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The Effectiveness of Non-Stimulants for the Treatment of Attention Deficit Hyperactivity Disorder in the Pediatric Population

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by

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a complex psychiatric disorder, commonly of childhood onset, with profound implications when ineffectively treated. The core symptoms of inattention, hyperactivity, and impulsivity have implications on social interactions, educational performance, relationships, and emotional stability (National Institute of Mental Health, 2017). There is a growing interest for the use of non-stimulant medications due to the concern over stimulants abuse potential and other adverse effects. The purpose of this literature review was to increase the knowledge of Advanced Practice Psychiatric Nurses (APPNs) on the effectiveness of non-stimulants for the treatment of ADHD in the pediatric population. More specifically, the research on the non-stimulants atomoxetine, clonidine extended-release (ER) and guanfacine ER will be analyzed. APPNs have the obligation under their the scope of practice to stay current on evidence-based practice, promote research, and provide holistic care to the psychiatric mental health population (American Nurses Association, 2014). By increasing their knowledge, APPNs will further their ability to provide safe and effective care to the pediatric population with ADHD. Furthermore, this knowledge can be used to share with patients and their families during collaborative treatment planning. This paper was designed to review current research articles from 2007 to present on three ADHD specific non-stimulant medications. A review of literature was performed using Harley E. French Library of the Health Sciences utilizing the search engines of CINAHL, PubMed, and PsycInfo. The literature reviewed found statistically significant results supporting these non-stimulants as effective medications for children and adolescents with ADHD.

The Effectiveness of Non-Stimulants for the Treatment of Attention Deficit Hyperactivity Disorder in the Pediatric Population

Attention deficit hyperactivity disorder (ADHD) is defined as a neurobehavioral/neurodevelopmental disorder primarily of childhood onset. Inattention, hyperactivity, and impulsivity are labeled as core symptoms of ADHD, which are also the main symptoms that are targeted by psychotropic medications (National Institute of Mental Health, 2017). However, targeting these core symptoms with medications has been difficult. The common use of stimulants has been under scrutiny by parents/guardians, media, and health care professionals due to their abuse potential and other adverse effects like appetite suppression and insomnia (Lakhan & Kirchgessner, 2012). Therefore, there is a demand to find medications that are safe and effective. Thus, the growing interest for non-stimulants has emerged to treat ADHD.

According to the American Psychiatric Association (2013), 5% of children have ADHD. There is new criteria for ADHD in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V), thus it is estimated that the prevalence may be closer to 8-12% (Botero-Franco, Palacio-Ortiz, Arroyave-Sierra, & Pineros-Ortiz, 2016). With the increase in the number of children being diagnosed with ADHD, the number of children being treated with medications is also increasing. Among adolescents, it is the most prevailing behavioral disorder and most common reason to seek treatment for behavioral concerns (Hogue, Bobek, Tau, & Levin, 2014). It is estimated that there has been a 28% increase in the pharmacological treatment of ADHD in children from 2007 to 2012 (Centers for Disease Control and Prevention, 2017). With the increasing diagnoses

of ADHD, use of medications, and concern over stimulants, the use of non-stimulants is also increasing in the pediatric population.

Without proper treatment, ADHD can have a profound effect on a child's development. Children with ADHD are affected in their social functioning, education, interpersonal relations, emotional stability, and family relations (National Institute of Mental Health, 2017). When there is no treatment or treatment is ineffective at treating the core symptoms, children have great difficulty thriving in school, socializing with others, coping with their symptoms, and are at increased risk for substance abuse and other co-morbid learning and behavioral disorders (Shier, Reichenbacher, Ghuman, & Ghuman, 2013). There is also growing concern over the use of stimulants and growing trend in the use of non-stimulants. Therefore, Advanced Practice Psychiatric Nurses (APPNs) should be knowledgeable in how to safely and effectively treat ADHD in children. This literature review will provide insight into the effectiveness of non-stimulants in the treatment of ADHD in the pediatric population. The focus of the literature review will be on the ADHD-specific non-stimulants atomoxetine (Strattera), clonidine ER (Kapvay), and guanfacine ER (Intuniv).

Purpose

The purpose of this literature review is to provide APPNs with current evidence-based knowledge on the effectiveness of non-stimulants to guide their prescribing decisions for the treatment of ADHD in the pediatric population. According to the American Nurses Association (2014), education is the 8th Standard of Practice under their scope and standards practice for which the APPN utilizes evidence-based research findings to enhance clinical knowledge. This literature review will also adhere to

Standard 10, Quality of Practice, by enhancing the APPN's knowledge to improve their quality of care, improve their prescriptive decision-making process and therefore enhance the outcome/effectiveness of the treatment of ADHD in the pediatric population. Furthermore, Standard 5D Prescriptive Authority and Treatment, states for the APPN to be knowledgeable in medication's efficacy, side effects, mechanism of actions, and the consumers individualized needs when using their prescriptive authority (American Nurses Association, 2014).

This paper provides education to the APPN on the effectiveness of atomoxetine (Strattera), clonidine ER (Kapvay), and guanfacine ER (Intuniv) so the APPN can use this knowledge when choosing treatment plans for children with ADHD while following the Scope and Standards of Practice by the American Nurses Association. This paper will define key terms, review and summarize current evidence-based research findings, describe search methods that were utilized for the research, and discuss the implications of these findings in regards to the APPN's role in practice, research, education, and health policy. With the growing percentage of children being diagnosed and being treated for ADHD, this knowledge is prudent to improving the quality of care the APPN delivers to this young population.

Significance

Effectively treating ADHD in the pediatric population does not come easy due to concerns regarding safety and tolerability of ADHD medications. Using stimulants to treat ADHD in children has been well researched and proven to be highly effective, however, these medications have an abuse potential and may cause undesirable side effects that cause clinicians and parents to prefer not to use these medications and look to

other medications that can be effectively used (Martinez-Raga, Ferreros, Knecht, De Alvaro, & Carabal, 2017). The desire for clinical guidelines for ADHD in pediatrics has not been overseen. The American Academy of Child and Adolescent Psychiatry (2017) is creating its first clinical practice guidelines for treating ADHD due to this demand. Furthermore, the American Academy of Pediatrics has a strong recommendation for children and adolescents to be treating with Food and Drug Association (FDA) approved ADHD medications (American Academy of Family Physicians, 2017). With the well-known and highly publicized knowledge of stimulants holding an abuse potential, the education of non-stimulants that are FDA approved for ADHD which do not have an abuse potential should also be publicized regarding their effectiveness. Since non-stimulants are gaining popularity to treat ADHD in the pediatric population, the APPN needs to be knowledge regarding the their effectiveness to treat ADHD in this population.

It is highly important to know how to effectively treat ADHD with the pediatric patient because ADHD can have negative outcomes that sustain throughout childhood and extend into adulthood. Children with ADHD have poorer academic performance which leads to an increased risk for failing or dropping out. There is also an increase in relationship problems with other children and family members (Riera, Castells, Tobias, Cunill, Blanco, & Capella, 2017). Adolescents with ADHD were found to have a poorer working memory as evident on magnetic resonance imaging in the caudate region, furthermore, abnormalities were found in the limbic, frontal, and striatal areas (Roman-Urrestarazu et al., 2016). Young adults with ADHD are more likely to have legal and substance abuse problems, and are more prone to injuries (Kovshoff, Williams, Vrijens, Danckaerts, Thompson, Yardley, & Sonuga-Barke, 2012). Overall, the toll on children

with ADHD can be exhibited on their mental health, academics, social functioning, and interpersonal relationships, which leaves them at increased risk for other comorbid mental health disorders when left untreated or ineffectively treated (National Institute of Mental Health, 2017).

The APPN's knowledge of non-stimulant effectiveness will be a valuable tool to utilize as more and more patients and families are seeking out health care providers that are specialized in psychiatry. Children with ADHD are considered a vulnerable population due to their young age and mental health diagnoses thus treatment management is best to fall under a specialized experienced clinician in this field to yield the best patient outcomes (Kovshoff, Williams, Vrijens, Danckaerts, Thompson, Yardley, & Sonuga-Barke, 2012). Due to the DSM-V changing its age criteria for symptoms to present prior to age 12 verses age 7 in the DSM-IV, it is anticipated that diagnoses will increase thus will the increase in demand for APPN's and their prescribing knowledge and authority to treatment these children (American Psychiatric Association, 2013). Without a doubt, having the knowledge of non-stimulant effectiveness will positively increase the safe and effective quality-of-care the APPN can provide the pediatric ADHD population.

Theoretical Framework

Understanding the pathophysiology of ADHD can help provide a neurobiological framework to utilize in effectively treating ADHD pharmacologically. In order to know if a medication is effective at treating a disease, one must understand the pathophysiology of the disease itself. A prescriber then can choose a medication that has a mechanism of action that targets the pathophysiology of the disease. When analyzing if a medication is

effective for a treating a disease, it should target the pathophysiology of the disease itself and result in positive clinical outcomes of improving symptomology. Under this framework, children and adolescents with ADHD will have improved outcomes because the non-stimulant medications are working to target the pathophysiology of the ADHD.

According to Stahl (2013), "in ADHD, imbalances in NE [norepinephrine] and DA [dopamine] circuits in the prefrontal cortex hypothetically causes inefficient information processing in prefrontal circuits, and thus the symptoms of ADHD" (p. 475). More specifically, the neurotransmitters dopamine (DA) and norepinephrine (NE) are decreased in the prefrontal cortical area of the brain, which results in decreased stimulation of their receptors. However, symptomology of ADHD not only results from a decrease in these neurotransmitters but also can results from an excessive amount, therefore, there needs to be a moderate level of both DA and NE for proper prefrontal cortex functioning thus improving the symptoms of ADHD. Overall, there should be a moderate amount of DA to their D_1 receptors and moderate amount of NE to their α_{2A} receptors (Banaschewski et al., 2005). In fact, "properly tuned D_1 receptor stimulation will reduce noise while α_{2A} receptor stimulation will increase the signal, resulting in appropriate prefrontal cortex functioning, guided attention, focus on a specific task, and control of emotions and impulses" (Stahl, 2013, p. 483).

Atomoxetine is known as a norepinephrine transporter (NET) inhibitor, which selectively inhibits NE reuptake in the prefrontal cortex. This reuptake inhibition causes an increase in NE and therefore an increase in DA since NETs can also transport DA. By targeting NETs, which are plentiful in the prefrontal cortex, atomoxetine can target symptoms of ADHD. Furthermore, this increase in NE and DA occurs through tonic

signaling by downregulation of any phasic actions of NE and DA resulting in the desired moderate tonic controlled release. There is also no abuse potential with atomoxetine because there are few NE neurons with NETs in the nucleus accumbens, which is known as the reward/abuse center of the brain, additionally, there is no phasic firing which occurs with immediate release stimulants (Stahl, 2013).

Another way to target NE in the prefrontal cortex is by using an α_2 receptor agonist such as clonidine. α_{2A} receptors are highly concentrated in the prefrontal cortex thus agonizing α_{2A} receptors causes an increase NE here, which then targets ADHD symptoms. Even though clonidine is an α_2 receptor agonist, it is not selective to the α_{2A} receptor. Clonidine also has actions on imidoazoline, α_{2B}, and α_{2C} receptors, which can be blamed for clonidine's side effects, but also why clonidine can also have other therapeutic effects not specific to the ADHD symptomology (Stahl, 2013). The extended-release (ER) form of clonidine known as Kapvay, allows of tonic (controlled release) of NE throughout the day.

Similar to clonidine, guanfacine is also an α_2 receptor agonist. However, guanfacine is highly selective to the α_{2A} receptor, approximately 15-60 times more selective than clonidine (Stahl, 2013). Therefore, guanfacine is more potent to the α_{2A} receptors in the prefrontal cortex in targeting the core symptoms of ADHD that are manifested in this area of the brain.

Understanding the role of the DA and NE and their receptors in ADHD is essential to guide the APPN's prescribing decision-making. Therefore, it is imperative that the APPN is also knowledgeable on the mechanism of action of non-stimulants at targeting the key neurotransmitter pathways and their receptors that are underlying the

pathogenesis of ADHD. With this knowledge, the APPN can prescribe non-stimulants knowing that their mechanism of action can effectively target the pathophysiology of ADHD leading to improved symptoms. In this review of literature, evidence-based research articles on atomoxetine (Strattera), clonidine ER (Kapvay), and guanfacine ER (Intuniv) will be discuss as well as their clinical outcomes.

Definitions

ADHD: An abbreviation for Attention Deficit Hyperactivity Disorder, which is a neurobehavioral disorder commonly of childhood onset with three primary symptoms of inattention, hyperactivity, and impulsivity (National Institute of Mental Health, 2017).

Pediatric: Generalized term for the population of children and adolescents (National Institute of Mental Health, 2017).

Children: Human being prior to puberty; ages 6-12 (National Institute of Mental Health, 2017).

Adolescents: Human being during the pubertal time; ages 13-18 (National Institute of Mental Health, 2017).

ER: An abbreviation for "extended-release" formulation of a mediation, which causes a slow, controlled-release of a medication over a longer period of time. Similar names for extended-release are SR "sustained-release" and CR "controlled-release". In some publications one may see extended-release abbreviated as XR (Stahl, 2013).

Effectiveness/efficacy: Producing the desired effect of a medication's intention (Stahl, 2013).

Statistically significant: In research, the relationship of a study's findings was not due to chance; p-value is less than 5% (Stahl, 2013).

Process

A literary search was performed using the University of North Dakota's Harley E. French Library of the Health Sciences to locate research articles on the effectiveness of non-stimulants for the treatment of ADHD in the pediatric population. The search engines of PubMed, CINAHL, and PyscInfo were utilized due to their specialization in nursing, medicine, health, life, and psychology.

The literature search began with PubMed with the use of MeSH (medical subject heading) terms and using limitation of the last 10 years, peer-reviewed, and English language. The use of the MeSH terms "ADHD" AND "pediatric" AND "atomoxetine" resulted in 129 articles, "ADHD" AND "pediatric" AND "clonidine ER" resulted in 24 articles, and "ADHD" AND "pediatric" AND "guanfacine ER" resulted in 39 articles. A review of the titles, abstracts, and keywords within the articles were scanned and 21 articles were found applicable to the literature review topic. After reading the articles, eight were chosen for inclusion into the literature review portion of the paper.

The CINAHL database was then searched using Boolean Connectors and CINAHL Headings and the limitations of 2007-2017, peer-reviewed, English language, and human subjects. "ADHD" AND "pediatric" AND "atomoxetine" was searched and resulted in 17 articles, "ADHD" AND "pediatric" AND "clonidine ER" and resulted in two articles, and "ADHD" AND "pediatric" AND "guanfacine ER" and resulted in two articles. After reviewing the articles, 13 were eliminated due to the content and age limitations not being congruent with the literature review topic and repetitive articles that were found during the PudMed search, leaving four articles that were chosen to be included in the paper.

PsycInfo was another database that was used to gather pertinent articles to the literature review topic with the use of Boolean Connectors with the same limitations as the CINAHL search. "ADHD" AND "pediatric" AND "atomoxetine" was searched and resulted in 33 articles, "ADHD" AND "pediatric" AND "clonidine ER" and resulted in seven articles, and "ADHD" AND "pediatric" AND "guanfacine ER" and resulted in seven articles. After reviewing the articles, 35 were found to not be applicable to the literature search topic or had repetitive data. Six articles were found to be repeat articles of the ones found in the PubMed and CINAHL searches and they were eliminated, leaving three articles for inclusion in the paper.

The information that is in this literature review has been obtained through the literature search, which is described above and has been formatted into an informative PowerPoint presentation (see Appendix). The PowerPoint presentation will be emailed to the University of North Dakota Psychiatric Mental Health Nurse Practitioner student class of 2018. Presenting this PowerPoint to this cohort during their senior year allows for the opportunity for them to share these findings during their clinical practicums. Increasing the knowledge of the effectiveness of non-stimulants for ADHD in the pediatric population to APPN's allows for evidence-based treatment planning for their patients.

Review of Literature

According to the American Academy of Pediatrics (2011), children with ADHD over the age of 6 have a strong recommendation, quality of evidence level A (strongest/highest recommendation), to be prescribed a food and drug administration (FDA)-approved medication for ADHD and/or behavioral therapy. Furthermore, these

guidelines state, “the evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order) (quality of evidence level A)”, (American Academy of Pediatrics, 2011, p. 2). With the support of the FDA by their approval for atomoxetine, clonidine ER, and guanfacine ER as ADHD specific non-stimulants, the APPN should be knowledgeable regarding each of these medication’s unique outcomes in targeting the symptomology of ADHD in the pediatric population. This literature review will analyze, critique, and summarize research articles that have addressed the effectiveness of these non-stimulants specifically in the pediatric population.

Atomoxetine (Strattera)

Two similar randomized control trials (RCTs) were found during this literature search that analyzed atomoxetine and a placebo. The first was a randomized, double blind placebo-controlled trial, which was conducted with atomoxetine in children and adolescents from age ranges 6-16 years old with a DSM-IV diagnosis of ADHD to determine efficacy. This trial took place in Russia, was 6-weeks long, and contained 105 patients with 72 receiving atomoxetine and 33 receiving the placebo. The results of this trial were statistically significant according to the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version (ADHD-RS-IV-Parent) scores; which includes scales for inattention, impulsivity, and hyperactivity. The comparative baseline to treatment response after 6 weeks for atomoxetine was 72.2% and the placebo 48.5% (Martenyi et al., 2010). It was also noted that patients who received atomoxetine had a more rapid clinical outcome response.

Secondly, according to Weiss, Tannock, Kratochvil, Dunn, Velez-Borras, Thomason, & Allen (2005), atomoxetine was found to be effective in treating ADHD symptoms in a RCT using atomoxatine and a placebo in 153 children with ADHD ages 8-12 years old. A similar scale was used as the previously mentioned study, however instead of parents evaluating the child, the teacher did using the ADHD-RS-IV-Teacher scale. This scale was administered at baseline and at 7 weeks resulting with the atomoxetine group having 69% decrease of at least 20% in symptoms of inattention, hyperactivity, and impulsivity compared to the placebo of 43.1% (Weiss, et al., 2005). As with the previously mentioned study, it was also found to have quick onset of symptom improvement starting at only one week.

Nagy, Häge, Coghill, Caballero, Adeyi, Anderson, and Cardo (2016) found another way to determine effectiveness of atomoxetine in children with ADHD by using the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P). In doing so, a randomized control, double-blinded trial of atomoxetine and lisdexamfetamine dimesylate was performed with 200 children with ADHD from ages 6 to 17 years old. For the focus of this literature review, only atomoxetine's effectiveness will be analyzed. The WFIRS-P "comprises 50 items, grouped into six domains (Family, Learning and School, Life Skills, Child's Self-Concept, Social Activities, and Risky Activities)" and was administered to parents or guardians at baseline and at 9 weeks (Nagy, et al., p.143, 2016). Atomoxetine was found to have statistically significant results showing a decrease in all six domains of the WFIRS-P with the largest decrease in the family, learning, and school domains.

An important limitation of these studies to note is their short duration of less than 12 weeks. Atomoxetine can take up to 12 weeks or more to reach maximum potential, therefore, any study that is less than 12 weeks may be not be resulting in the full treatment potential that atomoxetine has (Nagy, 2016). Subjective scales can also limit some of the studies validity due to its openness for human interpretation and subjectivity; however, due to the nature of the ADHD's symptomology it would be difficult to eliminate this bias. Strengths of the studies include the research designs of randomized blinded studies and specific patient populations and diagnoses. There remain gaps in the research for making more specific outcome measurement scales that are more inclusive of the patient's report, larger patient populations, and longer duration of studies.

A more recent study by Nakanishi, Ota, Iida, Yamamuro, Kishimoto, Okazaki, & Kishimoto (2017) utilized a more objective tool to measure the effectiveness of atomoxetine and the stimulant medication of methylphenidate. Oxyhemoglobin level measured by near-infrared spectroscopy (NIRS) was obtained during a stroop color-word test on 30 children with a diagnosis of ADHD ages 6-14. A probe was placed over the patient's frontal orbital regions to obtain oxyhemoglobin levels, which indicates prefrontal cortex activity. Levels were obtained every 0.1 seconds throughout the stroop color-word test, with readings averaged over 10 seconds. NIR measurements were obtained pre-treatment and 12 weeks after atomoxetine was started, which is a strength of the study by having a long enough time frame to match the therapeutic effects of atomoxetine. However, a major limitation was the small number of participants and their treatment group was not randomly assigned, a pediatric psychiatrist assigned them (with methodology unknown).

The results of the actual stroop word-color test was also analyzed which is an indicator of selective attention in execute functioning, known to be decreased in children with ADHD. There were statistically significant improvements in the stroop color-word test from pre-medication to 12 weeks after starting atomoxetine. It was also noted that there was positive correlation between age and scores. Furthermore, the NIRS oxyhemoglobin levels had substantial increases from pre-medication to 12 weeks after the start of atomoxetine. More specifically, the left lateral frontal lobe had the greatest increase in oxyhemoglobin levels. Interesting to note, although beyond the scope of this literature review, methylphenidate did not show any improvement in oxyhemoglobin levels (Nakanishi et al., 2017).

The meta-analysis by Schwartz & Correll (2014) helped pull together results of 25 double-blinded RCTs that used atomoxetine and a placebo with children with ADHD. Again, the results favored atomoxetine over the placebo, 44.6% of patients had improvement of symptoms of 40% or higher. However, there were 39.9% of patients who did not respond with over 25% improvement of their symptoms. The results were similar throughout the childhood years and results did not differ from children to adolescents. Therefore, the authors agreed that there are patient specific factors that need further research in why some pediatric patients respond well and other do not. When reviewing the studies, the authors felt that limitations for this RCT is generalizing the results to the whole pediatric ADHD population because only certain patients may be exposed to the opportunity to participate in these studies.

Clinical trials, as mentioned above, have shown atomoxetine to be effective at targeting the core symptoms of ADHD in children. There are factors that affect

atomoxetine's effectiveness. In order for atomoxetine to be effective it must be dosed appropriately and maintained in a therapeutic window. Children who lack the CYP2D6 enzymatic pathway or are rapid metabolizers will have a difficult time metabolizing the medication and maintaining that therapeutic window; therefore, the FDA makes prescribers aware of these dosing instructions for CYP2D6 sensitive children on its packaging label (Dean, 2012).

A review of literature by Kohn, Tsang, & Clarke (2012) concluded atomoxetine to be efficacious in children who also have anxiety or tic related disorders. The efficacy also was not altered by other comorbid conditions and allowed for atomoxetine to maintain a therapeutic effect. In addition, health related quality of life results were positively correlated with short and longer-term studies of atomoxetine in children with ADHD.

Clonidine ER (Kapvay)

Clonidine ER, the generic form is labeled Kapvay, is the only formulation of clonidine that is approved by the FDA for the treatment of ADHD in the pediatric population (immediate release is not). A systemic review by Chan, Fogler, & Hammerness (2016) found clonidine ER effective as monotherapy and as an adjunct with stimulants therapy for children with ADHD ages 6-17. Studies regarding the effects of clonidine ER monotherpay are limited due to a greater interest in clonidine ER/stimulant combination therapy.

As with atomoxetine, there was been a couple statistically significant RCTs performed using a placebo-control to determine the effectiveness of clonidine ER. A shorter RCT of only 8 weeks compared clonidine ER and a placebo looking at various

aspects of ADHD in children ages 6-17 years old. Statistically significant improvements were found between pre-medication and at the 8-week mark on scales of ADHD-RS-IV, Conner's Parent Rating Scale, Parent Global Assessment, and Clinical Global Impression of Improvement and Severity Scales. As with atomoxetine, clonidine ER demonstrated a quick response to treatment starting as soon as two weeks. A major limitation of this study is the short duration of the study and that it only had a sample size of 236 patients. The study also required same dose titrations during this 8-week period; which limits the individual therapeutic needs of the patient (Jain, Segal, Kollins, & Khayrallah, 2011).

Palumbo, Sallee, Pelham, Bukstein, Daviss, & McDermott, (2008) published a slightly longer RCT of 16 weeks, which strengthens the study, however, it was performed on only 122 children ages 7-12, which then limits the study due to its small size. Clonidine ER, methylphenidate, or a combination of the two medications were analyzed at pre-medication and every 4 weeks for a total of 16 weeks using 3 different scales: Conners Teachers Abbreviated Symptom Questionnaire, Conner's Abbreviated Symptom Questionnaire for Parents and Children's Global Assessment Scale.

Each scale produced differing results regarding the efficacy of clonidine ER. The Conner's Teachers Abbreviated Symptom Questionnaire did not result in improvement of ADHD symptoms in the clonidine ER monotherapy group, but did show improvement in the combination of clonidine ER/methylphenidate group. The Conner's Abbreviated Symptom Questionnaire for Parents and Children's Global Assessment Scale however did show improvement in ADHD symptoms whether it was in the clonidine ER monotherapy group or the combination group. Even though the results were not robust for clonidine ER, the authors believe clonidine ER is efficacious for certain ADHD patient subtypes

such as those with co-morbid behavioral and/or impulsive disorders (Palumbo et al., 2008).

To look even further into the efficacy of adding clonidine ER to stimulants, Kollins, Jain, Brams, Segal, Findling, Wigal, & Khayrallah, (2011), published a randomized double-blinded trial that used either clonidine ER or a placebo to a current stimulant treatment plan that was not effective. Clonidine ER was not evaluated as monotherapy. There were a total of 198 children and adolescents enrolled over this 8-week study. A strength of this study was reported to be a diverse patient population of males, females, children and adolescents. Limitations include excluding comorbid disorders; which eliminates many of the ADHD populations that have co-existing learning or behavioral disorders, and the variability in stimulant medications.

The ADHD-RS-IV scale was administered at baseline, week 2, week 5, then weekly through out the 8 week study. At week 2 there was no differences from baseline scores between the clonidine ER combination group and the placebo combination group. Starting at week 5 the clonidine ER combination group started to show statistically significant results, which continued throughout the remainder of the study. Hyperactivity and inattention subscale scores with the ADHD-RS-IV were analyzed showing statistical significant is these subcategories. To strengthen this study, the Conner Parent Rating Scale, Clinical Global Impression of Severity and Improvement, and Parent Global Assessment were also analyzed at the same week intervals as the primary ADHD-RS-IV scale and were all found to have statistically significant improvements in their scores for the clonidine ER combination group (Kollins et al., 2011).

Guanfacine ER (Intuniv)

In 2009, the FDA approved the extended release form of guanfacine ER called Intuniv. A literature review by Strange (2008) found guanfacine ER to have profound effects on executive functioning in children by improved attention spans, impulse control, planning, working memory, and distractibility. This is in support of the theory of guanfacine's mechanism of action working in the prefrontal cortex. Improvements in behaviors and motor control can be attributed to guanfacine's effects on the noradrenergic projections to the basal ganglia and cerebellum.

Two RCTs had profound impacts on the FDA decision to approve guanfacine ER in the pediatric population for ADHD. Sallee et al. (2009) published an RCT that was a double-blinded comparison of guanfacine ER and a placebo; the guanfacine ER group was divided into 3 separate dosage groups. Three hundred twenty-nine children and adolescents aged 6 to 17 years old were evaluated with the ADHD-RS-IV scale prior to the start of the trial and 9 weeks after the start of the trial. Averaged improvements in ADHD-RS-IV was reported for all three guanfacine ER dosage groups showing a reduction in score of 19.6, compared to the placebo which had a reduction of 12.2. More specifically, the subscales of the ADHD-RS-IV scale in categories of inattention, hyperactivity, and impulsivity, all had significantly improved scores in the guanfacine ER groups over the placebo group. Strict inclusion and exclusion criteria were strengths of the study with limitations included a short 9-week trial duration and a small number of adolescents compared to children (Sallee et al., 2009).

A very similar double-blind RCT of 345 children and adolescents (ages 6-17 years old) also compared guanfacine ER with 3 different dosage groups and a placebo.

Efficacy was also determined using the ADHD-RS-IV scale prior to the start of the trial and at 8 weeks. Again, subscales for inattention, hyperactivity, and impulsivity were analyzed with all categories resulting in statistically significant improvement in the guanfacine ER groups. The average changes in scores for the guanfacine ER groups were 17.16 and the placebo group was 8.48 (Biederman, Melmed, Patel, McBurnett, Konow, Lyne, & Scherer, 2008). This study also used secondary efficacy scales of Clinical Global Impression of Improvement, Parent's Global Assessment, Conner's Parent and Teacher Rating Scale–Revised, and Conner's' Teacher Rating Scale–Revised and found significant improvements in the guanfacine ER groups. Again, this study was limited by its short duration.

These two RCTs provided valid statistically significant results as indicated by the ADHD-RS-IV scale and subscales. Monotherapy for guanfacine ER for ADHD in the pediatric population was found to be efficacious. A literature review by Faraone, McBurnett, Sallee, Steeber, & López (2013) found varying results in the efficacy onset of action for guanfacine ER, ranging from 1-4 weeks. In addition, guanfacine ER was found to be favorable for pediatric patients with ADHD that had dominant oppositional symptoms.

In 2011, the FDA approved guanfacine ER as an adjunct to stimulant treatment for pediatric patients with ADHD aged 6-17. This combination was found to be beneficial in children who were not experiencing the full treatment potential of stimulant medications. In addition, ADHD-RS-IV scores saw improvements with guanfacine ER/stimulant combination therapy in children with opposition symptoms and those without (Childress & Berry, 2012).

The pivotal RCT approving guanfacine ER/stimulant combination treatment efficacious, was published by Wilens, Bukstein, Brams, Cutler, Childress, Rugino, & Youcha, (2012). This was a larger scale study of 461 participants of children and adolescents with ADHD aged 6-17. It was double-blinded with participants randomly adding either guanfacine ER or a placebo to their current stimulant medication. A strength of this study was that it also used the ADHD-RS-IV scale, which has been commonly used in other ADHD medication trials. A limitation of this study was the possible difficulty of assessing efficacy because a requirement was for a partial response in stimulant therapy already before entering the trial. A shorter duration of 9 weeks was another reported limitation.

Scores from the ADHD-RS-IV scale and subscales, in addition, Clinical Global Impressions of Severity of Illness and Improvement scales were averaged for the guanfacine ER/stimulant group and placebo/stimulant group. There were significant improvements in scores for all assessment scales for the guanfacine ER/stimulant group verses the placebo/stimulant group. The study had also compared morning and evening doses of each treatment group. When analyzing the guanfacine ER/stimulant treatment group, there were no differences in assessment scales for efficacy whether the medication was administered in the am or pm. Overall, guanfacine ER was shown effective as an adjunct to stimulant therapy for children and adolescents with ADHD (Wilens et al., 2012).

Results

The comprehensive literature search through CINAHL, PubMed, and PsycInfo resulted in 15 articles that were reviewed, evaluated, and deemed relevant to the literature

review topic of the effectiveness of non-stimulants in the treatment of ADHD in the pediatric population. A summary of the type of studies within these 15 articles include nine RCTs, three literature reviews, one non-randomized study, one meta-analysis, and one systemic review. RCT studies were found to be very beneficial because there was elaboration on the specific types of outcome measurement tools that were utilized. The most common scale that was used was the ADHD-RS-IV-Parent and the Clinical Global Impression and Severity Scale. Other scales that were also utilized were the ADHD-RS-IV-Teacher, WRIRS-P, Connors Parents and Teacher Rating Scale, and the Parent Global Scale. Most of these scales had either a parent/guardian or teacher completing the scale. The non-randomized study did not use a scale; the Stroop Word-Color Test and NIRS score was performed instead.

Six out of 15 chosen articles studied the effectiveness of atomoxetine with all in agreement of atomoxetine as being an effective medication for the treatment of ADHD in the pediatric population. The articles had statistically significant results supporting atomoxetine's effectiveness and two found atomoxetine to have more rapid onset than the placebo. One study found the NIRS (near-infrared spectroscopy) exam to have increased prefrontal cortex activity especially in the left lateral frontal lobe when on atomoxetine.

Four out of the total 15 articles found clonidine ER to have statistically significant results supporting its efficacy for the treatment of ADHD in the pediatric population. Two out of the three RCT's compared the effectiveness of clonidine ER as an adjunct medication to stimulant treatment. The systemic review highly supported the use of clonidine ER as an adjunct medication to stimulant therapy and found clonidine ER to be more helpful with behavioral symptoms.

Five out of the total 15 articles also found guanfacine ER to have statistically significant results. Guanfacine ER was found to be an effective adjunct to stimulant treatment in 3 out of the 5 articles. One article found guanfacine ER to be specifically efficacious in children with oppositional symptoms.

All 15 articles found atomoxetine, clonidine ER, and guanfacine ER as effective non-stimulants to treat ADHD in the pediatric population. The scales that were utilized measured inattention, hyperactivity, and impulsivity; also, depending on the scale, measured domains such as family, social, and psychological symptoms. These outcome measurement scales varied between research studies; however, due to their similar outcomes they were measuring, their outcomes were found to be clinically significant. The PowerPoint presentation (see Appendix) will include these results along with all the other sections of this paper and will be delivered to the University of North Dakota Psychiatric Mental Health Nurse Practitioner student class of 2018. The purpose of this literature review is to increase knowledge therefore feedback regarding this literature review is not required but is welcomed.

Discussion of Implications in Nursing

Practice

Implications of this literature review can impact the APPN's practice by providing the APPN with knowledge to deliver holistic patient-centered care. The decision to choose non-stimulants over the best practice guideline of stimulants, can demonstrate how the APPN is providing holistic care by addressing all aspects of the patients needs and concerns. When parents/guardians refuse for their child to be medicated for ADHD, it is important to explore their concerns and assess their

knowledge regarding available FDA approved ADHD medications for children and adolescents. Parents/guardians may not be aware that non-stimulant medications can effectively treat ADHD in the pediatric population; therefore, the APPN should offer a complete review of medication alternatives. The content of this literature review was not conclusive to determine if a non-stimulant should be prescribed, rather it reviews an option for treatment. Additional factors when prescribing that go beyond the scope of this literature review should be assessments for side effects, drug interactions, co-existing medical conditions, allergies, etc.

Due to the potential adverse outcomes that can occur if children and adolescents are not effectively treated for ADHD, the APPN should strive for providing the most up-to-date, comprehensive, knowledgeable care. It is important to not become stagnant in one's practice. Continuing to educate oneself is essential as new evidence-based research becomes published and understanding of the brain and how it relates to mental illness is ever increasing.

Research

The literature search and review of articles did reveal quantity and quality of research on the topic of non-stimulant effectiveness for ADHD treatment in the pediatric population. There was an abundance of research regarding stimulant treatment for ADHD and ADHD treatment for adults not used in this review. The literature search resulted in 15 articles that were specific to the ADHD pediatric population, which was very small compared to the search for the adult ADHD population. Furthermore, there was difficulty in finding research that was purely measuring the effectiveness of a non-stimulant. Many articles evaluated stimulant therapy and/or stimulant with adjunct non-

stimulant therapy. This was found to be particularly true when researching clonidine ER and guanfacine ER. These two non-stimulants had more research regarding their effectiveness when used as an adjunct with stimulants than atomoxetine did. Additional research would be beneficial to support clonidine ER and guanfacine ER as monotherapy medication treatment for ADHD in children and adolescents.

Even though the research articles provided statistically significant results, there was contrast throughout studies regarding outcome measurement scales. To ensure consistency and validity in research, standardized outcome measurement scales would be preferred. Interesting to note, most scales used were given to parent/guardians or teachers. More research is needed to determine what outcome measurement scale is best to determine effectiveness of a medication for pediatric patients with ADHD. A scale that also incorporates the patient's input may be useful.

In addition, limitations within each study could be improved upon. Sample size and duration of study were common limitations that are mendable. With the understanding of non-stimulant's mechanism of action in regards to duration time of peak effectiveness, proper study durations could be utilized. It is common for studies to have smaller sample sizes for pediatric research patients due to ethical concerns. However, larger samples sizes will increase validity and statistically significant results. Ongoing research is necessary to keep information current on the effectiveness of these and other medications for the treatment of ADHD.

Education

The purpose of this literature review is to give education to APPNs by providing information on the effectiveness of non-stimulants for children and adolescents with

ADHD. By presentation of a PowerPoint prepared educational tool, APPNs may gain knowledge of the research articles that have been published which have contributed to the FDA's decision to approve atomoxetine, clonidine ER, and guanfacine ER as non-stimulant treatment for ADHD in the pediatric population. The knowledge gained from this educational tool can be used for increasing the treatment options of children and adolescents with ADHD.

Understanding the mechanism of action of the non-stimulants, as described previously, is important when determining what medication is best for a patient. It is important for the APPN to be educated on medications, including their evidence-based research. That knowledge can be used not only for treatment decisions but also for providing pyschoeducation to their patients (American Nurses Association, 2014). With knowledge of the evidence-based research, the APPN can educate the patient and their parents/guardians regarding its effectiveness and how the medication will target the core symptoms of ADHD.

Health Policy

Implications of the findings of this literature review can be used as part of an educational tool to make changes to health policies at varying levels. Policies at hospitals, outpatient settings, and state levels can be impacted by the results of this literature review by APPN's advocating for updated policies for treatment options. Furthermore, the APPN can support continuing research by seeking out research studies and supporting their clients they choose to enroll.

Conclusion

ADHD is a complex disorder with the potential to leave profound effects on one's childhood and development when not treated effectively. This literature review focused on the effectiveness of non-stimulants for the treatment of ADHD in the pediatric population and found statistically significant results supporting their use. The literary search of atomoxetine, clonidine ER, and guanfacine ER found statistically significant results despite the use of differing yet similar outcome measurement scales. Even though the research proved significant results, which helped support the FDA in approving these non-stimulants for the treatment of ADHD in children and adolescents, continuing research is need to maintain these medications as treatment options for this population. The reviewed research studies were found to have limitations due to their short study duration. There is a need for more research studies with longer duration, greater sample size, and with a focused monotherapy experimental group to strength the validity of their findings.

With the results of this literature review and the developed educational PowerPoint tool, the APPN can make more knowledgeable decisions during treatment planning for their pediatric patient with ADHD. In addition to the APPN having increased knowledge to make their educated decision, the APPN will also have another educational tool to utilize during medication education with parent/guardians and the patient. The APPN will be equipped to engage in comprehensive treatment planning with families. Providing optimal quality of care to children and adolescents with ADHD gives these clients the opportunity for growth and development similar to their peers not affected by this condition. This literature review demonstrates that APPNs need to stay

informed of current research findings on ADHD treatment and support ongoing research of evidence-based treatment options in this area. It would be anticipated that APPNs who empower themselves with this type of knowledge would have professional growth and satisfaction in delivering care to pediatric patients with ADHD.

Appendix

Effectiveness of Non-Stimulants for the Treatment of Attention Deficit Hyperactivity Disorder in the Pediatric Population

This is a presentation of a literature review by:
Rebecca Gonzalez, Psychiatric Mental Health Nurse Practitioner student

Introduction to ADHD

- Neurobehavioral/ neurodevelopmental disorder
- Primarily of childhood onset
- Core symptoms: inattention, hyperactivity, impulsivity
- Core symptoms are targeted by pharmacology
  (National Institute of Mental Health, 2017)

- According to the American Psychiatric Association (2013), 5% of children have ADHD
- There is new criteria for ADHD in the DSM-V, thus it is estimated that the prevalence may be closer to 8-12%
  (Botero-Franco, Palacio-Ortiz, Arroyave-Sierra, & Pineros-Ortiz, 2016)

Introduction to the use of non-stimulants for ADHD

- There is a 28% increase in the pharmacological treatment of ADHD in children from 2007 to 2012 (Centers for Disease Control and Prevention, 2017)
- Implication of ineffective treatment include: difficulty with school performance, socializing with others, coping skills, & there is an increased risk for substance abuse and other co-morbid learning and behavioral disorders (Shier, Reichenbacher, Ghuman, & Ghuman, 2013)
- Use of non-stimulants is increasing due to…the increasing diagnoses of ADHD, increased pharmacological treatment, and concern over stimulants

This literature review analyzed the effectiveness of the 3 FDA approved non-stimulants

atomoxetine (Strattera)
clonidine ER (Kapvay)
guanfacine ER (Intuniv)

Purpose

Provide APPNs with current evidence-based knowledge on the effectiveness of non-stimulants to guide their prescribing decisions for the treatment of ADHD in the pediatric population

This knowledge is pertinent for APPNs to follow their Scope and Standards of Practice by the American Nurses Association

- 8th Standard of Practice-EDUCATION: APPN utilizes evidence-based research findings to enhance clinical knowledge
- 10th Standard of Practice-QUALITY OF PRACTICE: Enhancing the APPN's knowledge to improve their quality of care, improving their prescriptive decision-making process and therefore enhancing the outcome/effectiveness of the treatment of ADHD in the pediatric population
- 5D Standard of Practice-PRESCRIPTIVE AUTHORITY and TREATMENT: To be knowledgeable in medication's efficacy, side effects, mechanism of actions, and the consumers individualized needs when using their prescriptive authority

(American Nurses Association, 2014)

Significance

- Using stimulants to treat ADHD in children has been well researched and proven to be highly effective, however, they hold an abuse potential and cause many undesirable side effects that cause clinicians and parents to prefer not to use these medications and look to non-stimulants
  (Martinez-Raga, Ferreros, Knecht, De Alvaro, & Carabal, 2017)

- American Academy of Pediatrics has a strong recommendation for children and adolescents to be treated with FDA approved ADHD medications
  (American Academy of Family Physicians, 2017)

Significance

It is highly important to know how to effectively treat ADHD in the pediatric patient due to ADHD's potential negative outcomes that sustain throughout childhood and extend into adulthood which are…

- Poorer academic performance which leads to an increased risk for failing or dropping out
- Relationship difficulties with peers and family members
- Poorer working memory
- More likely to have legal and substance abuse problems
- More prone to injuries
- Increased risk for other comorbid mental health disorders

(Riera, Castells, Tobias, Cunill, Blanco, & Capella, 2017; Roman-Urrestarazu et al., 2016; Kovshoff, Williams, Vrijens, Danckaerts, Thompson, Yardley, & Sonuga-Barke, 2012; National Institute of Mental Health, 2017)

Theoretical Framework

APPN should understand the pathophysiology of the disease (ADHD) itself. A prescriber can then choose a medication that has a mechanism of action that targets the pathophysiology of the disease

- Understanding the role of the dopamine (DA) and norepinephrine (NE) and their receptors in ADHD is essential to guide the APPN's prescribing decision-making
- Symptomology of ADHD not only results from a decrease DA and NE but also can results from an excessive amount, therefore, there needs to be a moderate level of both DA and NE for proper prefrontal cortex functioning thus improving the symptoms of ADHD
- Overall, there should be a moderate amount of DA to their D_1 receptors and moderate amount of NE to their a_{2A} receptors

(Banaschewski et al., 2005; Stahl, 2013)

Definitions

ADHD: An abbreviation for Attention Deficit Hyperactivity Disorder, which is a neurobehavioral disorder commonly of childhood onset with three primary symptoms of inattention, hyperactivity, and impulsivity

Pediatric: Generalized term for the population of children and adolescents

Children: Human being prior to puberty; ages 6-12

Adolescents: Human being during the pubertal time; ages 13-18.

ER: An abbreviation for "extended-release" formulation of a mediation, which causes a slow, controlled-release of a medication over a longer period of time. Similar names for extended-release are SR "sustained-release" and CR "controlled-release". In some publications one may see extended-release abbreviated as XR

Effectiveness/efficacy: Producing the desired effect of a medication's intention

Statistically significant: In research, the relationship of a study's findings was not due to chance. The p-value is less than 5%.

Process

Utilized the University of North Dakota's Harley E. French Library of the Health Sciences

Search Engines and results…

- **PubMed:** 8 articles were chosen for inclusion into the literature review
  - Limitations: last 10 years, peer-reviewed, and English language
  - MeSH terms: "ADHD" AND "pediatric" AND "atomoxetine" resulted in 129 articles, "ADHD" AND "pediatric" AND "clonidine ER" resulted in 24 articles, and "ADHD" AND "pediatric" AND "guanfacine ER" resulted in 39 articles

Process

- **CINAHL:** 4 articles that were chosen to be included in the literature review
  - Limitations: 2007-2017, peer-reviewed, English language, and human subjects
  - Boolean Connectors and CINAHL Headings: “ADHD” AND “pediatric” AND “atomoxetine” was searched and resulted in 17 articles, “ADHD” AND “pediatric” AND “clonidine ER” and resulted in two articles, and “ADHD” AND “pediatric” AND “guanfacine ER” and resulted in two articles

- **PsycInfo:** 3 articles that were chosen to be included in the literature review
  - Limitations: 2007-2017, peer-reviewed, English language, and human subjects
  - Boolean Connectors: “ADHD” AND “pediatric” AND “atomoxetine” was searched and resulted in 33 articles, “ADHD” AND “pediatric” AND “clonidine ER” and resulted in seven articles, and “ADHD” AND “pediatric” AND “guanfacine ER” and resulted in seven articles

Review of Literature

Strong recommendation, **level A** to be prescribed a FDA approved medication for ADHD and/or behavioral therapy

"The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order)" (American Academy of Pediatrics, 2011, p. 2)

Literature Review: **Atomoxetine (Strattera)**

- Double blind placebo-control Randomized Control Trial (RCT):
  - Children/adolescents aged 6-16 years old with ADHD
  - Took place in Russia
  - Duration of 6-weeks long
  - Contained 105 patients with 72 receiving atomoxetine and 33 receiving the placebo
  - Results of this trial were statistically significant according to the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version (ADHD-RS-IV-Parent) scores
  - Comparative baseline to treatment response after 6 weeks for atomoxetine was 72.2% and the placebo 48.5%
  - Patients who received atomoxetine had a more rapid clinical outcome response

(Martenyi et al., 2010)

Literature Review: **Atomoxetine (Strattera)**

- Double blind placebo-control RCT
  - 153 children with ADHD ages 8-12 years old
  - 7 week duration
  - ADHDRS-IV-Teacher scale
  - Atomoxetine group having 69% decrease of at least 20% in symptoms of inattention, hyperactivity, and impulsivity compared to the placebo of 43.1%
  - Atomoxetine was found to have quick onset of symptom improvement starting at only one week

(Weiss, et al., 2005)

Literature Review: **Atomoxetine (Strattera)**

- Double blind RCT comparing Strattera and Vyvanse
  - 200 children with ADHD from ages 6 to 17 years old
  - Duration of 9 weeks
  - Used the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P)
  - Atomoxetine was found to have statistically significant results showing a decrease in all six domains of the WFIRS-P with the largest decrease in the family, learning, and school domains
- Limitations of these RTCs: short duration (atomoxetine can take up to 12 weeks or more to reach maximum potential), subjective scales, sample size
- Strengths of these RTCs: research designs of randomized blinded studies, specific patient populations, and diagnoses

(Nagy, 2016)

Literature Review: **Atomoxetine (Strattera)**

- Non-randomized trial measured the effectiveness of atomoxetine and the stimulant medication methylphenidate
  - 30 children with a diagnosis of ADHD ages 6-14
  - 12 week duration
  - Oxyhemoglobin levels measured by near-infrared spectroscopy (NIRS) was obtained during a Stroop Color-Word Test
  - Statistically significant improvements in the stroop color-word test
  - Results showed a positive correlation between age and scores
  - NIRS oxyhemoglobin levels had substantial increases from pre-medication to 12 weeks after the start of atomoxetine
- Limitations: small sample size and their treatment group was not randomly assigned (assigned by a pediatric psychiatrist)
- Strength: duration of study matched duration for max effect of atomoxetine

(Nakanishi et al., 2017)

Literature Review: **Atomoxetine (Strattera)**

- Meta-analysis of 25 double-blinded RCTs that compared atomoxetine and a placebo
  - Results favored atomoxetine over the placebo, 44.6% of patient had improvement of symptoms of 40% or higher
  - There were 39.9% of patient who did not respond with over 25% improvement of their symptoms
  - Results did not differ from children to adolescents

- Limitations for the RCTs: generalizing the results to the whole pediatric ADHD population because only certain patients may be exposed to the opportunity to participate in these studies

(Schwartz & Correll, 2014)

Literature Review: **Atomoxetine (Strattera)**

- Literature Review
  - Atomoxetine was found to be efficacious in children who also have anxiety or tic related disorders
  - Efficacy was not altered by other comorbid conditions
  - Health related quality-of-life results were positively correlated with short and longer term studies
  - Children who lack the CYP2D6 enzymatic pathway or are rapid metabolizers will have a difficult time metabolizing atomoxetine

(Kohn, Tsang, & Clarke, 2012)

Literature Review:
Clonidine ER (Kapvay)

- Systemic Review
  - Found clonidine ER effective as monotherapy and as an adjunct with stimulant therapy for children with ADHD ages 6-17

    (Chan, Fogler, & Hammerness, 2016)
- Double-blind placebo-control RTC
  - 236 children with ADHD ages 6-17 years old
  - 8 week duration
  - Statistically significant results with outcome scales of ADHD-RS-IV, Conner's Parent Rating Scale, Parent Global Assessment, and Clinical Global Impression of Improvement and Severity Scale
  - Clonidine ER saw a quick response to treatment starting at soon as two weeks
  - Limitation: short duration and sample size, required same dose titrations during this 8-week period (limits the individual therapeutic needs of the patient)

    (Jain, Segal, Kollins, & Khayrallah, 2011)

Literature Review:
Clonidine ER (Kapvay)

- Double-blind RCT comparing Clonidine ER, methtylphenidate, or a combination of the two medications
  - 122 children with ADHD ages 7-12
  - 16 week duration
  - Conner's Teachers Abbreviated Symptom Questionnaire: showed no improvement in the clonidine ER monotherapy group, but did show improvement in the combination of clonidine ER/ methylphenidate group
  - Conner's Abbreviated Symptom Questionnaire for Parents and Children's Global Assessment Scale: showed improvement in ADHD symptoms whether it was in the Clonidine ER monotherapy group or the combination group
  - Clonidine ER was found to be efficacious for certain ADHD patient subtypes such as those with co-morbid behavioral and/or impulsive disorders

(Palumbo et al., 2008)

Literature Review:
Clonidine ER (Kapvay)

- Double blind RCT that used either clonidine ER or a placebo to a current stimulant treatment plan that was not effective
  - 198 children and adolescents enrolled over this 8 week study
  - Conner Parent Rating Scale, Clinical Global Impression of Severity and improvement, and Parent Global Assessment, ADHD-RS-IV scale all found statistically significant improvements in their scores for the clonidine ER combination group
  - Starting at week 5 the clonidine ER combination group started to show statistically significant results which continued throughout the remainder of the study
  - Limitation: exclusion of comorbid disorders (eliminates many of the ADHD populations that have co-existing learning or behavioral disorders), variability in stimulant medications, no clonidine ER monotherapy group
  - Strength: diverse patient population of males, females, children and adolescents

(Kollins et al., 2011)

Literature Review:
Guanfacine ER (Intuniv)

- Literature Review
  - Found guanfacine ER to have profound effects on executive functioning in children by improved attention spans, impulse control, planning, working memory, and distractibility
  - Improvements in behaviors and motor control were attributed to guanfacine's effects on the noradrenergic projections to the basal ganglia and cerebellum

    (Strange, 2008)
- Double blind RCT compares guanfacine ER/stimulant combination and placebo/stimulant combination
  - 461 participants of children/adolescents with ADHD aged 6-17
  - 9 week duration
  - ADHD-RS-IV scale, Clinical Global Impressions of Severity of Illness and Improvement scales
  - Significant improvement in scores for all assessment scales for the guanfacine ER/stimulant group verses the placebo/stimulant group
    - Limitation: short duration, requirement was for a partial response in stimulant therapy already before entering the trial

    (Wilens et al., 2012)

Literature Review:
Guanfacine ER (Intuniv)

- Double blind RCT with placebo-control
  - 329 children/adolescents aged 6 to 17 years old with ADHD
  - 9 week duration
  - Guanfacine ER was divided into 3 separate dosage groups
  - Improvements in ADHD-RS-IV was reported for all three guanfacine ER dosage groups showing a reduction in score of 19.6, compared to the placebo which had a reduction of 12.2
  - Limitations: short 9 week trial duration and a small number of adolescents compared to children
  - Strength: Strict inclusion and exclusion criteria

(Sallee et al., 2009)

Literature Review:
Guanfacine ER (Intuniv)

- Double blind RCT with placebo-control
  - 345 children/adolescents aged 6-17 years old with ADHD
  - 8 week duration
  - 3 different guanfacine ER dosage groups
  - Average change in ADHD-RS-IV scores for the guanfacine ER groups were 17.16 and the placebo group was 8.48
  - Secondary efficacy scales of Clinical Global Impression of Improvement, Parent's Global Assessment, Conners' Parent and Teacher Rating Scale–Revised, and Conners' Teacher Rating Scale–revised found significant improvements in the guanfacine ER groups
  - Limitations: short duration

(Biederman et al., 2008)

Literature Review: **Guanfacine ER (Intuniv)**

- Literature review
  - Guanfacine ER was found to be favorable for pediatric patients with ADHD that had dominant oppositional symptoms
  - Found varying results in the efficacy onset of guanfacine ER, ranging from 1-4 weeks
  - Combination therapy with a stimulant was found to be beneficial in children who were not experiencing the full treatment potential of stimulant medications
  - ADHD-RS-IV scores saw improvements with guanfacine ER/ stimulant combination therapy in children with opposition symptoms and those without

(Faraone, McBurnett, Sallee, Steeber, & López, 2013; Childress & Berry, 2012)

Results

- Fifteen articles included nine RCTs, three literature reviews, one non-randomized study, one meta-analysis, and one systemic review
- RCT studies were found to be very beneficial because there was elaboration on the specific types of outcome measurement tools that were utilized
- Most common scale that was used was the ADHD-RS-IV-Parent and the Clinical Global Impression and Severity Scale
- Most of these scales had either a parent/guardian or teacher completing the scale
- The non-randomized study did not use a scale; the Stroop Word-Color Test and NIRS score was performed instead

Results

- Six articles studied the effectiveness of **atomoxetine**:
  - All 6 articles agreed atomoxetine was an effective medication for the treatment of ADHD in the pediatric population with statistically significant results
  - Two articles found atomoxetine to have more rapid onset than the placebo
  - One study found the NIRS exam to have increased prefrontal cortex activity especially in the left lateral frontal lobe when on atomoxetine

Results

- Four articles studied the effectiveness of **clonidine ER:**
  - All 4 articles agreed clonidine ER was an effective medication for the treatment of ADHD in the pediatric population with statistically significant results
  - Two out of the three RCT's compared the effectiveness of clonidine ER as an adjunct medication to stimulant treatment
  - One systemic review highly supported its use as an adjunct medication to stimulant therapy and found clonidine ER to be more helpful with behavioral symptoms

Results

- Five articles studied the effectiveness of **guanfacine ER:**
  - All 5 articles agreed guanfacine ER was an effective medication for the treatment of ADHD in the pediatric population with statistically significant results
  - Three articles found guanfacine ER to be an effective adjunct to stimulant treatment
  - One article found guanfacine ER to be specifically efficacious in children with oppositional symptoms

Implications in…

Nursing Practice

- Choosing to prescribe non-stimulants over the best practice guideline of stimulants, can demonstrate how the APPN is providing holistic care by addressed all aspects of the patients needs and concerns
- Continue to further one's educate is very important because new evidence-based research becomes published and knowledge behind understanding the brain and how it relates to ADHD is increasing

Research

- Limited research on non-stimulant monotherapy; many articles were evaluating stimulant therapy and/or stimulant with adjunct non-stimulant therapy
- More research is needed to determine what outcome measurement scale is best to determine effectiveness of a medication, studies with longer duration, greater sample size, and with a focused monotherapy experimental group to strength the validity of their findings

Implications in…

Education

- It is important for the APPN to be educated on medications, including their evidence-based research, to guide treatment decisions and to provide pyschoeducation to their patients
  (American Nurses Association, 2014)
- With knowledge of the evidence-based research, the APPN can educate the patient and their parents/ guardians regarding its effectiveness and how the medication will target the core symptoms of ADHD

Health Policy

- Policies at hospitals, outpatient settings, and state levels can be impacted by the results of this literature review by APPN's advocating for updated policies for treatment options
- APPN can support continuing research by having their patient enroll in research studies

Conclusion

- ADHD is a complex disorder with the potential to leave profound effects on one's childhood and development when not treated effectively
- Atomoxetine, clonidine ER, and guanfacine ER were found to have statistically significant results despite the use of differing yet similar outcome measurement scales
- Continuing research is needed to maintain these medications as treatment options for this population

With the results of this literature review, the APPN can make evidence-based decisions during treatment planning for their pediatric patient with ADHD

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