, began taking ADHD medications at age 11, beginning with guanfacine (Tenex, 6-12 hours duration of action) and methylphenidate (Ritalin, 3-4 hours duration of action). It is reasonable to assume that both Tenex and Ritalin would be clinically active at any morning appointments, while only Tenex would be active at afternoon appointments. The patient's first strabismus appointment at age 12 while on these medications was an afternoon appointment (only Tenex active), and the patient was ortho at both near and distance. The patient's second appointment, however, was a morning appointment during which both medications would have been active, and the patient exhibited an X(T) of 25 PD at near while remaining orthotropic at distance. After

stopping ADHD medications at age 15, the patient became orthotropic at near and developed an X(T) at distance of 25 PD which successfully resolved to orthophoria with glasses.

Stereoacuity remained stable across all visits.

Patient 8 is an 18-year-old male who began taking methylphenidate CR (3-5 hours duration of action) and guanfacine ER (8-12 hours duration of action) at age 11. The patient's strabismus appointments all took place in the late afternoon, thus only guanfacine ER would have been biologically active during his strabismus measurements. The patient's exotropic deviation and stereoacuity remained stable while on these medications, but due to worsening dissociated vertical deviation, the patient required strabismus surgery two years after beginning treatment for ADHD.



## DISCUSSION

Intermittent exotropia is a condition of non-constant ocular misalignment that affects roughly 1% of the population.<sup>32</sup> No pharmacotherapy exists for X(T), although cases have been reported of improvement of X(T) in patients who were given central nervous system stimulant medications.<sup>21-24</sup> To our knowledge, however, a review of the literature did not identify any systematic, larger-scale studies investigating the efficacy of stimulant medications on X(T).

We report here the largest study performed to date investigating the association of stimulant and non-stimulant ADHD medications with X(T). In a group of eight patients with both X(T) and ADHD, stimulant and non-stimulant medications did not show a consistent effect on X(T) severity, and X(T) remained stable for most patients during ADHD medication use.

Prior case reports have demonstrated improvement in X(T) with stimulant medications including dextroamphetamine and diethylpropionate, but this effect was only present within 1.5 hours following ingestion of medication and disappeared at one week after medication ingestion.<sup>21,22</sup> Dextroamphetamine is a central nervous system stimulant medication that continues to be used for ADHD, and diethylpropionate is an appetite-decreasing stimulant medication that is not used in ADHD treatment. When evaluating the pharmacokinetics of dextroamphetamine, this medication has a duration of action of four to six hours, so it is expected that its clinical effects would not be seen at one week after medication administration.

To draw conclusions from our study regarding the association of ADHD medications with changes in intermittent exotropia, it was necessary to examine the pharmacokinetic profiles of the ADHD medications the patients in our study were taking and to determine if the medications were still active at the time of the patients' strabismus appointments. When medications were biologically active, there was a trend toward stable X(T) measurements, with two exceptions: one patient improved, and one worsened. However, it is important to recognize that any effect of medication on X(T) that is not sustainable beyond a very short time window would not be clinically beneficial for patients with X(T). A medication that has a duration of action less than 12 hours would also be less biologically active later in the day when patients with X(T) tend to have worse control due to fatigue.

ADHD treatment historically started with the use of short-acting stimulant medications, but the field of child psychiatry is shifting more toward the use of longer-acting medications for primary treatment, with the addition of shorter acting medications later in the day to extend the duration of clinical efficacy. As healthcare providers are shifting toward the use of longer acting medications to treat ADHD, it is possible that any effects that stimulant medications have on intermittent exotropia will become more apparent to parents and teachers, since it will be more likely that medications will be biologically active for a longer time throughout the day. In addition, any effect would not be influenced by the timing of the patients' strabismus appointments.

Medical treatment of ADHD has also been incorporating newer drugs that have mechanisms of action different from traditional stimulant medications. For example, guanfacine is an alpha-2 receptor agonist that is increasingly being used for ADHD treatment given its long duration of action and added benefit as a sleep aid. It also avoids some of the unpleasant side effects of stimulant medications, such as weight loss, and can treat comorbid conditions like anxiety, PTSD, and tic disorder. Future studies examining the relationship between ADHD medications and intermittent exotropia will need to differentiate between non-stimulant medications and stimulant medications, as it is possible that they might have different effects on intermittent exotropia via their different mechanisms of action.

It is interesting to note that the only medication in our study that improved X(T) parameters was atomoxetine, a medication that is both one of the longest-acting medications available for ADHD treatment (24 hours duration of action) and a non-stimulant medication that functions as an alpha-2 receptor agonist. Given the shorter duration of many of the other medications patients used in our study, this finding may suggest that a beneficial effect of ADHD medications on X(T) might be seen if future studies time strabismus measurements when medications are definitively active. The case reports by Hertle et al. were able to make such measurements and consequently showed improvement in X(T).<sup>21,22</sup> Conversely, given only one patient was treated with atomoxetine, it is unclear whether it is a promising medication that might help maintain alignment for longer periods of time. Larger studies are needed with atomoxetine to clarify this potential effect.

Intermittent exotropia exhibits great variability in its behavior, making it difficult to compare our findings with the “natural course” of X(T). Intermittent exotropia was found in one study by von Noorden et al. to worsen in 75% of patients over the course of three years, remain stable in 9%, and improve in 16%, while another study by Hiles et al. reported X(T) remaining stable in 81% of patients.<sup>12,13</sup> Our findings suggest that most of our patients had X(T) that remained stable with ADHD medication use. However, other parameters like stereoacuity and grade of control are more likely to be of clinical relevance since deterioration in these parameters are the more common indications for strabismus surgery.

Strabismus surgery is usually indicated for X(T) if a patient exhibits exotropia  $\geq 50\%$  of his/her waking hours, due to the risk of subsequent visual suppression and amblyopia.<sup>1</sup> However, surgery is also offered on an elective basis if a patient’s X(T) is causing social distress or related issues with quality of life.<sup>1</sup> In addressing the question of whether ADHD medications help patients avoid strabismus surgery, we found that three patients proceeded to strabismus surgery while taking ADHD medications. The reasons leading to surgery were worsened stereoacuity in one patient, worsened control in one patient, and worsened control and alignment in one patient. In addition, two patients underwent surgery roughly two years after stopping ADHD medications. With such a limited sample size, however, it is not possible to draw conclusions from our study about whether ADHD medications keep X(T) patients from surgical intervention.

There were several limitations in our study. Our sample size was small, making it difficult to make any conclusions about our findings, particularly concerning trends in stereoacuity and grade of control. Future studies would require larger patient cohorts that would allow for statistical analysis of results as well as prospective investigations that allow for verification of stimulant medication usage and X(T) following stimulant medication use as well as the ability to take strabismus measurements within the timespan of a medication's biologic activity. Future studies could also look specifically at the most long-acting medications, such as Strattera and Methylphenidate XR, to assess their specific impact on X(T).

In summary, our study of 8 patients with X(T) and ADHD taking ADHD medications showed that patients remained predominantly stable in exotropic deviation, stereoacuity, and grade of control when taking ADHD medications. Our results show that further study would be beneficial to understand if longer-acting medications would help X(T) patients avoid the need for surgical correction.

## REFERENCES

1. Hatt SR, Gnanaraj L. Interventions for intermittent exotropia. *Cochrane Database Syst Rev.* 2013(5):CD003737.
2. Bholra R, Miller AM, Plumb RC, Kozak A, Epley KD, Levin MR, Prakalapakorn SG, Cavuoto KM. Intermittent Exotropia. EyeWiki. September 29, 2021. Accessed December 13, 2021.
3. Scott DA, Sherr EH. RERE-Related Disorders. 2019 Mar 21. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
4. Chew E, Remaley NA, Tamboli A, Zhao J, Podgor MJ, Klebanoff M. Risk factors for esotropia and exotropia. *Arch Ophthalmol.* 1994;112:1349-1354.
5. Lee SA, Sunwoo IN, Kim KW. Diverge paralysis due to a small hematoma in the tegmentum of the brainstem. *Yonsei Med J.* 1987;28(4):326-328.
6. Zou D, Casafina C, Whiteman A, Jain S. Predictors of surgical success in patients with intermittent exotropia. *J AAPOS.* 2017;21(1):15-18.
7. Al-Haddad C, Ismail K, Houry R, Sayyid SA, Moussawi ZE. Recurrence of intermittent exotropia after bilateral lateral rectus recession. *Middle East Afr J Ophthalmol.* 2020;27(2):123-127.
8. Lee CM, Sun MH, Kao LY, Lin KK, Yang ML. Factors affecting surgical outcome of intermittent exotropia. *Taiwan J Ophthalmol.* 2017;8:24-30.
9. Holmes JM, Hatt SR, Leske DA. Is intermittent exotropia a curable condition? *Eye.* 2015;29:171-176.
10. Nusz KJ, Mohny BG, Diehl NN. The course of intermittent exotropia in a population-based cohort. *Ophthalmology.* 2006;113(7):1154-1158.
11. Mohny BG, Cotter SA, Chandler DL, Holmes JM, Wallace DK, Yamada T, Petersen DB, Kraker RT, Morse CL, Melia BM, Wu R, PEDIG. Three-year observation of children age 3 to 10 years old with untreated intermittent exotropia. *Ophthalmology.* 2019;126(9):1249-1260.
12. K. VNG, Campos EC. Exodeviations. In: *Binocular Vision and Ocular Motility.* St Louis, MO: Mosby; 2002:356-413.

13. Hiles DA, Davies GT, Costenbader FD. Long-Term observations on unoperated intermittent exotropia. *Arch Ophthalmol*. 1968;80(4):436-442.
14. Mohney BG, McKenzie JA, Capo JA, Nusz KJ, Mrazek D, Diehl NN. Mental illness in young adults who had strabismus as children. *PEDIATRICS*. 2008;122(5):1033-1038.
15. Chung SA, Chang YH, Rhiu S, Lew H, Lee JB. Parent-reported symptoms of attention deficit hyperactivity disorder in children with intermittent exotropia before and after strabismus surgery. *Yonsei Med J*. 2012;53(4):806.
16. Kilgore KP, Barraza RA, Hodge DO, McKenzie JA, Mohney BG. Surgical correction of childhood intermittent exotropia and the risk of developing mental illness. *Am J Ophthalmol*. 2014;158(4):788-792.
17. Li Q, Bai J, Zhang J, Gong Q, Liu L. Assessment of cortical dysfunction in patients with intermittent exotropia: an fMRI study. *PLOS One*. 2016;11(8):e0160806.
18. He X, Hong J, Liu Z, Wang Q, Li T, Qu X, Fei N, Li W, Fu J. Decreased functional connectivity of the primary visual cortex and the correlation with clinical features in patients with intermittent exotropia. *Front Neurol*. 2021;12:638402.
19. Spencer RF, Tucker MG, Choi RY, McNeer KW. Botulinum toxin management of childhood intermittent exotropia. *Ophthalmology*. 1997;104(11):1762-1767.
20. Faraone SV. The pharmacology of amphetamine and methylphenidate: relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neurosci Biobehav Rev*. 2018;87:255-270.
21. Hertle RW, Maybodi M, Bauer RM, Walker K. Clinical and oculo-graphic response to Dexedrine in a patient with rod-cone dystrophy, exotropia, and congenital aperiodic alternating nystagmus. *Binocul Vis Strabismus Q*. 2001;16(4):259-264.
22. Hertle RW, Maybodi M, Mellow SD, Yang D. Clinical and oculo-graphic response to Tenuate Dospan (diethylpropionate) in a patient with congenital nystagmus. *Am J Ophthalmol*. 2002;133(1):159-160.
23. Tsutsui J, Watanabe S, Takaya S. Orthoptic use of bemegrade in 3 cases of exotropia. *Nihon Ganka Kyo*. 1967;18(5):593-6.
24. Tsutsui J. Pharmacological orthoptics. *Ganka*. 1967;9(2):92-9.
25. Grönlund MA, Aring E, Landgren M, Hellström A. Visual function and ocular features in children and adolescents with attention deficit hyperactivity disorder, with and without treatment with stimulants. *Eye (Lond)*. 2007;21(4):494-502.

26. Martin L, Aring E, Landgren M, Hellström A, Grönlund MA. Visual fields in children with attention-deficit/hyperactivity disorder before and after treatment with stimulants. *Acta Ophthalmol.* 2008;86(3):259-64.
27. Redondo B, Molina R, Vera J, Muñoz-Hoyos A, Barrett BT, Jiménez R. Accommodative response in children with attention deficit hyperactivity disorder (ADHD): the influence of accommodation stimulus and medication. *Graefes Arch Clin Exp Ophthalmol.* 2020;258(6):1299-1307.
28. Soyer J, Jean-Louis J, Ospina LH, Bélanger SA, Bussièeres JF, Kleiber N. Visual disorders with psychostimulants: a paediatric case report. *Paediatr Child Health.* 2019;24(3):153-155.
29. Mohny BG, Holmes JM. An office-based scale for assessing control in intermittent exotropia. *Strabismus.* 2006;14(3):147-150.
30. Adams WE, Leske DA, Hatt SR, Holmes JM. Defining real change in measures of stereoacuity. *Ophthalmology.* 2009;116(2):281-285.
31. American Academy of Pediatrics. Common ADHD Medications and Treatments for Children. Healthy Children. September 27, 2019. Accessed December 14, 2021.
32. Govindan M, Mohny BG, Diehl NN, Burke JP. Incidence and types of childhood exotropia: a population-based study. *Ophthalmology.* 2005;112(1):104-8.