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The Use of Drug Therapy for Attention Deficit Hyperactivity Disorder (ADHD) in the Management of Oppositional Defiant Disorder (ODD): A Literature Review

Shaina Flowers
University of Central Florida



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**The Use of Drug Therapy for Attention Deficit Hyperactivity Disorder (ADHD) in the
Management of Oppositional Defiant Disorder (ODD): A Literature Review**

by

Shaina Flowers

A thesis submitted in partial fulfillment of the requirements
for the Honors in the Major Program in Nursing
in the College of Nursing
and in the Burnett Honors College
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Orlando, Florida

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Thesis Chair: Leslee D'Amato-Kubiet, Ph.D., ARNP

Abstract

Children with oppositional defiant disorder (ODD) and a concurrent Axis I diagnosis are often prescribed drug therapy for attention deficit hyperactivity disorder (ADHD) to manage disruptive behavior. However, ODD symptoms tend to be poorly controlled, raising questions about the effectiveness of drug therapy in children with the condition. Safety and long term consequences of pharmacological agents for ODD are important factors clinicians must consider before initiating treatment. The purpose of this literature review is to examine the pharmacodynamics and efficacy of drug therapy used for ODD in school-age children and adolescents. Additionally, awareness of poor behavior patterns and recognition of symptoms associated with ODD in children among health care providers was explored. A literature review exploring ODD and drug therapy for ODD and related behavioral disorders was conducted from various online databases. Results from 15 reviewed studies suggest that pharmacologic therapy is typically prescribed for ODD symptoms when a comorbid condition such as ADHD, a mood disorder, or an anxiety disorder is present. Drug therapy for ADHD has demonstrated effective behavioral outcomes in reducing ODD symptom severity in children and tolerable side effects when used for short-term therapy. Studies have demonstrated success and better control of ODD symptoms with a focused drug therapy regimen. Overall, the benefits of drug therapy can potentially outweigh the risks of adverse effects, and improve the quality of life in children with ODD. In conclusion, uncovering the reasons for poorly controlled ODD in children can be of clinical significance to health care providers and can support decision making when considering drug therapy for children with this condition.

Dedication

For my mother and friends who have always supported me in all my endeavors. Furthermore for Elijah and Donnell who ignited my interest in this topic I pray you never give up hope on leading a satisfying and fulfilled life.

Acknowledgements

To my committee, thank you for being patient with me. I am continually grateful for your support.

Table of Contents

Introduction	1
Problem	3
Purpose	4
Methods	5
Background	6
Prevalence of ODD and ADHD Comorbidity	6
Brief Description of Scales Used to Measure Symptom Severity	6
ADHD Rating Scale, Version IV (ADHD-RS-IV)	6
Conners' Parent Rating Scale-Revised: Short Form (CPRS-R: S)	6
Swanson, Nolan, & Pelham Rating Scale IV (SNAP-IV)	6
Clinical Global Impressions Scale (CGI)	7
Child Health Questionnaire (CHQ)	7
Review of Literature	8
Atomoxetine Studies	8
Non Peer Reviewed Clinical Trial	10
Clonidine in combination with a Psychostimulant Study	11
Mixed Amphetamine Salts Extended Release Study	12
Immediate Release Methylphenidate Study	13
Discussion	14
Efficacy of ADHD Agents	14

Safety of ADHD Agents	15
Previous Broad Diagnosis Criteria and DSM-V	15
Information for School Nurses	16
Implications	17
Conclusion	19
Limitations	20
Further Research	21
Appendix A: Table of Evidence	22
References	26

Introduction

Oppositional defiant disorder (ODD) affects young children through the adolescent age and is characterized by aggressive behavior, rebelliousness toward authority, and poor anger control. Due to the nature of symptoms, ODD creates poor psychosocial interactions across the lifespan including, unhealthy relationships with family members, friends, school teachers, and additional authority figures.

Oppositional defiant disorder is diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). The diagnosis of ODD in children is conducted by observing a pattern of behaviors that must be displayed for at least six months and include at least four of the following: often loses temper, often argues with adults, often actively defies or refuses to comply with adults' requests or rules, often deliberately annoys people, often blames others for his or her mistakes or misbehaviors, is often touchy or easily annoyed by others, is often angry or resentful, and is often spiteful or vindictive (Hamilton & Armando, 2008). Furthermore, the behavior must cause significant impairment in social, academic, or occupational functioning; must occur independently of other mental disorders; and must not meet the criteria for conduct disorder or antisocial personality disorder if the client is over the age of 18 (Hamilton & Armando, 2008). Diagnosis of ODD can be problematic since health care providers must differentiate between typical childhood misbehavior and actual disruptive conduct. In addition, ODD is often accompanied by comorbid mental health conditions such as attention deficit hyperactivity disorder (ADHD) or mood disorder, which further complicate diagnoses.

The cause of ODD is unknown, however researchers believe there are environmental, biologic, and genetic influences that contribute to its etiology. Environmental factors include but

are not limited to, parental overreaction to behavior at a young age, lower socioeconomic status, and maternal depression (Harvey, Metcalfe, Herbert, & Fanton, 2011). Furthermore, research suggests decreased sensitivity to hormones and catecholamine's such as, cortisol, epinephrine, and norepinephrine, occurs with ODD and alters the child's response to punishment.

Impairments in the frontal lobe and cingulate cortex may contribute to lack of motivation, sensitivity to reward for positive behavior, and impulse and emotional control (Matthys, Vanderschuren, & Schutter, 2013). Due to the evidence of chemical and hormonal imbalances, drug therapy is utilized as a treatment option to control behavior of children living with ODD. Since ODD and ADHD are often comorbid conditions, ADHD agents are commonly prescribed to control symptoms of both conditions. However, the effectiveness, safety, and maintenance abilities of ADHD agents on ODD symptom severity reduction is still being examined.

Problem

Behavioral therapy is the first line of treatment for ODD including interventions at the child and parent levels. Behavioral therapy alone is not always effective when a comorbid disorder is present. Therefore, pharmacologic treatment is initiated as an alternative method to manage ODD symptoms. A plethora of pharmacologic agents are used for ODD treatment including, stimulants (Ritalin, Concerta, Aderall), selective norepinephrine reuptake inhibitors (Atomoxetine), mood stabilizers, antidepressants, and antipsychotics (Smith & Coghill, 2010). A major problem concerning drug therapy in children with ODD arises due to the lack of research and knowledge surrounding safety, efficacy, and long-term success of treatment with ADHD drugs on children and adolescent's ODD symptoms. The pharmacodynamics and pharmacokinetics are poorly understood in children as well. The presence of comorbid conditions such as ADHD, depression, or anxiety with ODD influences the choice and effectiveness of pharmacological agents. ODD can be difficult to diagnose which can lead to poor management. Nurses have the opportunity to intervene at the elementary school by raising awareness regarding ODD symptoms and increasing knowledge about risk factors that can hinder early recognition of the illness.

Purpose

The purpose of this literature review was to explore the effectiveness of ADHD pharmacologic agents used to manage ODD. The focus was on whether pharmacologic agents used for ODD are safe, effective, and have long-term sustainability of symptom control on children and adolescents. Emphasis was placed on the pharmacokinetics and pharmacodynamics of prescribed medicines (for ODD) in adolescents. The secondary purpose was to address issues with poor control of ODD symptoms. The literature review discussed the role of school nurses and existing education gaps. Several subtopics related to poor management of ODD including lack of knowledge among parents, frequent comorbid conditions, and broad diagnosis criteria were researched as well.

Methods

Research was obtained from EBSCO which collected articles from a variety of databases including CINAHL, ERIC, MEDLINE, PsycARTICLES, PsycBOOKS, PsycINFO, and Academic Search Premier. To narrow the results, limitations were set to full text, peer reviewed, written in the English language, subject age of 6 to 17, publication date from 2000 – 2013, and human focused. For CINAHL specifically, an additional inclusion was met for any author that was a nurse. ODD and medications were used as inclusion criteria, while demographics and behavioral therapy were used as exclusion criteria. The search yielded 638 articles. With the addition of the key search terms medication* and children*, 172 studies were remaining. The articles were reviewed and chosen based relevance to pharmacologic treatments for ODD and the disease process. 30 total articles were utilized in the literature review. For the table of articles, 40 were eliminated for not being peer reviewed clinical trials or not focusing on one medication. An additional four were excluded for not focusing on an ADHD medication specifically, leaving a total of six articles for analysis. The six articles selected were all randomized, double-blind, placebo-controlled clinical trials. A supplemental search was done in EBSCO involving ODD, nursing, and treatment to obtain information about the nurses role in management. Lastly, a search was done outside of the EBSCO database to find articles related to the diagnosis of ODD.

Background

Prevalence of ODD and ADHD Comorbidity

According to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000) ODD affects about 2 – 16 % of the general population. Before puberty ODD is more common in males however after puberty, prevalence is equal among sexes. Lastly, about half of the children with ADHD have ODD as well (4th ed., text-rev.; *DSM-IV-TR*; American Psychiatric Association, 2000).

Brief Description of Scales Used to Measure ADHD and ODD Symptom Severity

A variety of scales are used to quantify ADHD and ODD symptoms. From knowledge the researcher knows the scales are either parent, teacher, or clinician rated.

ADHD Rating Scale, Version IV (ADHD-RS-IV)

The ADHD-RS-IV (DuPaul, Power, Anastopoulos, & Reid, 1998), based on diagnostic criteria from the DSM-IV, is an 18-item scale consisting of two subscales: inattention and hyperactivity. There is a parent questionnaire and a teacher questionnaire focusing on symptom frequency over six months to assess treatment response in children and adolescents with ADHD (Goodman et al., 2010).

Conners' Parent Rating Scale – Revised: Short Form (CPRS-R:S)

The CPRS-R: S (Conners, 1997) has 27 items and is used to assess ADHD symptoms such as inattention, hyperactivity/impulsivity, learning problems, executive functioning, aggression, peer relations, and family relations. The scale evaluates oppositional behavior as well.

Swanson, Nolan, & Pelham Rating Scale IV (SNAP-IV)

The SNAP-IV (Swanson, 1992) evaluates ADHD, ODD, and additional psychiatric disorders that occur in childhood. Inattention, hyperactivity/impulsivity, and DSM-IV criteria for

ODD are subscale focus areas. The SNAP-IV is used in clinical trials to measure the efficacy of ADHD treatment (Bussing et al., 2008).

Clinical Global Impressions Scale (CGI)

The CGI scale (Guy, 1976), is used by researchers to measure global functioning of an individual before and after medication treatment. There are two components of the scale to measure severity (CGI-S) and improvement (CGI-I) (Busner & Targum, 2007). According to Busner & Targum (2007) the CGI scale summarizes, “patient history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient’s ability to function”.

Child Health Questionnaire (CHQ)

The CHQ (Landgraf, Abetz, & Ware, 1996) is utilized by researchers to evaluate the influence of health issues on a child’s functioning and well-being (Waters, Salmon, & Wake, 2000). The CHQ is not specific to ADHD or ODD but can be used to assess any illness during childhood.

Review of Literature

Atomoxetine Studies

An eight week, randomized, double-blind, placebo study was conducted on children ages 8 – 18 with ADHD and with or without comorbid ODD (Newcorn, Spencer, Biederman, Milton, & Michelson, 2005). Of 293 subjects, 115 had ODD and 178 did not. Tools to measure the effectiveness of atomoxetine on symptom management included, the ADHD-RS-IV-Parent version, CPRS-R: S, CGI-S, and a parent questionnaire. Results showed that atomoxetine was more effective than the placebo in decreasing ADHD and ODD symptoms. ADHD children with comorbid ODD needed a higher dose of 1.8 mg/kg/day to see results. Children with only ADHD showed improvement with only 1.2 mg/kg/day (Newcorn, et al., 2005). Using the CHQ Psychosocial Summary scale, quality of life was assessed. Improvements were seen in individuals with and without ODD however, subjects with ODD had lower scores at baseline. The findings showed that children with ADHD and comorbid ODD exhibit a decrease in functioning compared to children with only ADHD. (Newcorn et al., 2005). Adverse effects were described to be typical of atomoxetine and significance was not discussed.

An eight week, multi-site, randomized, placebo-controlled trial was done on children ages 6 – 15 with ADHD and comorbid ODD. The purpose was to measure the efficacy of atomoxetine on 137 children that failed to improve in a six week psychological, parent training program (Dell'Agnello et al., 2009). Various rating scales were used by the researchers and parents to measure the efficacy of atomoxetine. Results revealed that atomoxetine improved ADHD and ODD symptoms, especially inattention, hyperactivity, and oppositional behavior. Best results were seen with atomoxetine and concurrent psychotherapy for the parent and child. As for safety, 45.8% of children on atomoxetine complained of nausea, vomiting, and abdominal

pain while 43.0% complained of anorexia. Additional adverse effects with atomoxetine included somnolence (29.9%), headache (21.5%), influenza (8.4%), nervousness (6.5%), and insomnia (4.7%). Only three participants withdrew from the trial because of adverse events (Dell'Agnello, et al., 2009). The study results showed atomoxetine was effective and tolerated well.

An additional study examined the effectiveness of atomoxetine in controlling ODD and ADHD symptoms (Bangs et al., 2008). The researchers conducted an eight week study consisting of 131 children, ages 6 – 12, who were randomly chosen to receive 1.2 mg/kg/day of atomoxetine or a placebo. Efficacy was measured using the SNAP-IV ODD total scores. There was a significant decrease in ODD symptom severity with the atomoxetine treated group at weeks two and five, however no noticed improvement at week eight. ADHD symptom severity decreased through the entire study. As for safety, atomoxetine was well tolerated. Some adverse effects were seen more when compared to the placebo group. For example, atomoxetine subjects reported decreased appetites (24.4%), nausea (20.5%), and fatigue (17.3%) as compared to 1.4%, 8.6%, and 5.7% for the placebo group. Diastolic blood pressures were increased (9.7% increased 5 mm HG or more above the 95th percentile) and weights decreased (3.5% from baseline) in the atomoxetine group (Bangs, et al., 2008).

Researchers analyzed 98 children from two similar studies involving atomoxetine versus a placebo in ADHD children with comorbid ODD (Kaplan et al., 2004). The studies examined the efficacy and safety of atomoxetine in children ages 7 – 13. Both studies were double-blind, randomized, placebo-controlled trials. Efficacy was measured utilizing the ADHD-RS-IV and through interviews with the parents and children. Researchers found atomoxetine to be very effective in reducing ADHD symptoms, but not ODD symptoms when compared to the placebo group. The medication was very well tolerated and only caused minimal adverse effects such as

decrease in appetite and emotional lability. Of the 98 participants, one dropped out because of hostility and two others withdrew because of nervousness (Kaplan et al., 2004).

Hazell et al. (2006) conducted a randomized, double-blind, placebo-controlled study to examine the influence of comorbid ODD on relapse of symptoms during nine months of treatment with atomoxetine for ADHD. The research was a continuation of a 10 week atomoxetine trial for subjects that responded well to treatment. Dosages of the 10 week trial ranged from 0.5 mg/kg/day to 1.8 mg/kg/day of atomoxetine. To progress in the open-label trial, participants had to achieve at least a 25% reduction from baseline data on the ADHD RS total score. Consequently, successful participants were ages 6 – 15 and were randomly chosen to either continue receiving atomoxetine or switch to a placebo. Of 416, 292 continued with atomoxetine and 124 received placebo. 17% of patients with ODD and ADHD relapsed while 26% of patients with ADHD without ODD relapsed during the study. In the study, atomoxetine treatment was effective in preventing relapse of symptoms and even benefited patients that relapsed anyway. For example, of all relapsed patients, the ones on atomoxetine benefited longer than the ones that received the placebo (Hazell et al., 2006). Although the study did not focus on ODD symptoms specifically, results showed that atomoxetine is effective for treatment of ADHD with comorbid ODD over a longer period of time.

Non Peer Reviewed Clinical Trials

Dittman et al. (2011) completed a nine week, randomized, placebo-controlled, double-blind on 180 children (ages 6 – 17) diagnosed with ADHD and comorbid ODD. The purpose was to examine the effectiveness of atomoxetine and to compare fast versus slow titration. The preferred dose was 1.2 mg/kg/day. Results showed a significant decrease of ADHD and ODD symptoms with atomoxetine. In regards to safety, adverse effects such as fatigue, sleep disorders,

nausea, and gastrointestinal issues were seen in 60.0% of the fast titrated group and in 44.3% of the slow titrated group (Dittman, et al., 2011). Slowly increasing the medication dose was better tolerated. To summarize, atomoxetine was effective in reducing ADHD and ODD symptoms and relatively safely.

Wehmeier et al. (2011) conducted a randomized, placebo-controlled, double-blind, nine week study to observe the effects of atomoxetine on quality of life (QOL) in children ages 6-17 with ADHD and comorbid ODD or conduct disorder (CD). The dose of atomoxetine was started low at 0.5 mg/kg and titrated either fast or slow to a target dose of 1.2 mg/kg. Although the main focus of the research was QOL, safety and effectiveness was examined weekly for the first three weeks and then bi-weekly until the ninth week. Results were measured through the use of the SNAP-IV and additional behavioral scales. Researchers found the use of atomoxetine to be more successful at reducing ADHD, ODD, and CD symptoms compared to the placebo. There was no significant difference in the fast or slow titrated groups. For safety, more than 10% of participants and at least one member in each sub-group (fast titrated, slow titrated, and placebo) experienced adverse effects. Fatigue, nausea, headache, vomiting, upper abdominal pain, and anorexia were reported the most (Wehmeier et al., 2011).

Clonidine in Combination with a Psychostimulant Study

Hazell and Stuart (2003) studied the use of clonidine in combination with a psychostimulant to decrease hyperactivity and aggression in children with ADHD combined with ODD or CD. The six week, single blind trial consisted of 60 participants ages 6 – 14 that had been treated for less than three months with methylphenidate or dexamphetamine. Subjects were randomly assigned to receive a 0.10 mg morning and evening dose of clonidine or a placebo.

Using the CPRS-R: S to gauge results, the clonidine-treated participants yielded better results compared to the placebo group. For example, 57% of the subjects that received clonidine had scores decrease more than 38% on the rating scale as compared with a 21% decrease in the placebo group. As an added benefit, clonidine helped in decreasing side effects from the concurrent psychotropic medications. There were expected adverse effects in the clonidine treated group including dizziness and drowsiness but only in the early stages of the trial. The results of the study suggest that clonidine works well as an adjunct with a psychostimulant in decreasing ADHD and ODD or CD symptoms.

Mixed Amphetamine Salts Extended Release (MAS XR) (Adderall XR) Study

Spencer et al. (2006) conducted a four week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, forced-dose-escalation study. Before the study began, there was a one to four week period where all psychotropic medications were discontinued and a placebo was administered. After the discontinuation, there were 308 participants ranging from ages 6-17, randomly chosen to receive either 10, 20, 30, or 40 mg/d of MAS XR or a placebo. All 308 participants were diagnosed with ODD but only 244 had comorbid ADHD. Efficacy was measured using ODD portions of the SNAP-IV parent and teacher rating. Participants and parents also attended regular check-up visits in order for researchers to collect data regarding safety. The data included recording reported adverse effects and observing trends in vital signs, 12-lead electrocardiographic (ECG) findings, laboratory results, and physical examinations. Results showed the largest decrease in symptoms with the MAS XR 30 and 40 mg/d groups in participants with and without comorbid ADHD. Regarding safety, adverse effects were reported more often from the MAS XR including decreased appetite (25.3%), insomnia (19.5%),

headache (18.5%), and abdominal pain (10.7%). Weight loss ranged from 1.1 – 3.5 pounds in the MAS XR group as compared to no weight loss in the placebo group.

Immediate Release Methylphenidate Study

A two week study consisting of 31 children ages 6 – 12 was conducted to observe the effectiveness of methylphenidate in controlling ODD symptoms. All participants had ODD, ADHD, and either Tourette's or chronic multiple tic disorder (Gadow, Nolan, Sverd, Sprafkin, & Schneider, 2008). Under double-blind conditions, subjects were given placebo and three doses of methylphenidate (Novartis Brand Ritalin-IR 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg) administered twice daily. Efficacy was measured by one physician observation and computer vigilance testing every two weeks, at a clinic. Parents and teachers completed rating scales two times per week throughout the entire study as well (Gadow et al., 2008). Although there were differences between parent and teacher ratings, improvement of ODD symptoms were seen with methylphenidate as compared to the placebo. In reference to safety, the higher the dosage of methylphenidate, the higher the adverse effects. For example, parents rated physical complaints higher with the methylphenidate dosages. There was a directly proportional relationship between higher methylphenidate dosages and higher heart rates and systolic blood pressures as well (Gadow, et al., 2008).

Discussion

Efficacy of ADHD agents

Ten articles were reviewed and four ADHD medications were observed for efficacy in controlling ODD symptoms. The medications included atomoxetine, clonidine, MAS XR (Aderrall XR), and methylphenidate. Overall, the four medications were relatively effective in reducing ODD symptom severity.

Of the ten studies reviewed, six discussed atomoxetine. The atomoxetine clinical trials, with the exception one, showed a greater decrease in ODD symptoms with medication compared to a placebo. Bangs et al. (2008) found that overall, atomoxetine reduced ODD symptoms and while there was progression throughout the study, there was no significant improvement noted over the last three weeks. The effective dosage of atomoxetine varied amongst studies. Dittman et al. (2011), Wehmeier et al. (2011), and Bangs et al. (2008) found 1.2 mg/kg/day to be effective in decreasing disruptive behaviors. On the other hand, Newcorn et al. (2005) found 1.2 mg/kg/day of atomoxetine sufficient to help ADHD, however individuals with comorbid ODD showed improvements at 1.8 mg/kg/day. Dell'Agnello et al. (2009) used a range of atomoxetine dosages (0.85 – 1.33 mg/kg/day) for ADHD patients with and without comorbid ODD. There was no specification made on whether the comorbid ODD patients required higher dosages. Lastly, one study observed children taking atomoxetine over nine months and results showed an overall prevention of relapse of ODD symptoms (Hazell et al., 2006). Thus atomoxetine must be titrated to reach an effective dosage which should be individualized to each patient.

Clonidine in combination with either methylphenidate or dexamphetamine showed to be effective in treating ODD symptoms (Hazell & Stuart, 2003). However, due to the small sample size more research is warranted. In regards to MAS XR, larger doses were needed to yield

desirable results in ODD management (Spencer et al., 2006). Lastly, the methylphenidate dosages produced reduced ODD symptom severity (Gadow et al., 2008).

Safety of ADHD agents

ADHD pharmacologic agents are often well tolerated in children and adolescents because of the short half-lives of the medications. The most common adverse effects seen with atomoxetine included anorexia/decreased appetites, nausea, vomiting, fatigue, abdominal pain, sleep disorders, and decrease in body weight. One study had three participants discontinue due to adverse effects and observed less growth in height over the course of the trial (Dell'Agnello et al., 2009). MAS XR had similar adverse effects as atomoxetine including decreased appetite, weight loss, headache, insomnia, and abdominal pain (Spencer et al. 2006). Clonidine caused mostly dizziness and drowsiness which were expected. An interesting unexpected but positive effect of clonidine was a decrease in undesirable effects of concurrent psychotropic medications (Hazell & Stuart, 2003). Clonidine acts on central alpha receptors which decreases heart rate and blood pressure, hence the sedative effects. Lastly the immediate release methylphenidate, a commonly prescribed stimulant, caused an increase in heart rate and systolic blood pressure (Gadow et al., 2008).

Previous Broad Diagnosis Criteria and DSM-V

Broad diagnosis criteria made ODD difficult to identify. Symptoms had to be present over a period of six months, however frequency was not specified in the DSM-IV criteria. The DSM-IV stated the word, "often" in the symptom list which left interpretation up to the healthcare provider (Keenan, 2012). With no methods to measure and gauge ODD symptoms,

diagnosis was difficult in differentiating between normal childhood misconduct and truly disruptive behavior. Contrastly, the DSM-V criteria has been made more specific in hopes of creating an easier diagnosis process. Symptoms have been placed into three groups including, angry/irritable mood, argumentative/defiant behavior, and vindictiveness. Exclusion criteria for CD has been removed as well (American Psychiatric Association, 2013). Frequency of symptoms have been defined to address the issue of differentiating between normal childhood behavior and true signs of the disorder. Lastly, since ODD affects children and families across the lifespan, a severity rating has been added to gauge the extensiveness of the illness (American Psychiatric Association, 2013). Many of the issues with broad diagnosis criteria have been addressed in the DSM-V criteria. Providers now have an improved, proficient method to correctly diagnosing ODD.

Information for school nurses

School nurses should be familiar with the presentation of ODD symptoms. Indications of ODD include but are not limited to, refusal to follow commands from adults, easily annoyed by others, hostility, verbally aggressive tendencies, spiteful behavior, stubbornness, and inability to maintain healthy relationships with peers (Kledzik, Thorne, Prasad, Hayes, & Hines, 2012). A child with such widespread behavioral issues will most likely be known by various teachers and school staff. School nurses can be more effective when equipped with the knowledge to recognize ODD symptoms and intervene to assist with initiation of treatment. Early intervention is important because untreated ODD will steadily progress and cause greater problems later in life (Pardini & Fite, 2010). School nurses can play a huge role in treatment teams by helping to improve academic performance and assisting with the patient's relationships with family and

friends (Barcalow, 2006). School nurses can be actively involved with facilitating and observing a child's progression in treatment.

School nurses should be knowledgeable about all treatment options for students, including drug therapy, and what adverse effects to expect. Teachers and school nurses are often great sources of information when attempting to measure the efficacy of drug treatment in the school setting.

Implications

ODD affects 2 – 16 % of children and causes problems across the life span (4th ed., text-rev.; *DSM-IV-TR*; American Psychiatric Association, 2000). Control of symptoms is important for quality of life for the child and family because ODD has been linked to later criminal charges and lifelong conduct problems (Pardini & Fite, 2010). Early recognition, diagnosis, and effective and safe treatment are imperative to prevent future issues for affected children and adolescents. Pardini and Fite (2010) stated that ADHD symptoms worsen ODD and CD symptoms over time. The commonality of comorbid conditions with ODD, especially ADHD, further stresses the importance of knowledge of effective drug therapies. Although best results are seen with psychotherapy and drug therapy for ODD with comorbid disorders, more psychiatrists and primary care physicians are solely using the drug therapy route (Harpaz-Rotem & Rosenheck, 2006). Healthcare providers should be educated on the most effective and safe drug therapy options in order to develop adequate treatment plans for patients. Extensive experimentation with several drugs on young children to find the right combination can become unethical and potentially dangerous. Lastly, nurses should know the presentation of ODD

(common signs and symptoms), how to effectively react to disruptive behavior, and what resources are available to the affected clients and families to facilitate child improvement.

Conclusions

All of the articles synthesized suggest that ADHD agents are generally effective in controlling ODD symptoms and are relatively safe in school-age children. Adverse effects from drug therapy in children with ODD are present with all types of drug therapy and ODD symptom control has shown that the risks outweigh the benefits in this population. Drug therapy in combination with psychotherapy for both the parent and child has been shown to be a very effective form of treatment. School nurses can play a huge role in intervening and providing resources for treatment in order to prevent progression of oppositional behavior. Healthcare providers collaborating with families and their children with ODD and having knowledge of the most effective and safe options can allow for an increase in quality of life for patients and families.

Limitations

Six atomoxetine clinical trials were found which suggests effectiveness for the drug, however other ADHD agents are not as well researched in regards to ODD symptom control. Of the atomoxetine trials, two were not peer reviewed therefore while the articles were supportive of the effectiveness of atomoxetine in ODD symptom control, they were not approved by experts before publishing. The two non peer reviewed were not listed in the table of articles and the researcher found an adequate amount of peer reviewed atomoxetine studies to support conclusions. Only three additional clinical trails studying three different stimulants were found and critiqued. Although the three trials showed effectiveness in reducing ODD symptoms, further studies would have to be done for results to be generalizable to a larger population. Lastly, only one trial was found that studied the effectiveness of atomoxeitine over a matter of nine months. More research must be conducted to examine the sustainability of positive effects from ADHD agents in ODD symptom control.

Further research

Additional research needs to be conducted to further examine the effectiveness of clonidine, MAS XR, and immediate release methylphenidate on controlling ODD symptoms. An additional study should be initiated investigating provider awareness of ODD symptoms and treatment to gauge education needs and increase knowledge among healthcare workers.

Appendix A: Table of Evidence

Study (Author, Date, Journal)	Duration	Drug and Mean Daily Dose	Inclusion Criteria (age range)	Efficacy and Safety	Limitations
Newcorn et al., (2005). <i>Journal of the American Academy of Child & Adolescent Psychiatry</i> , 44(3), 240-248. doi: 10.1097/00004583-200503000-00008	8 weeks	Atomoxetine -0.5 mg/kg/day (n=44) -1.2 mg/kg/day (n=83) -1.8 mg/kg/day (n=85)	293 subjects -8 – 18 -Normal intelligence (IQ \geq 80) -Diagnosed with ADHD with or without comorbid ODD according to DSM-IV criteria -Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent version, investigator-administered and –scored scale \geq 1.5 SDs above age and gender normals	-Subjects with ADHD and ODD showed most improvements at 1.8 mg/kg/day -Subjects without ODD showed significant improvement at 1.2 mg/kg/day -Individuals with ADHD and comorbid ODD may need higher dosages of atomoxetine to achieve desired effects	-Efficacy of atomoxetine in controlling ODD symptoms was the secondary purpose of the study -Separating the subjects into smaller groups decreased the validity of the study findings. Further research is needed.
Dell’Agnello et al., (2009). <i>European Neuropsychopharmacology</i> , 19(11), 822-834. doi: 10.1016/j.euroneuro.2009.07.008	8 weeks	Atomoxetine -Mean starting dose: 0.61 \pm 0.08 mg/kg/day (0.44-0.80) -Mean titrated dose: 1.10 \pm 0.13 mg/kg/day (0.85-1.33)	137 subjects -6 – 15 -Diagnosed with ADHD and ODD based on DSM-IV criteria -Score \geq 1.5 SD above age normal for ADHD subscale of SNAP-IV -SNAP-IV ODD subscale score of at least 15 -CGI-S \geq 4 -IQ \geq 70	-ODD subscale changes were -2.7 \pm 4.1 with the atomoxetine treated subjects (overall decrease in symptom severity) -At least 25%, 30%, or 40% improvement in ADHD subscale scores -45.8% of atomoxetine group reported nausea, vomiting, and	-Potential for bias because the researchers work for or are affiliated with the sponsor of the study: Eli Lilly Italy -Due to the duration there is no way to tell whether atomoxetine beneficial effects will persist over time

				<p>abdominal pain -43% of atomoxetine group reported anorexia/decreased appetite -3 atomoxetine treated subjects did not complete the study due to adverse effects -There was a small decrease in body weight and less height gain in atomoxetine treated subjects. However, nothing of significance.</p>	
<p>Bangs et al., (2008). <i>Pediatrics</i>, 121(2), e314-20.</p>	8 weeks	<p>Atomoxetine -Mean final dose: 1.2 ± 0.28 mg/kg per day -Mean maximum dose: 1.52 ± 0.54 mg/kg per day</p>	<p>131 subjects -6 – 12 -ADHD (any subtype) with comorbid ODD as primary diagnosis according to DSM-IV criteria -SNAP-IV ADHD subscale score ≥ 15 at both visits 1 and 2. -Clinical Global Impressions-Severity Scale score ≥ 4 at both visits 1 and 2.</p>	<p>-Effective at controlling ODD symptoms at weeks 2 and 5 but no significant difference at week 8. -More decreased appetite, nausea, fatigue. -Increased diastolic blood pressures and increased amount of weight loss.</p>	<p>-No evidence atomoxetine would decrease ODD symptom would improve in absence of comorbid ADHD -Not possible to predict if reduced ODD symptom effects would last -Improvements seen in weeks 2 and 5 could have been due to sedation effects -Allowing children with anxiety and dysthymic disorders</p>

					may have interfered with effectiveness of atomoxetine because these individuals struggled more.
Hazell & Stuart. (2003). <i>Journal of the American Academy of Child & Adolescent Psychiatry</i> , 42(8), 886-894. doi: 10.1097/01.CHI.0000046908.27264.00	6 weeks	Clonidine -0.20 mg/day (n=25) -0.15 mg/day (n=4) -0.10 mg/day (n=6)	67 subjects -6 – 14 -White -Treated for minimum of 3 months with either methylphenidate or dexamphetamine -Attended clinics supervised by authors -IQ ≥ 70 -History of normal cardiac function	-For subjects treated with clonidine, there was an increased reduction in Conduct and Hyperactivity Index Scores -Conners Parent Rating subscale scores showed a 25% improvement in the clonidine treated subjects -Side effects of concurrent psychotropic medication decreased in Clonidine treated patients -Symptom such as irritability, prone to crying, and anxiety were decreased with the clonidine treated group -Drowsiness and dizziness were the two main physical adverse effects	-Small sample size -Validity and generalizability of the findings to a larger population may be limited due to the small sample size and the allowance of children with anxiety and below normal intellectual function to participate -A plethora of parents were able to correctly guess whether their child was getting clonidine or a placebo which may have led to bias -Duration too short to determine lasting benefits -No ECG data was collected

<p>Spencer et al., (2006). <i>Clinical Therapeutics</i>, 28(3), 402-418.</p>	<p>4 weeks</p>	<p>Mixed amphetamine salts extended release (MAS XR) (Adderall XR) -10 mg (n=60), --20 mg (n=58) -30 mg (n=69) -40 mg (n=61)</p>	<p>308 subjects - 6 – 17 -ODD with or without comorbid ADHD -Normal blood pressure and electrocardiographic reading -No additional illness that could interfere with the effectiveness and safety of MAS XR</p>	<p>-Effective in decreasing from baseline ODD severity with MAS XR 30 mg/d and MAS XR 40 mg/d -MAS XR adverse effects: anorexia (25.3%), insomnia (19.5%), headache (18.5%), abdominal pain (10.7%) -1.1 to 3.5 pound decrease in body weight in MAS XR groups</p>	<p>-Shorter duration -Dosages were not titrated to achieve optimal effects -Low baseline ODD subscale scores (less severe ODD symptoms)</p>
<p>Gadow et al., (2008). <i>Journal of Child Neurology</i>, 23(9), 981-990.</p>	<p>2 weeks</p>	<p>Methylphenidate (Novartis Brand Ritalin-IR) -0.1 mg/kg, 4.5 mg -0.3 mg/kg, 9.3 mg -0.5 mg/kg, 14.3 mg</p>	<p>31 subjects - 6 – 12 -Met DSM-IV criteria for ODD, ADHD and either Tourette's or chronic multiple tic disorder. -Previously part of a placebo-controlled, double-blind study of safety and efficacy of methylphenidate in school-age children with chronic tic disorder.</p>	<p>-Mother and teacher ratings showed reduction in ODD symptom severity -Increase in heart rate and systolic blood pressures directly proportional to increase in methylphenidate dosage.</p>	<p>-Short duration -The cause of ODD and ADHD in individuals with tic disorders is unknown, therefore response to medication may differ in children without a tic disorder -Rating scales completed by mothers are less effective at measuring severity of oppositional behavior at home.</p>

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