LOW-DOSE ABILIFY® AND THE TREATMENT OF DISRUPTIVE BEHAVIORS IN CHILDREN WITH AUTISM SPECTRUM DISORDERS

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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To my children,
Life’s greatest blessing and joy
ACKNOWLEDGMENTS

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LOW-DOSE ABILIFY® AND THE TREATMENT OF DISRUPTIVE BEHAVIORS IN CHILDREN WITH AUTISM SPECTRUM DISORDERS

By

Tina Marie Malcolm D’Alessandro

December 2012

Chair: Jennifer Ann Harrison Elder
Major: Nursing Sciences

The effectiveness of low-dose Abilify® (aripiprazole) in decreasing severe disruptive behaviors including tantrums, self-injury and aggression was evaluated using a single subject A-B-A design. Three subjects with autism spectrum disorder (ASDs), ages 7-11, participated in the nine week study. Behavioral observations were conducted at baseline, and during Weeks 5 (intervention), 7 (intervention), and 9 (placebo). Significant behavioral improvements were observed in all subjects during Weeks 5 and 7. Disruptive behaviors increased during Week 9 (placebo phase) but did not return to baseline levels. Other efficacy measures included the Aberrant Behavior Checklist Irritability Subscale, (ABC-I), the Clinical Global Impression Improvement Score, (CGI-I), and the Parenting Stress Index, short form (PSI). All subjects achieved a positive response on the ABC-I, defined as a ≥ 25% reduction in score from baseline to Week 7. A positive response was also observed on the CGI-I in all subjects (CGI-I score ≤ 2). Parenting stress scores decreased between baseline and Week 7 by > 5.7 (SD: 0.33) for all subjects’ parents, also considered a positive response. The study showed that Abilify®, at doses lower than recommended by the Food and Drug Administration, can be efficacious in treating disruptive behaviors in children with ASDs and that behavioral improvement is also associated
with decreased levels of parenting stress. While the preliminary results are promising, additional studies of low-dose Abilify® in treating disruptive behavior in children with autism are needed.
CHAPTER 1
INTRODUCTION

Epidemiology

The prevalence of Autistic Spectrum Disorder (ASD) is 1:88 children (Center for Disease Control and Prevention, 2012). This makes the diagnosis more common than pediatric cancer, AIDS, and diabetes combined (Center for Disease Control and Prevention, 2007). Features of ASD vary from nonverbal children with severe mental retardation and self-injurious behaviors to individuals with above-average intelligent quotients (IQs), language use impairment and poor social interaction skills (American Psychiatric Association, 2000; Lord & Spence, 2006). The continuum of pervasive developmental disorders, commonly referred to as autism spectrum disorders (ASDs), is comprised of five separate diagnoses: autistic disorder, Asperger’s disorder, pervasive development disorder not otherwise specified (PDD-NOS), Rett’s disorder and childhood disintegrative disorder (American Psychiatric Association, 2000). These are lifelong disorders with unclear etiology and no known cure (Autism, n.d.; Sutera et al., 2007). For the purpose of this manuscript, the term ASDs will be used to reflect the broader spectrum of clinical characteristics included in three of the pervasive developmental disorders defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR): autistic disorder (AD), Asperger Syndrome (AS) and pervasive developmental disorder – not otherwise specified (PDD-NOS) (American Psychiatric Association, 2000).

Prevalence estimates of ASDs have increased in recent years although debate continues regarding whether increased incidence is accurate or indicative of past rates underestimating the true prevalence (Autism, n.d.; Mitka, 2010). Current reports from the U.S. Centers for Disease Control and Prevention (CDC) indicate that 1 child in 88 was classified in 2008 as having an ASD compared to 1:110 in 2006 versus 1:153 in 2002. Further breaking down the numbers
reveals that ASD prevalence is rising across all racial, ethnic, sex and cognitive functioning subgroups. The prevalence in boys was reported to be 1 in 54, 1998 estimates, compared to 1 in 70, 1996 estimates. Prevalence in girls was reported to be 1 in 252, 1998 estimates, compared to 1 in 315 girls, 1996 estimates. Changes in estimated ASD prevalence during 2006-2008 indicate a 16% increase among non-Hispanic white children, a 42% increase among non-Hispanic black children and a 29% increase among Hispanic children (Center for Disease Control and Prevention, 2006). While increased recognition of the disorder by parents and medical providers is likely, the possibility that more children are being affected cannot be ruled out (Mitka, 2010). The Autism and Developmental Disabilities Monitoring (ADDM) Network data reported by the CDC confirms that estimated prevalence of ASDs continue to increase, underscoring the need for continued monitoring, identification of risk factors and support for persons with ASDs and their families (Center for Disease Control and Prevention, 2012).

**Historical Background**

Leo Kanner first described children with autism as exhibiting symptoms of aloofness and separateness from the world, narrow interests, repetitive behaviors, and poor language skills (Kanner, 1943). At approximately the same time, 1944, an Austrian pediatrician, Hans Asperger, described a group of school-age children with intact cognitive and language skills who experienced difficulties with social interaction, behavioral problems, idiosyncratic verbal communications and strong, often unusual areas of interest and intellect ranging from low ability to high ability with precocious language skills (Lyons & Fitzgerald, 2007).

Wing (2005) expanded upon Asperger’s observations and introduced diagnostic criteria into American psychiatry along with renaming the disorder Asperger Syndrome (AS). Diagnostic criteria for AS in the Diagnostic and Statistical Manual of Mental Disorders Text Revision 4th edition (DSM-IV-TR) clarifies the diagnosing of AS by adding exclusion criteria to
autism diagnostic criteria (Table 1-1) (American Psychiatric Association, 2000). AS is generally not considered to be as debilitating a disorder as autism; however, individuals with AS often present with significant social, mood and behavioral dysregulation beginning in childhood and requiring pharmacologic intervention (McPartland & Klin, 2006).

**Diagnostic Criteria for ASD**

Children with ASDs exhibit behavioral impairments to various degrees in three general areas: 1) social interaction, 2) verbal and nonverbal communication, and 3) repetitive, restricted, stereotypic patterns of behavior, interests, and activities. To meet diagnostic criteria for autism, symptom onset must begin before age three (American Psychiatric Association, 2000). Lack of speech is considered a hallmark of the diagnosis of autism especially when the child also displays a lack of desire to communicate and lack of compensatory gestures (American Academy of Pediatrics, n.d.). Approximately one-third of children with autism begin to say words but then stop speaking between 15 and 24 months of age (Parr, et al., 2011). Asperger Syndrome (AS) is characterized by language and early motor milestones generally considered to be within normal developmental parameters (single-word use by 24 months of age and speaking in phrases by 36 months) (Ozonoff, Garcia, Clark, & Lainhart, 2005). While speech may be fluent in a child with AS, it typically is limited to topics that hold an all-consuming interest for the child. Their style of speech is commonly described as overly formal or pedantic. Their use of language is predominantly self-centered and odd with a disregard for the thoughts and opinions of others (Johnson, Myers & the Council on Children with Disabilities, 2007). Children given the diagnosis of Pervasive Development Disorder Not Otherwise Specified (PDD NOS) do not meet the criteria for autism or Asperger Syndrome, although they exhibit many autistic symptoms included in the triad of ASD impairments including impaired social interaction, compromised social communication and restricted or repetitive behaviors. This is a diagnosis of exclusion and
includes atypical autism presentations that may not meet the criteria for a diagnosis of autism due to late age at onset, sub threshold or atypical symptomatology (American Psychiatric Association, 2000).

**Problem**

An increasing proportion of children with ASDs exhibit tantrums, destructiveness and self-injurious behaviors (RUPP, 2002). Disruptive, aggressive and self-injurious behaviors complicate the management of ASDs. These externalizing behavioral problems are closely related to parental stress (Reed & Osborne, 2012). These behaviors have increasingly and successfully been addressed in children with ASDs using pharmacology.

While all of the atypical antipsychotics have been researched to some degree, research regarding the use of risperidone, a twice or three times per day dosed medication has received the greatest attention and approval by the Food and Drug Administration (FDA) (RUPP, 2002; Stachnik & Nunn-Thompson, 2007). ABILIFY® (aripiprazole) followed, receiving FDA approval for treatment of irritability associated with autistic disorder in children and adolescents between 6-17 years-old (Mechcatie, 2009). Additional research is needed regarding the efficacy and dosing of atypical antipsychotics, also referred to as neuroleptics, in treating the severe disruptive behaviors often exhibited in children with ASDs.

**Ethical Considerations**

Of all prescription drugs currently available and approved for use by the FDA, only 20% to 30% have been approved for use in the pediatric population (Knox & Burkhart, 2007). Many providers use medications approved for use only in the adult population to treat children. This practice is referred to as off-label prescribing. Estimates are as high as 60% regarding off-label prescriptions written in the U.S. each year; with a majority of these prescriptions written for
pediatric patients. Extrapolating data from adult drug studies and applying this data to children has resulted in children being referred to as therapeutic orphans (Spetie & Arnold, 2007).

A primary concern with off-label prescribing is that many drugs are metabolized differently in children compared to adults; therefore, the safety and efficacy of medications tested on adults does not automatically transfer to the pediatric population. Weight adjusted doses are not generally applicable in children between ages 2-6 due to the increased rate in which medications are eliminated both through the liver and kidneys (Greenhill et al., 2003). Drugs may be toxic to children during certain phases of development. Children often experience adverse effects from medications that may not be experienced by adults using the same medication. The potential for physiological and anatomical vulnerability exists when treating children with pharmacotherapy (Spetie & Arnold, 2007).

Legal liability, economic factors and ethical considerations all contribute to the general reluctance surrounding evaluating drug safety and efficacy in children (Cote, Kauffman, Troendle, & Lambert, 1996). Distinguishing between effective treatments for children versus treatments based on research findings from adult subjects is vital in providing optimal care for children. Based in the principle of justice, children have the right to medical treatment grounded in sound research achieved through research involving the pediatric population rather than research with adult subjects.

**Drug Studies and Children**

Examining the effects of drugs on behavior is studied predominantly with a group comparison approach and large, multi-site randomized controlled trials. For example, at multiple sites, the Autism Network conducted a comparison of risperidone and placebo in treating symptoms of aggression, self-injurious behavior and severe tantrums in children with autism.
between the ages of 5 and 17 (RUPP, 2002). An alternative to traditional between-group designs is single-case experimental or single subject experimental designs (SSE).

**Single-Subject Experimental Designs**

The strength of SSE is their usefulness with small numbers of patients generating reliable, systematically generated data supporting evidence-based practice. Replication of single-case experimental studies of individuals leads to inferences regarding the generalizability of findings to other similar individuals. SSE offers an innovative approach to pharmacotherapy research and provides detailed information regarding the process necessary to produce significant behavioral change. This information is typically not identified in large between-group designs. SSE designs are particularly well suited for developmental-behavioral pediatrics and situations when large randomized controlled clinical drug trials are not feasible (Barlow, Nock, & Hersen, 2009). SSE is a logical research approach for clinicians in specialized settings for the following reasons: (1) matching large groups of patients with similar symptomatology is often impossible and cost prohibitive; (2) large group studies result in individual variations being masked by the group average while in SSE the size of the individual behavioral change is easily observed, facilitating the evaluation of clinical utility; (3) statistical error may be introduced when applying group statistics to individuals; (4) the dynamic nature of behavior makes representative sampling of individual behavior difficult to achieve; (5) replication of SSEs leads to inferences regarding generalizability to other similar individuals, and (6) withholding treatment from control group subjects raises ethical considerations (Kazdin, 1982).

**Theoretical Framework**

**General Systems Theory**

A system consists of interacting parts. The basic concepts of a general systems theory were introduced in the 1930s through 1950s (Berman, Snyder, Kozier, & Erb, 2008; Von...
Bertalanffy, 1950). Von Bertalanffy’s general systems theory recognizes the importance of the whole being greater than the part. Input, throughput, output, and feedback to the system are main tenets of the general systems theory. According to Von Bertalanffy (1950), inherent system conditions contribute to the hierarchy of systems and impact an organism’s ability to maintain itself in a steady state.

A theoretical concept that includes the interrelatedness of family members, based upon the general systems theory is that of the family systems theory (Begun, 1996; Carter & McGoldrick, 1980; Seligman & Darling, 1989). The family system is not static. As the family system strives to meet the needs of family members and the demands upon individuals and families from society, it continually changes and adapts. Phenomena affecting one family member (such as the diagnosis and symptomatology of ASD) inevitably impact all family members (Lutz, Patterson & Klein, 2012).

ASDs rank among the most stressful of childhood developmental disabilities (Gray, 2006). These children typically exhibit higher levels of behavioral difficulties compared to children with other chronic conditions (Herring, et al., 2006). There is a strong association between child behavior problems in children with ASDs and parenting stress (Osborne, McHugh, Saunders & Reed, 2008). Families with children diagnosed with ASDs have higher levels of stress compared to families with children who have other disabilities (Reed & Osborne, 2012). Parental stress is most strongly correlated, not with a child’s level of impairment, but rather with the child’s level of negative behavior (Estes et al., 2009). Maladaptive behaviors frequently include aggressive behaviors occurring outside the expected social context. The frequency, intensity, severity and/or duration of the aggression is problematic since these behaviors are often disproportionate to their cause or in complete absence of any identifiable antecedent
The physical and psychological needs, time demands and energy required to care for children with ASDs present unique challenges for parents who assume multiple roles as advocate, educator and caregiver of their child (Lutz et al., 2012).

**Theory and Research in Nursing Science**

Focusing on the individual with ASD within the context of the family, provides the conceptual framework for this study based upon Imogene King’s (1981) conceptual framework for nursing and her theory of goal attainment. Systems evolve and adapt over time in response to conditions affecting the system. Change in one element of the system affects all elements of the system. King (1981) defines health as the dynamic life experiences of a human being implying continuous internal and external adjustment to environmental stressors through the optimum use of one’s resources to achieve maximum potential. King (1981) views health and the environment as interrelated systems: “Health is the function of persons interacting with the environment. Environment is a function of balance between internal and external interactions,” (p. 127).

King’s conceptual framework involves three interacting systems: personal or individual systems, interpersonal or group systems and social or societal systems. The personal system includes concepts of perception and self. Perceptions are individualized and may be accurate or distorted. Accurate perception is necessary for goal setting and attainment but may be compromised due to internal and external stressors. The perception of self is described by King as a dynamic, open system influenced through interactions with others. Chronic illness, access to and experiences within the health care system as well as available support networks all impact ideas, attitudes and values composing one’s interpretation of self (King, 1981).

Within the interpersonal system, coping, roles, interactions, transactions and communication are key concepts. Both nonverbal and verbal communication is involved in interactions between individuals (King, 1981; Norris & Hoyer, 1993). Perception regarding the
roles of others, for example, the health care provider’s perception of parents in their role as caregivers or the parents’ perception of their personal roles, their child’s role and the roles of health care providers influence interactions and transactions (Goodwin, Kiehl, & Peterson, 2002). Judgments are made in response to perceptions resulting in reactions, action and interaction. Nursing’s role in this process is to act as a facilitator during interactions with parents and child. The nurse must perceive when education is appropriate and sufficient; while the client must perceive whether or not the education is necessary and valid based upon their personal priorities/concerns. The clients (parents and child) are viewed as partners in goal setting and goal attainment rather than in a sick role (Goodwin, et al., 2002).

Mutual goal setting requires active participation from all parties throughout their interaction and transaction. King (1981) assumes that individuals are rational and capable of engaging in competent decision-making. While Hanucharurnkul (1989) argues that King’s theory is not applicable in instances involving clients who are not capable of intelligent and rationale interactions with a nurse (such as children with significant development delays), this author refutes Hanucharurnkul’s claims based upon the inherent responsibility of parents for their children and the role of parents as decision makers. The accepted role of parents as decision makers and responsible providers for the care and wellbeing of their child can be understood in the broader context of King’s third system: the social system. The capacity of human beings to interact meaningfully with one another, pursuing commonly identified goals, allows patients to progress on all three levels of King’s conceptual framework (Aggleton & Chalmers, 1990). Meaningful interactions involving a child with ASD must include the parent and child interacting with the provider in a triad rather than the traditional provider-client dyad.
Consistent with King’s model, the life events of human beings include dimensions of
both health and illness. Family health is conceptualized in relationship to social systems with the
family identified as the primary social unit for an individual and the basic structural and
functional unit of society (Frey, 1989). A functional or healthy family adjusts to internal and
external stressors using healthy coping mechanisms to address situational crises as well as
maturation within the family unit (King, 1983). In a study by Frey (1989), 103 families having
children with diabetes mellitus were evaluated using a correlational design to test the hypotheses
that parent and child social support have a direct positive effect on family and child health.
Social support of the parents’ was identified as significant in the health and functioning of
families and children. It is true that the higher the level of perceived social support, the greater
the health of the family and the greater degree of social support for the child (Frey, 1989).

King defines the third component of her conceptual framework as “an organized
boundary system of social roles, behaviors, and practices developed to maintain values and the
mechanisms to regulate the practices and rules” (King, 1981, p. 115). The social system involves
an individual’s relationships with family members and other external systems (Burney, 1992).
Key concepts related to social systems include organization, authority, power, status and
decision-making. Power is client controlled and directed. The knowledge, skill, and expertise of
the RN/NP support the client, and for the purpose of a client unable to act on his/her own behalf,
their parent(s), in decision making. Status is recognized as ability and authority to make
decisions. Decision-making is a process in which the client selects one action from alternatives.
The client determines when the decision making process is necessary and what decision (if any)
to make. Appropriate (timely), sufficient (adequate amount of information) and effective
(cognitively processed by the client) education from the RN/NP can provide a foundation for
decision-making (Goodwin, et al., 2002). King (1981) recognizes that inaction is always an allowable decision and must be accepted if this is the informed decision of the client (Goodwin, et al., 2002).

King’s conceptual framework provides a structure for delivering holistic family care (Scott, 1998. The concepts support the basic nursing process method of assessing, planning, implementing and evaluating. The nursing process is a series of interrelated actions with both the nurse and the client possessing autonomy and rights of self-determination (King, 1997). Both parties (nurse and client) must determine to enter into the interaction (Goodwin, et al., 2002). The transactional process leads to mutual goal setting and the achievement of goals or outcomes providing the basis for evidence based practice (Meleis, 2007).

An additional concept defined by King is the environment as a social system (1990). King states that environment is both external and internal. The environment of a child would include systems such as the child’s family, school, athletic team, peers, and religious system as well as the child’s internal environment. The “internal environment of human beings transforms energy to enable them to adjust to continuous external environmental changes” (King 1981, p. 5).

Genetic, biochemical, physiological, psychological and neuroanatomical research all attempt to explain the causes of ASDs, or from King’s standpoint, the internal factors contributing to this disorder. Research regarding etiology is described as a “fragmented tapestry stitched from differing analytical threads and theoretical patterns” (Belmonte, et al., 2004, p. 928). Attempts at synthesizing theoretical explanations of ASDs support a connectivity model of autism. Brain activation in cortical regions involved in inhibitory control is under-connected in children with ASDs, specifically in the frontal and parietal regions (Kana, Keller, Minshew, &
Just, 2007). Additionally, a disruption of the dopaminergic and serotonergic systems are believed to contribute to aggressive behavior (Ecker, Spooren & Murphy, 2012). Targeting inhibitory and excitatory circuits, addressing the disruption to internal regulation, through the use of pharmacotherapy, requires further research (Rippon, Brock, Brown, & Boucher, 2007).

While a child with ASD has difficulties with internal regulation or adjustment, symptomatology such as stereotypic movements and disruptive or aggressive behaviors are expressed externally. Changes to a child’s internal state, for example through the use of psychopharmacology, will modify the child’s external state. The use of medication to decrease a child’s disruptive behavior is hypothesized to modify the entire system: a decrease in tantrums, self-injury and aggression in a child with an ASD will decrease parental stress improving the wellbeing of the family unit. King’s interactive systems are depicted in Figure 1.1. Adopting a complex adaptive systems approach requires accurate assessment of parental needs. Interventions based upon accurately and mutually identified goals encourage families to regain equilibrium (Scott, 1998; King, 1995).

### Purpose of Study

The purpose of this study was to examine the efficacy of the atypical antipsychotic Abilify® at doses lower than previously studied in treating disruptive behaviors in children with ASDs employing a single-subject design. The research question was identified based upon observations at Nemours Children’s Clinic, Jacksonville, Florida where psychiatric providers noted that doses as low as 1 to 2 mg. of Abilify® often provided control of disruptive behaviors and were well tolerated. Data regarding the potential benefit of this medication in treating disruptive behaviors within this special pediatric population were evaluated. The unique action of Abilify® as a partial DA D₂, 5HT₁A and 5HT₂A agonist sets this psychotropic medication apart from other medications classified as atypical antipsychotics (Stigler, Posey, & McDougle, 2004).
Additionally, Abilify®, aripiprazole, is a once daily dosed medication compared to risperidone, dosed two or three times each day. The use of once-daily dosing improves patients’ adherence to therapy and may improve health outcomes related to increased adherence. It may also be financially beneficial in terms of decreased medication costs (Clifford-Middel, 2004; McLaughlin, Hogue, & Stang, 2007; Richter, Anton, Koch, & Dennett, 2003).

**Hypothesis**

The partial dopamine agonist, Abilify®, will be well tolerated at low doses by children diagnosed with ASDs exhibiting significant disruptive behaviors and will decrease disruptive behaviors. A decrease in disruptive behaviors will have a positive effect on parents, reducing parental stress. Children function within a family system and it has been well documented that parents of children with developmental delays have higher levels of parental stress compared to parents with normally developing children (Lecavalier et al., 2006). Imogene King’s (1981) conceptual theory for nursing and her theory of goal attainment provide the theoretical underpinnings for this research based upon the involvement of three interacting systems, the child, the parents and the nurse researcher. Through their interactions, changes within the individual systems of the child and parent will occur supported by visual observations (behavioral observations of the child) and decreases in disruptive behaviors as evidenced by improved scores on the Aberrant Behavioral Checklist (Aman & Singh, 1994), and decreased parental stress as reported in the Parenting Stress Index (Abidin, 1995).

King’s Theory of Goal Attainment lies within the interpersonal system incorporating concepts of communication, interactions, perception, roles and transactions (Evans, 1991). Subjects in research often fail to distinguish between clinical care and research. Misconceptions are common regarding understanding the purpose and aim of the research (Beauchamp & Childress, 2009). The interaction involved in the informed consent process, provides the nurse
researcher with extended time to address therapeutic misconceptions through lengthy one-on-one conversation with the parent(s). In a review of dozens of trials of various interventions to decrease therapeutic misconceptions during the informed consent process, greatest success was found using lengthy conversations between the subject/parent and a member of the research team or a neutral educator and the research participant compared to other interventions such as the use of multimedia or enhanced consent forms (Flory & Emanuel, 2004).

In Chapter 2, research results from studies evaluating the use of all currently available atypical antipsychotics in treating disruptive behaviors in children with ASDs will be reviewed. Chapter 3 reviews the design and measures used in this research study. Chapter 4 reviews the results from this research and Chapter 5 includes the discussion and conclusions.
Table 1-1. Characteristics of children with autism spectrum disorders

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<th>Impaired Social Interactions</th>
<th>Repetitive, Restricted, Stereotypic Behavior</th>
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<th>Delayed or Abnormal Functioning before Age 3</th>
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<tr>
<td>Markedly deficient regulation of social interaction involving non-verbal behaviors, for example eye contact, facial expression, body posture, and gestures; Lack of peer relationships appropriate for developmental level; Absence of social or emotional reciprocity</td>
<td>An abnormal preoccupation of interests either in focus or intensity involving restricted and stereotyped behavior; Performing routines or rituals with no apparent function in a rigid manner; repetitive, stereotyped motor mannerisms, for example hand flapping or spinning; Persistent focus on parts or objects or specific items</td>
<td>Symptoms cause clinically significant impairment in social, occupational and/or personal functioning</td>
<td>Lack of age appropriate social interaction; language use for social communication is delayed or absent; Imaginative or symbolic play is absent or severely delayed.</td>
</tr>
</tbody>
</table>

* Autism: Minimum of six symptoms from the above list with clinically significant impairment in social, occupational or personal functioning.

* Asperger’s Syndrome: Minimum of two symptoms of impaired social interaction, 1 or more symptoms of repetitive, restricted, stereotypic behavior and evidence of clinically significant impairment in social, occupational or personal functioning with no clinically important delays in cognition, speech, self-help skills or adaptive behaviors with the exception of social interaction.

* PDD-NOS: Child does not meet criteria for a diagnosis of autism or Asperger’s disorder although they do exhibit severe, pervasive developmental disturbances that do not meet criteria for a diagnosis of schizophrenia, schizotypal personality disorder or avoidant personality disorder (American Psychiatric Association, 2000).
CHAPTER 2
LITERATURE REVIEW

History of the Use of Atypical Antipsychotics in Autism Spectrum Disorders

The Center for Disease Control and Prevention (CDC) analyzed 2003-2004 data from the National Health Interview Survey (NHIS) and the National Survey of Children’s Health (NSCH) reporting that approximately 83% of children with ASDs have moderate or high levels of hyperactivity and conduct problems compared to 15% of children without ASDs (CDC, 2006). Antipsychotics are the most widely used drugs for relieving significant behavioral symptoms in children with ASDs (Benvenuto, Battan, Porfirio, & Curatolo, 2012).

Of the atypical antipsychotics, risperidone and aripiprazole have been the most extensively studied. Both are approved by the Food and Drug Administration for treatment of pediatric patients with irritability associated with ASDs, including symptoms of self-injury, aggression and tantrums (Aman, 2009; Ortho-McNeil-Janssen, 2009; Otsuka Pharmaceutical Company 2008). Risperidone is approved for treatment of irritability in children with ASDs between the ages 5 to 16 years and aripiprazole is approved for children between the ages of 6 to 17 years (Stigler, Erickson, Mullett, Posey, & McDougle, 2010). In a search of the literature from 2002 to 2012 several scant studies evaluating the efficacy of olanzapine, ziprasidone, quetiapine, and paliperidone were also identified. Pediatric clinical trials and open-label studies of atypical antipsychotics used in the treatment of children with ASD and published in peer reviewed journals since 2002 were included in this review. Keywords included autism, Autism Spectrum Disorder (ASD), Pervasive Development Disorder (PDD), Asperger Syndrome (AS), and juvenile, or child, or children, or adolescent and atypical antipsychotic or risperidone, or olanzapine, or quetiapine, or aripiprazole, or ziprasidone, or paliperidone, or asenapine, or
paliperidone or iloperidone and “maladaptive behaviors” or “disruptive behaviors,” or tantrums or self-injury or aggression.

Whenever possible, double-blind studies were evaluated. Open-label studies were reviewed as well due to a limited number of randomized double-blind clinical trials. Clozapine, the first marketed atypical antipsychotic/neuroleptic was excluded from this study due to its higher than usual risk of potentially fatal agranulocytosis and the stringent parameters regarding monitoring white blood counts (Opgen-Rhein & Dettling, 2008).

**Pharmacologic Treatment for ASD**

Pharmacotherapy is only used in the presence of behavioral indications (Benvenuto et al., 2012; McCracken et al., 2003). The goal of treatment is to alleviate the most troublesome behavioral symptoms presenting the greatest challenges for teachers, parents and medical professionals caring for these children and interfering with intensive education and socialization plans (Malone, Gratz, Delaney, & Hyman, 2005; Rapin, 2002). While stimulants, antidepressants and antipsychotics are effective to varying degrees in managing symptoms, pharmacologic agents do not cure autism (Benvenuto et al., 2012; McCracken et al., 2003).

The first antipsychotic investigated in short-term as well as long-term studies was haloperidol. While a positive reduction in symptoms, including hyperactivity, aggression, temper tantrums, self-injurious behaviors, irritability, social withdrawal and stereotypic behaviors have been reported, the high risks of extrapyramidal symptoms including tardive dyskinesia limits the use of this medication (Malone et al., 2005; West & Waldrop, 2006). The concern regarding drug-related dyskinesias with the use of conventional antipsychotics, including haloperidol, has prompted clinical research to shift and focus on the use of atypical antipsychotics. The use of atypical antipsychotics in children with ASD is supported by the efficacy of these medications in treating similar behavioral symptoms in other disorders. For
example, atypicals are commonly prescribed to treat the negative symptoms of schizophrenia, and aggression related to conduct disorder.

**Risperidone**

Six randomized double blind placebo controlled trials (RCTs) evaluating the efficacy and tolerability of risperidone in treating behavioral symptoms often associated with ASDs have been conducted since 2002. One was excluded from this review due to including subjects with ages ranging from 8 to 56 (Hellings et al., 2009). Two additional open label studies of children followed by double-blind discontinuation phases are included in this review (RUPP, 2005; Troost et al., 2005) as well as one secondary analysis of an earlier randomized clinical trial (Pandina, Bossie, Youssef, Zhu & Dunbar, 2007).

The most recent study was by Aman et al. (2009). Aman and his colleagues compared the effects of risperidone and parent training on improving maladaptive behaviors. In this 24-week, three-site, controlled clinical trial, 124 children with ASDs and severe behavioral problems were randomized with a planned 1:2 randomization to receive medication alone (n = 49) or a combination of medication and parent training (n = 75). The 1:2 randomization was based on the assumption that most families would prefer combined treatment to medication alone. The groups did not differ regarding Clinical Global Impressions-Improvement scores at endpoint. However, medication combined with parent training, did result in significant reductions on the Aberrant Behavior Checklist subscales for irritability, stereotypic behavior and hyperactivity/noncompliance compared with medication alone ($p = 0.01$, $p = 0.04$ and $p = 0.04$ respectively) suggesting that further research regarding the combined effects of medication and intensive therapeutic interventions is warranted.

Miral et al. (2008) conducted a 12-week trial of 30 patients with ASDs, ages 8 to 18. Subjects were randomized to receive flexible-dosed risperidone or haloperidol. The study length
was twelve weeks, \( n = 32 \), with changes measured by the Ritvo-Freeman Real Life Rating Scale (RF-RLRS) the Aberrant Behavioral checklist (ABC) the Turgay DSM-IV PDD rating scale and the Clinical Global Impression Scales for severity and improvement (CGI-S, CGI-I). Improvement in symptoms was significant for both groups. Extrapyramidal symptoms were measured using the Chouinard Extrapyramidal Symptoms Rating Scale (ESRS) with changes from baseline significant \((p \leq 0.05)\) for the haloperidol group while scores for the risperidone group were not significant (Miral et al., 2008).

Nagaraj, Singhi and Malhi (2006), conducted a RCT over an eighteen month period of 39 children ages 2 to 9 years with autism, comparing levels of aggressiveness, hyperactivity and irritability, social and emotional responsiveness and communication skills. Nineteen children received risperidone and twenty children received placebo. Total scores on the Childrens’ Global Assessment Scale (CGAS) and on the Childhood Autism Rating Scale were primary outcome measures. Improvement was defined as an increase of 20\% or greater from baseline CGAS score and a 20\% or greater reduction in the CARS score from baseline to endpoint. The differences favoring risperidone were statistically significant, \( p < 0.001 \) and \( p = 0.035 \) respectively.

Luby and colleagues (2006) conducted a six-month trial examining the safety and efficacy of risperidone in a group of 23 preschool children aged between 2.5 to 6 years. Subjects were randomized to receive flexible dosed risperidone \((0.5 – 1.5 \text{ mg/day})\) or placebo. The children in the risperidone group \((n = 11)\) displayed significantly greater severity of symptoms at baseline compared to the placebo group as measured by the CARS \((p = 0.03)\). The groups combined CARS scores were significantly improved at endpoint \((p < 0.01)\) although behavioral differences between the two groups were statistically non-significant. The authors indicate that
many of the children participating in this study were also receiving intensive behavioral therapy, a confounding factor limiting the findings of this study.

Another randomized, double blind study investigating the efficacy and safety of risperidone for treating disruptive behavior symptoms associated with ASDs, was conducted by Shea et al. (2004). This study occurred over an 8-week period and included 79 autistic children ages 5 to 12 years. The mean dose of risperidone, 0.04 mg/kg/day, was well tolerated by the children participating in this study. Behavioral symptoms were assessed at baseline and during subsequent appointments throughout the study using the Aberrant Behavior Checklist (ABC) the Nisonger Child Behavior Rating Form (N-CBRF) the Clinical Global Impression-Change (CGI-C) and a Visual Analog Scale (VAS).

Results from week two through the study endpoint were significant for all instruments, ($\alpha = 0.05, p \leq 0.05$). At study endpoint, children receiving risperidone exhibited a 64% improvement over baseline irritability in the ABC sub-scale compared to 30.7% of children in the placebo group. In the hyperactivity/noncompliance subscale of the ABC, children receiving risperidone experienced a 69.2% improvement in symptoms compared to 39.5% of children in the placebo group. Conduct problems, anxiety, hyperactivity and over sensitivity significantly improved in the treatment group compared to the placebo group as measured by the N-CBRF. The CGI-C indicated more than twice the number of risperidone-treated children exhibited clinical improvement in symptoms at endpoint compared to placebo-treated children (87.2% versus 39.5%). The VAS asked parents to rate the severity of participants’ troublesome behavior, reporting significant improvement in aggression and tantrums/negative mood in the treatment group compared to the placebo group (Shea et al., 2004).
The most common medication side effect reported in this study was transient somnolence. This side effect resolved in 86% of the subjects either spontaneously, or with a dose reductions or a change in dosing regimen. Other reported side effects included upper respiratory infection (37.5%), rhinitis (27.5%), and increased appetite (22.5%). In the risperidone group, one subject experienced extrapyramidal side effects (EPS) due to an accidental overdose (Shea et al., 2004).

Limitations of this study include its short duration of time and the use of one instrument, the VAS, without established psychometrics. Strengths of the study include its being a randomized double-blind clinical trial that utilized three well established instruments to assess outcomes. Additionally, this study replicated an earlier study by the Research Units on Pediatric Psychopharmacology Autism Network (RUPP) conducted at multiple sites comparing risperidone to placebo in treating symptoms of aggression, self-injurious behavior and severe tantrums in children with autism between the ages of 5 and 17 (RUPP, 2002). Data from Shea et al., (2004), support the 2002 findings from RUPP.

The RUPP (2002) study enrolled 101 subjects with a mean age of 8.8 ± 2.7 years. This randomized, double-blind trial compared risperidone to a placebo over an eight-week period. The ABC irritability subscale (ABC-I) and the Clinical Global Impressions-Improvement Scale (CGI-I) were the primary outcome measures. Behavioral symptoms of irritability, hyperactivity and aggression were all found to significantly improve in the experimental group compared to the placebo. A positive response to treatment was defined as a 25% decrease in the irritability score and a rating of much improved or very much improved on the CGI-I scale (RUPP, 2002).

The experimental group received risperidone 0.5-3.5 mg/day (mean 1.8 ± 0.7 mg/day). At eight weeks, 69% of treatment responders were in the risperidone group compared to 12% in
the placebo group. Response in the risperidone group was reevaluated after six months in the extension phase of the study. Treatment response was reported at 68% after six months (RUPP, 2002).

Weight gain and increased appetite were significantly greater in the risperidone group compared to the placebo group. Other side effects were mild and included fatigue and drowsiness which subsided by week 6 and week 4 respectively. Findings from this study support results from open-label trials of risperidone treatment in children with autism and other pervasive development disorders (RUPP, 2002).

Pandina, Bossie, Yousseff, Zhu & Dunbar (2007) conducted a secondary analysis of the data from Shea et al. (2004). This analysis evaluated treatment response based upon the criteria from RUPP (2002) defined as a ≥ 25% improvement in the ABC-I sub-scale in addition to a CGI-C score of much improved or very much improved. Combined improvement in the ABC-I and CGI-C was significant (p = 0.0008), occurring in 58% of the risperidone group compared to 21% of the placebo group (Pandina et al., 2007).

Two additional studies were begun as open-label treatment studies with randomized, double-blind, placebo-substitution discontinuation protocol (RUPP, 2005; Troost et al., 2005). A two-part, multi-site study of risperidone in children between the ages of 5 to 17 years was conducted in 2005 by RUPP. The study enrolled 63 of the 101 subjects from the earlier RUPP (2002) study into an open-label four month treatment phase with risperidone. After four months of treatment, 38 of the 63 subjects agreed to continue in the study and in a double-blind fashion were randomly assigned to either continue risperidone or to gradually receive a placebo substitution. The aims of this study included determining if the short-term efficacy of risperidone was maintained over time; determining if the side effects from treatment remained
tolerable over time; and determining if sustained behavioral improvements were feasible with the discontinuation of risperidone after six months of treatment.

The relapse rate as measured by scores on the ABC-I was significantly higher in the placebo-treated group than in the group continuing with risperidone (62.5% compared to 12.5% respectively). Continued treatment with risperidone was associated with continued maintenance of behavioral improvements measured by the ABC sub-scales for hyperactivity, stereotypic behavior and lethargy/social withdrawal. Generally, the side effects associated with risperidone were not clinically significant with the exception of weight gain. Subjects gained an average of 5.1 kg. EPS was absent in all subjects during the discontinuation phase. This study followed inclusion criteria from the earlier 2002 RUPP study, limiting subjects to children diagnosed with autism experiencing severe behavioral problems (RUPP, 2005). The generalizability of this study to children with milder forms of ASDs is unknown.

Troost et al. (2005) conducted an open-label treatment study with risperidone followed by double-blind discontinuation evaluating the long-term efficacy of risperidone in treating behavioral symptoms associated with ASDs. Thirty-six children between the ages of 5 and 17 years participated. The majority of subjects had above-average or average IQ’s (50%) or borderline IQ’s (33%). Two subjects (17%) had mild or moderate retardation. Rating scales included the Clinical Global Impressions of Severity Scale (CGI-S) and the ABC-I. Only subjects with treatment response based upon criteria established in an earlier studies (RUPP, 2002) defined as a ≥ 25% improvement in the ABC-I subscale in addition to a score of much improved or very much improved on the CGI-C score after 8 weeks in the open-label treatment, were eligible to participate in the double-blind placebo substitution phase. Twenty-six subjects (72%) met continuation criteria. Short-term responders to risperidone continued on the
medication for an additional 16 weeks. Two subjects withdrew before the discontinuation phase due to parental perception that weight gain was unacceptable. The remaining 24 subjects participated in the discontinuation phase. A significantly ($\rho \leq 0.05$) increased rate of relapse was observed in the placebo group (67%) compared to the risperidone treatment group (25%) with higher levels of irritability and stereotypy reported in the placebo group compared to the risperidone group.

Significant side effects included increased appetite and weight gain. No EPS or withdrawal effects such as dyskinesias were observed. These results support findings from the previously discussed double-blind discontinuation study (RUPP, 2005). A summary of results from clinical trials with risperidone in this patient population appears in Table 2-1. Risperidone has demonstrated its utility for targeting irritability and other associated symptoms in children with ASDs, although such side effects as weight gain and increased prolactin levels are concerning, resulting in its overall effectiveness and tolerability not being uniformly optimal (Robb, 2010).

**Abilify®**

Two RTCs evaluating the efficacy and tolerability of Abilify®, aripiprazole, in treating behavioral symptoms often associated with ASDS have been conducted since 2002 (Marcus et al., 2009; Owen et al., 2009). Results from three open-label research studies are also included in this review. A fourth open-label study by Rugino and Janvier (2005) was excluded from the study due to evaluation of behaviors including different mental health diagnoses, ASDs ($n = 9$), bipolar disorder and comorbid attention-deficit hyperactivity disorder ($n = 7$).

The clinical efficacy and tolerability of aripiprazole use in children with developmental disorders was evaluated in an open label trial including children diagnosed with pervasive developmental disorder (Stigler, Posey, & MacDougle, 2004). The study included 5 male youths
between the ages of 5 and 18, median age 12.2 years. Study participants were evaluated using the CGI-I scale after receiving aripiprazole for a minimum of 20 weeks (maximum 24 weeks), treating symptoms of aggression, agitation and self-injurious behavior. All 5 patients had positive responses to the medication as indicated by ratings of much improved or very much improved on the CGI-I. The most common side effects reported were mild somnolence and weight loss due to switching from other agents more likely to cause weight gain. Specific measures assessing improvements in target symptoms were not included. Improvement was measured using one instrument, the CGI-I.

Stigler and colleagues (2009) conducted an open-label study of 25 children, between the ages of 5 and 17 years, over a fourteen-week period measuring improvements in disruptive behaviors with the CGI-I and the ABC-I. The average dose of aripiprazole was 7.8 mg/day. Subjects initially received 1.25 mg/day for 3 days then the dose was increased to 2.5 mg/day through week 2. Doses were increased to a maximum of 15 mg/day through weeks 6 if optimal clinical response had not occurred and adverse effects were tolerable. Subjects were considered treatment responders if they had a CGI-I score of 1 or 2 at endpoint and a 25% or greater improvement on ABC-I scores. Twenty-two of 25 subjects (88%) completed the study. The mean CGI-I score at endpoint was 1.6 ± 0.9, \( p \leq 0.0001 \). The mean ABC-I score at endpoint was 8.1 ± 7.5, \( p \leq 0.0001 \). Preliminary findings included lessening of irritability, aggression, and hyperactivity, and improvements in social responsiveness and communication. Four of the investigators in this study are affiliated with Bristol-Myers Squibb, the parent company of Otsuka Pharmaceuticals, which produces Abilify\textsuperscript{®}, the brand name of aripiprazole.

Two randomized, placebo-controlled studies have been conducted to evaluate the short-term efficacy and safety of aripiprazole in the treatment of irritability and other disruptive
behavior in children and adolescents with ASDs (Marcus et al., 2009; Owen et al., 2009). Study duration for both Marcus et al. (2009) and Owen et al. (2009) was 8 weeks. Subjects between the ages of 6-17 were randomized to receive aripiprazole or the placebo.

The Marcus and colleagues (2009) study included 218 children and adolescents, ages 6 to 17 years, mean age 9.7 years. Subjects were randomized to received placebo or aripiprazole 5 mg., or aripiprazole 10 mg., or aripiprazole 15 mg., in a 1:1:1:1 ratio. Doses were increased on a forced titration schedule until reaching the assigned daily doses with subjects unable to tolerate their assigned dose being discontinued from the study. Twenty-one subjects withdrew due to medication side effects with the three most commonly reported being sedation, drooling, and tremor. Treatment-emergent extrapyramidal symptoms were reported in 11.8% of the placebo group and 22-23% in each medication treatment group.

The ABC-I mean change from baseline to endpoint was the primary efficacy measure. Endpoint mean scores for all subjects receiving aripiprazole showed significantly greater improvement in behavior compared to placebo ($p < 0.05$). Likewise, CGI-I endpoint scores, a secondary efficacy measure, demonstrated significantly greater improvement compared to placebo, for subjects receiving 5 mg/day, $p = 0.003$; 10 mg/day, $p < 0.001$; and 15 mg/day, $p < 0.001$ (Marcus et al., 2009). All investigators involved in their study were affiliated with either Bristol-Myers Squibb or Otsuka Pharmaceuticals.

Owen et al. (2009), in a smaller study (n = 98), also used the ABC-I as the primary efficacy outcome measure and the CGI-I score at endpoint as the key secondary outcome measure. Findings were similar to those of Marcus and colleagues (2009) and are reported in table 2-2. Minimal side effects were reported in the aripiprazole treated patients and most were described as mild to moderate. Most commonly reported side effects were fatigue and
somnolence. Eight subjects treated with aripiprazole and four subjects receiving placebo reported extrapyramidal symptoms (Owen et al., 2009). Individuals from both aripiprazole blinded studies had the opportunity to continue after the 8-week studies in an open-label, 52-week extension trial (Marcus et al., 2011).

Marcus et al. (2011) reported on the long-term efficacy, safety, and tolerability of aripiprazole in a 52-week open-label, flexible-dose study. Eligible subjects were enrolled from the two 8-week randomized trials reported above as well as de novo subjects. A total of 333 subjects were enrolled in this research study to receive treatment: de novo (history of treatment with aripiprazole and reported positive response but not previously enrolled in RCTs), n = 86; prior aripiprazole, n = 174; prior placebo, n = 70, with 199 subjects completing the 52 weeks of treatment. Confounding factors in this study included subjects receiving concomitant antidepressants, psychostimulants, and antiepileptics with no indication regarding whether or not changes in dosing of the concomitant psychotropic medications were permitted.

Subjects began the study with all receiving 2 mg/d of aripiprazole with both the clinicians and subjects blinded to treatment assignments from the previously reviewed RTCs. If deemed appropriate by the investigator, dosing was increased as frequently as every 4 days based upon the patient’s clinical response and medication tolerability. Increases occurred incrementally from the subject’s current dose level to the next level (2 mg., 5 mg., 10 mg., and 15 mg.). The primary efficacy measure was the ABC, including all five of the subscales: irritability, lethargy/social withdrawal, stereotypic behavior, hyperactivity, and inappropriate speech. The CGI-I was among the secondary efficacy measures. Results from this study support the findings from both RCTs and are summarized in Table 2-2.
Olanzapine

Since 2002, three studies, either open label or RCT, were identified involving treatment of ASDs in children with olanzapine. One was a small (n = 11) double-blind, placebo controlled study (Hollander et al., 2006), another was an open-label trial of olanzapine in children with ASDs (Kemner, Willemsen-Swinkels, De Jonge, Tuynman-Qua, & Van Engeland, 2002). The third was a prospective open-label trial conducted with 40 male children (Fido & Al-Saad, 2008).

In the only double-blind, placebo-controlled trial, olanzapine was compared to placebo over eight weeks, with n = 11 children between the ages of 6 and 14 years. Six children were diagnosed with autism, one child with Asperger Syndrome, and four children with PDD-NOS. The primary outcome measure was the CGI-I. Secondary measures included the CY-BOCS, and the Overt Aggression Scale –Modified irritability and aggression subscales. A significant response was observed in 3 of the 6 subjects receiving olanzapine compared to 1 of 5 in the placebo group (p = 0.012) based on CBI-I scores. Response was not significant on other outcome measures. Weight gain was the only significant side effect reported, 3.4 kg ± 2.2 kg in the olanzapine group compared to 0.68 kg ± 0.68 kg in the placebo group (p = 0.028). No patients experienced EPS during this trial. Limitations of the study include a small and unequal sample size (6 children in the olanzapine arm and 5 children in the placebo arm) (Hollander et al., 2006). However, behavioral improvements based upon the CGI-I, support findings of larger studies conducted using the atypical antipsychotic, risperidone.

An open-label study of olanzapine involving 25 children ages 6-16, diagnosed with ASD, evaluated the safety of olanzapine and its usefulness in treating communication problems (Kemner et al., 2002). Twenty-two children completed the trial and were included in the statistical analysis. Outcome measures included the ABC, the TARGET, and the CGI. Significant improvements were found on the ABC subscales for irritability, hyperactivity and
excessive speech although results of the CGI-I indicated only three children were considered
global responders (much or very much improvement) with other children showing minimal
improvement. Improvement of behavior considered by parents to be socially inadequate was
measured with TARGET. End scores were significantly lower than initial scores. Weight gain
and sedation were side effects. The average weight gain in 14 children reporting this side effect
was 5.8 kg. Due to small effects on the CGI-I, with only three subjects being global responders,
the clinical relevance of olanzapine in treating behavioral symptoms related to ASD should be
questioned (Kemner et al., 2002). Like the Luby preschoolers in the risperidone trial (Luby et
al., 2006), the low response rates in this trial may have been related to lower baseline irritability
levels of 11/45 maximum on the ABC-I. FDA registration trials for medication to treat
irritability in ASDs require a score on the ABC-I ≥ 18 at baseline (Robb, 2010).

The most recent study identified (Fido & Al-Saad, 2008) was an open-label trial
conducted with n = 40 male children ages 7 to 17 (mean age 12.2 ± 2.2 years). The efficacy and
safety of olanzapine in the treatment of disruptive behaviors in children with autism was
evaluated over a 13-week treatment period. The primary efficacy measures were the Aberrant
Behavior Checklist (ABC) and Clinical Global Impressions-Severity (CGI-S) comparing
baseline measures to end of treatment. Significant reductions in the ABC subscale scores for
irritability, lethargy, hyperactivity (p < 0.001), and stereotypic behavior, as well as inappropriate
speech (p < 0.005) were reported. According to the CGI-S score, 12 out of 40 patients (30%)
were considered “improved” compared to baseline, a statistically significant difference (p <
0.05).

There has been one case report on olanzapine that warrants mention involving a 13-year-
old male treated intramuscularly with olanzapine for severe disruptive behaviors after
discontinuation of risperidone. The young man developed rhabdomyolysis, requiring prompt discontinuation of the olanzapine and forced diuresis and alkalization of his urine. Within one week his elevated lab values (creatine kinase and liver function tests) began to normalize (Karakaya, Yis, Kurul & Turkmen, 2010). Other reports regarding adverse reactions to olanzapine have been reported to the FDA including creatine kinase elevations ranging from 6,000 to 100,000 IU/L\(^{-1}\) requiring diuresis and alkalization to prevent renal failure from the myoglobinuria (Robb, 2010).

**Quetiapine**

Two open label studies evaluating the efficacy of quetiapine in treating adolescents suffering from ASDs were identified as well as one retrospective study, included in this review due to the scarcity of studies published regarding the efficacy of quetiapine in treating disruptive behaviors in children with ASDs. Findlings et al. (2004) enrolled nine males, including six subjects who had been treated previously with other psychotropic medications. Symptoms were evaluated using the five subscales (irritability, agitation, crying; lethargy, social withdrawal; stereotypic behavior; hyperactivity, noncompliance; and excessive speech) of the ABC as well as the CGI-I. Both the Abnormal Involuntary Movement Scale (AIMS) (National Institute of Mental Health, 1985) and the Neurological Rating Scale (NRS) were obtained during each visit to assess for extrapyramidal side effects (EPS) (Findling et al., 2004).

Six of the subjects completed this twelve-week study. While several instruments, including the Children’s Psychiatric Rating (Campbell & Palij, 1985) scale, and the lethargy, stereotypy and hyperactivity subscales of the ABC indicated statistically significant improvement, substantial clinical benefit was observed in only two of the patients. The end-of-study measures from the CGI were not significant. Sample size and potential for a placebo response due to the lack of a control group for comparison are limitations of this study.
In a retrospective chart review by Hardan, Jou, & Handen (2005) of ten patients treated with quetiapine over a period of 18 months, 60% of the children responded favorably to treatment. Subjects were considered responders if their CGI-I score was very much improved or much improved. The CGI-I measurement parameters show consistency in many of the studies evaluating the efficacy of atypical antipsychotics in children with ASDs.

The Connors Parent Scale (CPS) (Goyette, Conners, & Ulrich, 1978) was used by Hardan et al. (2005) to assess disruptive behaviors during monthly follow-up appointments. Paired t-tests with a significance level set at $\rho \leq 0.05$ showed a significant improvement on the CPS subscales for inattention and hyperactivity. No significant differences were identified on the anxiety, learning or psychosomatic subscales. This study was small and provided no controls regarding cognitive functioning and comorbid psychopathology.

The most recent study of quetiapine evaluated eleven adolescent patients (8 males, 3 females) in an open-label 8-week study. The CGI-I evaluated aggressive behaviors. No significant findings were reported (Golubchik, Sever, & Weizman, 2011). The benefits of treating ASD associated behavioral symptoms with quetiapine are not well supported in the literature. Further research using open-label and double-blind placebo-controlled studies are needed (RUPP, 2002, 2005).

**Ziprasidone**

Evidence supporting the use of ziprasidone in children with ASDs is primarily anecdotal. One case series of 12 patients was identified (RUPP, 2002). A case study by Goforth & Rao (2003) of a seven-year old boy was identified as well as a case study of a 15 year-old male by Duggal (2007). The most recent study was an open label pilot study by Malone, Delaney, Hyman & Cater (2007), $n = 12$. 
Six (50%) of the subjects in the case series (n = 12) were considered responders to treatment after six weeks based upon responses to the CGI-I of very much improved or much improved while two subjects, both with comorbid bipolar disorder were rated as much worse on the CGI-I. Sedation was the most common side effect reported. These data were not statistically analyzed (RUPP, 2002).

Ziprasidone was evaluated in a single case study of a 7-year old male with ASD demonstrating impulsivity, irritability, hyperactivity, and intermittent nocturnal awakenings. Previous failed therapies included mixed amphetamine salts, guanfacine, sertraline, and divalproex sodium. After 8 weeks of treatment, physician and parents both rated the child as much improved on the CGI. Sustained improvements were observed after 8 months of continuous treatment (Goforth & Rao, 2003).

Duggal (2007) reported a decrease in maladaptive behaviors including aggression, self-injurious behavior, and temper tantrums in a 15-year-old autistic male. Previous failed medication trials included methylphenidate alone and with risperidone or quetiapine. The patient returned for follow up after two weeks (ziprasidone dose: 20 mg on day 1, 40 mg. twice a day on day 2, 60 mg. twice a day during day three and subsequent days). Parents and provider rated the young man as much improved on the CGI. At the two-month follow up, improvement continued with a ziprasidone dose of 60 mg. twice-a-day and an unchanged methylphenidate dose of 60 mg/day.

An open-label pilot study was identified evaluating the efficacy of ziprasidone in treating symptoms of hyperactivity, aggression, self-injurious behaviors, tantrums, irritability, social withdrawal and stereotypic behaviors in children with ASDs. Malone, Delaney, Hyman & Cater (2007) enrolled twelve adolescents with autism (mean age 14.5 ± 1.8 years). Subjects were
treated for 6 weeks. Medication dose ranged between 20-160 mg/day, mean ziprasidone dose = 98.3 ± 40.4mg/day. Based on the CGI-I, 9 of the 12 subjects, 75%, were rated as responders (much improved or very much improved) at study endpoint. A key secondary efficacy measure, the ABC showed statistically significant decreases for the irritability and hyperactivity subscales (paired t-test, \( p = .05 \) and \( p = .01 \) respectively). There were no side effects or weight gain, prolactin levels remained stable and cholesterol levels decreased in study subjects. Two subjects did experience dystonia and an average increase in the QTc of 14.7 ms. Children with cardiac conduction anomalies including arrhythmias are not candidates for this medication (Robb, 2010). More rigorous research is needed to substantiate the findings of these studies.

Since 2011, three additional atypical antipsychotics have been approved for the treatment of schizophrenia in adults: asenapine, iloperidone, and paliperidone (Maher & Theodore, 2012). No clinical trials have been conducted regarding the use of the three most recently FDA-approved atypicals in treating irritability and associated symptoms in children with ASDs. Three case studies have been reported involving the use of paliperidone to treat irritability in individuals with ASDs. The subjects included a 20-year-old male, a 16-year-old female, and a 5 year-old male. The primary efficacy measure for each case study was the CGI-I. In each case study, subjects’ CGI-I endpoint scores indicated “much improved,” or “very much improved” in terms of their irritability and disruptive behaviors (Kowalski et al., 2011; Stigler, Erickson, Mullet, Posey & McDougle, 2010).

The most recent study reported by Stigler, Mullet, Erickson, Posey & McDougle, (2012) was an 8-week open-label study of paliperidone, \( n = 25 \) adolescents and young adults with autism. The mean final dosage of paliperidone was 7.1 mg/day (range 3-12 mg/day). Two subjects discontinued prior to study endpoint due to side effects of sedation and one discontinued
prior to study endpoint due to no noticeable therapeutic effect with treatment. The primary outcome measures included the CGI-I and the ABC-I. CGI-I endpoint scores were significantly decreased (‘much improved’ or ‘very much improved’) and scores on the ABC-I improved ≥ 25% in 84% of the subjects (n = 21), p < 0.001 for both measures.

Conclusion

Double-blind, placebo-controlled studies of risperidone and aripiprazole as well as results from a more limited number of studies involving other atypical antipsychotics demonstrate superiority over placebo in reducing irritability and other disruptive behaviors in children with ASDs. The most common instruments used in these studies to rate improvements in disruptive behaviors include the Aberrant Behavior Checklist (ABC) and Clinical Global Impressions (CGI) scores (National Institute of Mental Health, 1985). With the exception of risperidone and aripiprazole, use of atypical antipsychotics in children with ASDs is considered off-label. A retrospective study of commercial claims and encounters with children under age 21 with a diagnosis of ASDs (n = 2390) reports that 23.5% of patients were prescribed an atypical antipsychotics during 2002 (Oswald & Sonenklar, 2007). Estimates are as high as 60% regarding off-label prescriptions written in the U.S. each year; with a majority of these prescriptions written for pediatric patients. Extrapolating data from adult drug studies and applying this data to children has resulted in children being referred to as therapeutic orphans. This term was first coined in 1968 due to the lack of clinical trials involving the use of pharmaceuticals in children (Morales-Olivas & Morales-Carpi, 2006).

Aripiprazole is approved by the U.S. Food and Drug Administration for the treatment of ASDs with recommended dosing of 5-15 mg. It is approved for use in treating schizophrenia in adolescents and for short-term treatment of bipolar disorder in children aged 10 to 17 with typical doses ranging from 10 to 30 mg/day (Chang, 2008). Average dosages of aripiprazole in
reported research regarding its effectiveness and tolerability in treating children with ASDs ranged between 10 to 12 mg/day (Rugino & Janvier, 2005; Stigler, Posey & McDougle, 2004).

Increased dosing of atypical antipsychotics leads to greater receptor binding and is associated with an increase in side effects and adverse reactions (Corell, 2008). Research regarding the use of aripiprazole at lower doses than previously reported in treating disruptive behaviors in children with ASDs may provide valuable data regarding maximizing potential behavioral benefits while minimizing such risks of adverse reactions as metabolic effects, sedation, and psychotropic-induced extrapyramidal symptoms. Children with ASD are more sensitive to the dosing of dopaminergic medications. The National Institute of Mental Health (NIMH) stresses the need for evidence based practices and more research regarding identifying medications that work best in reducing aggression, self-injurious and obsessive-compulsive behaviors in children with autistic spectrum disorders. NIMH considers the use of atypicals in this population to be very effective but due to the narrow therapeutic window more research is needed identifying optimal dosing of these medications (U.S. Department of Health and Human Services, 2005).
Table 2-1. Summary of risperidone trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Number of Subjects, (Males), Age Range, Mean Final Dose</th>
<th>Outcome Measures</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Research Units on Pediatric Psychopharmacology Autism Network (RUPP); 2002, 2005</td>
<td>8 week, multi-site, randomized double blind trial (phase 1), treating tantrums, aggression and self-injurious behavior</td>
<td>N = 101, (82); 5-17 years; mean 8.8±2.7 Mean final dose: 1.8 mg ± 0.7 mg/d</td>
<td>ABC-I &lt; 56.9% with treatment versus &lt;14.1% with placebo (p≤0.001); CGI-I, 69% improvement with treatment versus 12% improvement with placebo</td>
<td>Improvement observed in stereotypy, aggression, tantrums, irritability, hyperactivity and self-injurious behaviors</td>
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<td>4 month open-label trial (phase 2) evaluating side effects and if short-term efficacy is maintained over time.</td>
<td>N = 63, (49); 5-17 years; mean 8.6 ± 2.8 Mean dose, week 0-1: 1.96 mg/d; mean dose week 16 = 2.08 mg/d</td>
<td>ABC-I score change not significant between phases comparing risperidone treatment groups</td>
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<td>8 week placebo controlled discontinuation (phase 3) to determine the feasibility of discontinuation of medication after 6 months of treatment.</td>
<td>N = 38 (♂ not specified); 32 subjects completed discontinuation phase</td>
<td>Placebo group relapse rate = 62.5%, continued medication group relapse = 12.5% (p=0.01).</td>
<td>National Institutes of Mental Healthy Data Safety and Monitoring Board ruled that the discontinuation phase be stopped due to rapid increase in aggressive behaviors with discontinuation</td>
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<tr>
<td>Study</td>
<td>Study Design</td>
<td>Number of Subjects, (Males), Age Range, Mean Final Dose</td>
<td>Measures</td>
<td>Symptoms</td>
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<td>Shea, S., Turgay, A., Carroll, A., Schulz, M., Orlic, H, Smith, I, et al. (2004)</td>
<td>8 week, double blind placebo controlled multi-center outpatient study</td>
<td>N = 79, (61); 5-17 years; mean 8.8 ± 2.7 years. Mean final dose = 1.8 mg ±0.7 mg/d</td>
<td>ABC-I &lt; 56.9% (risperidone) versus &lt; 14.1% placebo (p&lt;0.001); CGI-I = 69% improvement with treatment versus 12% with placebo (p&lt;0.001)</td>
<td>Improvement with treatment observed in stereotypy, irritability, aggression, hyperactivity, and self-injurious behaviors</td>
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<tr>
<td>Troost, Pl, Lahuis, B., Steenhuis, M., Ketelaars, C., Buitelaar, J., Van England, H., et al. (2005)</td>
<td>Phase 1: 8 week open-label treatment phase identifying short-term responders</td>
<td>Phase 1: N = 36, (22); 5-17 years; mean 9 years. Mean medication dose = 1.81 mg/d</td>
<td>Phase 1: CGI-I 69% much improved or very much improved</td>
<td>With treatment, improved speech, social reciprocity, decreased stereotypic behaviors, hyperactivity, anxiety, and emotional lability observed</td>
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<tr>
<td>Luby, J., Mrakotsky, C., Stalets, M., Belden, A., Heffelfinger, A., Williams, M., et al. (2006)</td>
<td>6-month randomized, double-blind, placebo-controlled trial</td>
<td>N=24, (17); 2.5-6 years; mean 4.1 years (49 months) Mean medication dose = 1.14 mg/day or 0.05 mg/kg/day</td>
<td>Childhood Autism Rating Scale (CARS); risperidone group: -4.6; placebo:-1.8; p=0.114</td>
<td>Symptom improvement was not significant between groups</td>
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<tr>
<td>Study</td>
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<td>Number of Subjects, (Males), Age Range, Mean Final Dose</td>
<td>Outcome Measures</td>
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<td>Nagaraj, R., Singhi, P., &amp; Malhi, P. (2006)</td>
<td>6-month randomized, double-blind, placebo controlled trial</td>
<td>N=40 (♀ not specified); 2-9 years; Forced titration schedule, final dose = 1 mg/day</td>
<td>CARS: -7.5, risperidone group; -1, placebo group; ( p &lt; .001 )</td>
<td>Aggressive behavior, hyperactivity decreased by 18% in treatment group, social responsiveness and nonverbal communication improved in 57% of treatment group</td>
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<td>Children’s Global Assessment Scale Score: 20% improvement in 17 of 20 children in risperidone group, compared to 2 of 21 children in placebo group ( (p = .035) ).</td>
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<td>Global Impression of Parents: not statically significant between groups</td>
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<td></td>
<td>12-Item Parent Questionnaire indicated significant improvement in treatment group for social responsiveness ( (p = .014) ), nonverbal communication, ( (p = .002) ), and aggression ( (p = .016) )</td>
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<tr>
<td>Study</td>
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<td>Miral, S., Gencer, O., Ianl-Emiroglu, F., Baykara, B., Baykara, A., Dirik, E. (2008)</td>
<td>Randomized, double-blind, placebo controlled 12 week trial</td>
<td>N = 30, (24); 7-17 years, mean age 10±2.9 (risperidone group), 10.9 ± 2.9 (haloperidol group). Both medications were initiated at .01 mg/kg/day and titrated to .04 mg/kg/day by end of week 2 then to .08 mg/kg/day for remainder of study</td>
<td>Aberrant Behavior Checklist, Turgay DSM-IV Pervasive Development Disorder Rating Scale and the Ritvo-Freeman Real Life Rating Scale : In all cases, the risperidone group had greater improvement in scores ($p \leq .005$); CGU-I scores were not significantly different baseline to endpoint between the two study groups</td>
<td>Greater improvement is symptoms (irritability, aggression, hyperactivity, social responsiveneess, communicati on) in risperidone treated group compared to haloperidol treated group</td>
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<tr>
<td>Aman, et al. (2009)</td>
<td>24-week, three site, randomized, parallel-group clinical trial</td>
<td>N = 124; 4-13 years. 2:1 randomization adopted due to assumption most families would prefer risperidone and parent training rather than medication alone. Combined group (COMB), n = 75; medication alone group, n = 49. Risperidone monotherapy: 0.5 mg – 3.5 mg/day with a change to Abilify® at week 8 if risperidone ineffective</td>
<td>Groups did not differ on the CGI at endpoint. COMB showed significant reductions on the ABC-Irritability, Stereotypic and Hyperactivity/Non compliance subscales ($p &lt; .05$). COMB was superior to medication alone on the Home Situation Questionnaire.</td>
<td>Both groups experienced a reduction in disruptive, aggressive behaviors. The Homes Situations Questionnaire indicates an additive benefit of parent training regarding improving aberrant behaviors.</td>
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<tr>
<td>Study</td>
<td>Study Design</td>
<td>Number of patients, (males), age range, Active drug/mean final dose</td>
<td>Outcome Measures</td>
<td>Symptoms</td>
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<td>Stigler, K., Posey, D. &amp; McDougle, C.</td>
<td>Naturalistic, open-label trial of aripiprazole for 8-16 week duration.</td>
<td>N = 5 males, ages 5-18 years. Mean dose of aripiprazole = 12.0 mg/day</td>
<td>All five patients responded based upon the CGI-I scale with ratings of much improved or very much improved. No changes in heart rate or blood pressure were reported, no extrapyramidal symptoms observed.</td>
<td>Aggression, hyperactivity, irritability and self-injurious behaviors</td>
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<td>Stigler, K., Diener, J., Kohn, A., et al.</td>
<td>14 week open-label study</td>
<td>N = 25; age 5-17 years, mean age = 8.6 Medication dose range: 2.5 mg/day – 15 mg/day.</td>
<td>ABC-I scores and CGI-I scores (much or very much improved) were significantly improved, ( p \leq 0.001 ) and ( p \leq 0.001 )</td>
<td>Irritability, aggression, hyperactivity, social responsiveness, and communication</td>
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<td>Owen et al. (2009)</td>
<td>8 week double-blind, randomized, placebo-controlled, parallel-group study with flexibly dosed aripiprazole or placebo</td>
<td>N = 98; age 6-17; ABC-I and CGI-I scores significantly greater with aripiprazole than placebo; ( p \leq 0.001 ).</td>
<td>Irritability, tantrums, aggression, self-injurious behaviors.</td>
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<tr>
<td>Study</td>
<td>Study Design</td>
<td>Number of patients, (males), age range, Active drug/mean final dose</td>
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<td>Marcus et al. (2009)</td>
<td>8 week double-blind, randomized, placebo-controlled, study, forced titration schedule of aripiprazole to 5 mg/d, n = 53; 10 mg/d, n = 59; 15 mg/d, n = 54</td>
<td>N = 218; age 6-17 years; mean age = 9.7; placebo group n = 52; aripiprazole</td>
<td>All medication groups demonstrated statistically significant improvements compared to placebo in the ABC-I scale (5 mg/d group ( p \leq 0.003 ); 10 mg/d group ( p \leq 0.001 ); 15 mg/d group ( p \leq 0.001 ). CGI-I was greater in aripiprazole treated subjects compared to placebo ( p \leq 0.001 ).</td>
<td>Irritability, tantrums, aggression, self-injurious behaviors</td>
</tr>
<tr>
<td>Marcus et al. (2011)</td>
<td>52 week, open label, flexible-dose study</td>
<td>N = 330, n = 244[completed Marcus et al. (2009) or Owen et al. (2009) studies] and n = 86 de novo subjects who had not participated in either trial; age 6-17; mean aripiprazole dose and insomnia. = 10.6 mg/day. 60.3% of subjects completed study</td>
<td>87% of children (286) experienced adverse events, most commonly weight gain, vomiting, nasopharyngitis, increased appetite, pyrexia, upper respiratory tract infection, insomnia.</td>
<td>Irritability, tantrums, aggression, self-injurious behaviors</td>
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CHAPTER 3
METHODOLOGY

Rigorous pharmacologic research specifically involving children is necessary to provide this population with optimal, evidence-based treatment. Based upon the principle of justice, children have the right to medical treatment grounded in sound research based upon data gathered involving the pediatric population rather than adults. Many drugs are metabolized differently in children compared to adults. The safety and efficacy of medications tested on adults does not automatically transfer to the pediatric population. Protecting children from harm and exploitation is arguably our most important duty as providers. Medications used in treating children should be based upon research conducted with children. The aim of this study is to obtain data regarding the effectiveness and tolerability of low dose Abilify® (aripiprazole) in treating significant disruptive behaviors among children and adolescents with ASD.

Design

Single Subject Versus Control/Experimental Groups

This was a single-case research design or single subject experimental design (SSE) evaluating the effectiveness and tolerability of low-dose Abilify® in treating severe disruptive behaviors in children with ASD. While group comparison approaches are most common in drug evaluations, the traditional experimental group/control group method does not lend itself readily to psychiatry (Barlow & Herson, 1973). Single-case experimental designs (SSEs) are well suited to evaluate the effects of drugs on behavior (Kazdin, 1982). There are several reasons why this design is better suited to the research question than more traditional approaches. These include: (1) matching large groups of patients with similar symptomatology is often impossible and cost prohibitive; (2) large group studies result in individual variations being masked by the group average while in SSE the size of the individual behavioral change is easily observed, facilitating
the evaluation of clinical utility; (3) statistical error may be introduced when applying group statistics to individuals; (4) the dynamic nature of behavior makes representative sampling of individual behavior difficult to achieve; (5) replication of SSEs leads to inferences regarding the ability to generalize to other similar individuals and (6) withholding treatment from control group subjects raises ethical considerations (Barlow & Hersen, 1973; Elder, 1997; Tervo, Estrem, Bryson-Brockmann & Symons, 2003).

A three-phase withdrawal design - including baseline measurements (no intervention), intervention measurements and return to baseline (ABA design) - was utilized. During the withdrawal phase, a placebo was administered. Repeated, systematic measurements of target behaviors occurred before, during and after the administration of the independent variable, Abilify® under controlled conditions. Target behaviors included aggressiveness, irritability, and self-injury. The starting dose of Abilify® was 1.0 mg/day x 7 days then it was increased to 2 mg/day. Medication was administered once daily. Table 3-1 illustrates this research design.

**Rationale for the A-B-A Design**

The A-B-A design is more favorable in evaluating the effects of Abilify® on aberrant behaviors compared to the A-B design due to the added control effects introduced by the third phase of this design, withdrawal of medication. In order to demonstrate a causal relationship between the introduction of Abilify® and improvement in aberrant behaviors, withdrawal of the independent variable was necessary. Measurements of behavior in two phases of the study baseline and return to baseline, without intervention, increased the degree of certainty that changes during the intervention phase were related to the intervention rather than spurious outcome effects. The A-B-A design improved the ability to infer causality compared to the A-B design (Barlow et al., 2009; Janosky et al., 2009). This design decreases threats to internal validity inherent in the more simple A-B design and is appropriate to the clinical setting. The A-
B-A design represents a true experimental design. Utilizing a research design with one intervention phase also takes into consideration the length of the research study and cost, important considerations regarding the feasibility of the study (Barlow et al., 2009; Janosky et al., 2009).

**General Description of Placebo**

Abilify® 2-mg tablets were blinded by placing a single 2-mg tablet into a size 3 white gelatin capsule supplied by Gallipot®, Inc. (2400 Pilot Knob Road, St. Paul, Minnesota 55120, Phone: 1-877-207-8895, Fax: 1-800-339-1596, E-mail: info@gallipot.com, http://www.gallipot.com/). The white gelatin capsule also served as placebo and was filled with cellulose microcrystalline, NF.

**Sampling**

A convenience and consecutive sampling approach was utilized to recruit research subjects. Continuing medication management following the completion of the research study was available for study subjects, an important consideration in the event that causation was established with aberrant behaviors returning to baseline or trends indicating an increase in disruptive behaviors during the withdrawal phase.

**Measures**

**Monitoring Measures**

Baseline measures included medical and psychiatric history, vital signs (weight, height, pulse, systolic and diastolic blood pressure), laboratory tests including a complete blood count, Chemistry 12 panel, and fasting lipids based upon guidelines regarding the use of atypical antipsychotics in children (Correll, 2008). Vital signs were obtained at every clinic appointment (4 visits) as well as an assessment for possible medication-related extrapyramidal side effects (EPS) using the Abnormal Involuntary Movement Scale (AIMS) (National Institute of Mental
Health, 1985). Diagnosis was confirmed upon enrollment in the study by administration of the Autism Diagnostic Interview-Revised (ADI-R), the current gold standard for diagnosing autism (Lord, Rutter, & Le Couteur, 1994). The Western Psychological Services Edition (WPS) of the ADI-R was purchased for the purpose of this study. It is an extended interview designed to cover the full-range of information necessary to establish a diagnosis of autism and assess autism spectrum disorders (Rutter, Le Couteur, & Lord, 2003). The primary investigator, Tina D’Alessandro, completed research training for the ADI-R at the University of Michigan Autism and Communication Disorders Center and established reliability with the ADI-R prior to the initiation of the study.

**Primary Outcome Measures**

Primary outcome measures reflected the most commonly used measures across this author’s literature review of research involving the use of atypical antipsychotics in treating children with ASDs. The Clinical Global Impressions Scale is suitable for both inpatient and outpatient settings evaluating the severity of a patient’s illness and improvement of symptoms following the initiation of psychopharmacology. The utility of this scale in psychiatric research is well established and has the advantage of being easily administered (Berk et al., 2008). The Aberrant Behavior Checklist was originally developed to measure problem behaviors in developmentally disabled populations and is widely used in treatment outcome studies of ASDs (Brinkley et al., 2007). An additional outcome measure, the Parenting Stress Index (PSI) was utilized to provide information regarding the severity of stressors experienced by parents.

**Clinical Global Impressions Scale.** The Clinical Global Impressions Scale (National Institute of Mental Health, 1985) was used as one of two primary outcome measures. This instrument was first developed for use in psychopharmacology trials and includes three sub-scales measuring severity of illness, global improvement, and medication effect (Berk et al.,
2008; Campbell & Palij, 1985). The instrument is within the public domain (National Institute of Mental Health, 1985). Severity of illness and global improvement are measured on 7 point Likert scales while medication effect is measured on a 4 point Likert scale. Severity of illness (CGI-S) requires the provider to assess the severity of a child’s illness during the first encounter and was reassessed during follow-up appointments in this study. Very much improved is indicated by a score of 1 with the opposite end of the scale, very much worse indicated by a score of 7. Scoring on the Clinical Global Impression-Improvement (CGI-I) is completed in the same manner. The CGI-I and medication effect or efficacy index are not assessed during the initial visit but will be assessed during each of the three clinic follow-up appointments by the researcher (Campbell & Palij, 1985).

Campbell and Palij (1985) were among the first to add validity to the use of this instrument in measuring treatment effect among children with ASDs. The a priori criterion for treatment response is an end of study CGI-I rating of 1 or 2, indicating that a patient is very much or much improved. The CGI is recommended as an outcome measure in all clinical drug trials in autism (Aman et al., 2004). More recently, Berk et al. (2008) tested the validity of the CGI as a clinical outcome measure. The CGI-S and CGI-I rating scales were both completed on 614 patients upon admission and discharge from an inpatient psychiatric unit. Fourteen psychiatrists participated in providing the clinician-rated measures. Data support that the CGI is sensitive to change with the correlation between admission and discharge ratings being highly statistically significant. This research used other routine measures including the Mental Health Questionnaire and the Depression Anxiety Stress Scale in a structural equation modeling formula to compare the measures and support or refute the changes reported in the CGI. Solid correlations between the scales added support to the existing body of research regarding the
validity of the CGI as a clinical outcome measure suitable for routine use in psychopharmacology trials (Berk et al., 2008).

**Aberrant Behavior Checklist (ABC).** The ABC is a 58-item standardized rating scale with five subscales including irritability, stereotypic behavior, social withdrawal, hyperactivity and excessive speech. The irritability subscale contains 15 questions about self-injurious behaviors, agitation, tantrums, aggression and mood lability (Aman et al., 1985a). The change in irritability from baseline to study endpoint (last observation) is of primary interest in this research study.

The ABC checklist is completed by a patient’s parent/guardian (Aman et al. 1985). Psychometric characteristics of this scale have been collected since 1985. Reliability as measured using coefficient alpha for each subscale is reported as high, median = 0.91 (Aman et al., 1985a; Karabekiroglu & Aman, 2009). Using Spearman correlations, inter-rater reliability varies across subscales ranging between moderate to moderately high with high test-retest reliability, Spearman correlation ≥ 0.96 (Aman et al., 1985b). Validity has been evaluated using convergent methods, criterion group validity, and assessment of inter-observer agreement. The ABC has been shown to be a reliable and valid behavior rating instrument (Aman et al., 1985a; Brinkley et al., 2007). The ABC was completed by a parent at baseline and at weeks 5, 7, and 9.

**Parenting Stress Index (PSI).** As a group, parents of children with ASDs report higher levels of stress compared to parents of children with other disabilities such as Down Syndrome (Lecavalier et al., 2006; Welterlin, Turner-Brown, Harris, Mesibov & Delmolino, 2011). Family impact also includes reports of lower maternal physical and mental wellbeing and a significant negative correlation between maternal stress levels and developmental progress in children (Montes & Halterman, 2007; Welterlin et al., 2012). Behavior problems in children with ASDs
are the most important predictor of parental stress. Research supports a child’s emotional and behavioral problems contributing to maternal stress, parent mental health problems and perceived family dysfunction significantly more than the child’s actual diagnosis of ASD (Lecavalier et al., 2006).

The PSI is used primarily in research to study the effects of stress on parenting behavior and as a pre-post measurement of intervention effectiveness. A short form of the PSI (PSI/SF) was developed that takes approximately 10 minutes to complete with reliability being similar to that of the long form. This instrument contains three subscales: parental distress (PD), parent-child dysfunctional interaction (P-CDI), and difficult child (DC) in addition to a total stress measure. Reliability coefficients for the three subscales are .87, .80, and .85 respectively, indicating a high degree of internal consistency for the measures. Test-retest reliability coefficients are significant (p< .001) for the three sub scales (.85, .68, .78 respectively) providing strong support for the stability of the scores across time (Abidin, 1995).

In a triple-blind study of Ritalin (n=23), Barkley, Fischer, Newby and Breen (1988) found the PSI to be useful as a means for parents to report information about their child’s behavior and levels of overall parental stress throughout the research trial. In a single subject research design evaluating the efficacy of a parent training intervention for children with autism, parent stress, as measured by the PSI, decreased slightly between pre and post-test measures for families receiving the intervention and increased among families in the control group, although actual data were not reported (Welterlin et al., 2012). In a randomized controlled trial (pilot study) of a behavioral intervention, the Autism 1-2-3 project, n =17 families, a significant difference in the pre and post-intervention scores (from 83.0 to 75.0, Wilcoxon Z = -2.87, p = 0.0004) was reported (Wong & Kwan, 2010).
Research examining the psychometric properties of the PSI-SF, based upon a sample of 141 parents, reports a mean total stress score of 95.9 ($SD = 17.2$). Severity of illness of the children was not reported (Zaidman-Zait, et al., 2010). For the purpose of this research, a positive response due to drug interaction was considered an improvement (decrease) in the total score of 5.7 or -.33 SD. Based upon the research of Zaidman-Zait, a decrease of 5.7 points would have decreased parental stress to 90.2, at the baseline of scores considered clinically significant. Rationale included the short duration of this study and reports in a pretest-posttest repeated-measures design evaluating an occupational therapy contextual intervention for improving therapy participation in children with autism spectrum disorders suggesting that parents need time to process their child’s progress and their reaction to the changes in their child’s behavior (Dunn, Cox, Foster, Mische-Lawson, & Tanquary, 2012).

**Behavioral Data Collection**

Videotaping of children in their home was performed a minimum of three sessions prior to initiation of the medication phase of the study. If baseline variability was present, data collection was extended to establish baseline. Baseline assessments occurred over a one to two week period followed by the initiation of phase B, introduction of the medication. Parents were blinded to medication versus placebo. Behavioral observations also occurred three times each week during weeks 5, 7 and 9.

A natural setting, the subject’s home, versus a laboratory setting was chosen for the behavioral observations since direct observations in the home reflect the natural setting in which the research subjects normally function (Kazdin, 1982). 10 to 15 minute observational periods are the most common duration in the behavioral literature. Elder, through a series of studies with autistic children determined that 15 minute video taping segments are ideal in that this time frame allows for 5 minutes of settling in and provides ample time for observing targeted
behaviors such as social initiating, social responding, and aberrant behaviors. Additionally, this time frame does not overtire the child or significantly inconvenience families (Elder, 1999). Videotaping (for the purpose of behavioral observations) was performed for 15 minute segments. A positive behavior response in this design methodology was considered a discernible decrease in aberrant behaviors (aggression, self-injurious behaviors, tantrums) apparent through visual analysis techniques that are part of single subject experimentation (Barlow & Hersen, 1984; Kazdin, 1982).

**Inter-Rater Reliability**

Coding and analysis of target behaviors was facilitated with the widely used computerized Observer Program. With this software, data was entered, labeled, organized and stored on a desktop computer with network access. To evaluate for possible rater drift throughout the course of this study, a second rater coded 25% of videotaped sessions. If inter-rater agreement fell below 80%, practice sessions would have be re-instituted until 90% criteria level was met.

Dr. Jennifer Elder, the dissertation committee chair for this author, developed, tested, and published results of an observer-training procedure for novice observers. Rater anecdotal reports describing the value of calibration sessions were validated by quantitative improvement in inter-rater agreement scores, pre-calibration range 0.70 to 0.82; post calibration range 0.86 to 0.93 (Elder, 1999). Ten five-minute practice videotapes of children who were observed in previous behavioral research by Dr. Elder were coded by Ms. D’Alessandro and her committee chair independently until 100% (1.0) agreement was obtained. These tapes were utilized for calibration sessions with Dr. Michael DeLaHunt, the second rater in this study and Tina D’Alessandro until 100% (1.0) agreement was obtained prior to initiation of the study. In the case of discrepancies, discussion was utilized to facilitate consensus.
Subject Selection

The study allowed the recruitment of up to 12 subjects from Nemours Children’s Clinic, Jacksonville, Florida. Information regarding this study was provided to all psychiatrists and psychologists at Nemours. An informational flyer was provided to potential subjects and their caregivers and flyers were posted in elevators and clinical areas throughout Nemours Children’s Clinic, Jacksonville for the purpose of recruitment of research subjects.

Inclusion and Exclusion Criteria

Subjects were enrolled as they were identified in the clinic with no preference based upon race or gender. Consent for treatment was obtained from parents or guardians and child assent from children ages 7 and above when feasible. The study protocol received approval from the University of Florida Institutional Review Board (IRB), the Nemours Children’s Clinic, Jacksonville, Florida Clinical Research Review Committee and the Nemours Children’s Clinic, Jacksonville, Florida IRB.

Inclusion criteria included the diagnosis of an ASD as delineated in the DSM-IV-TR and confirmed by the diagnostic evaluation tool, the Autism Diagnostic Interview-Revised; the presence of irritability including disruptive behaviors as previously defined; English speaking parents; participant age range between 6 and 11 years, the child’s ability to swallow a capsule, female participants who have not yet reached menarche, a Clinical Global Impression-Severity (CGI-S) score ≥ 4 and an Aberrant Behavior Checklist (ABC) irritability subscale score of ≥ 18 at baseline (Aman, & Singh, 1994).

Exclusion criteria included age less than 6 years or more than 11 years, weight < 15 kg. Non-English speaking parents, current use of mood stabilizers, paroxetine or fluoxetine, hypersensitivity or history of severe adverse reactions to neuroleptics, or uncontrolled seizure
disorders were also excluded. Children currently treated with another atypical antipsychotic were also not eligible for study enrollment.

**Data Evaluation**

Data evaluation included visual inspection of graphed data and nonparametric calculations of effect size as well as statistical analysis using Friedman’s ANOVA. Three nonparametric measures were chosen to calculate effect size, allowing comparison of the results, including mean baseline reduction (MBLR), the percentage of non-overlapping data (PND) and the percentage of data points exceeding the median (PEM).

Visual inspection included analyzing changes within-phase and between phases. The analysis of change between adjacent phases was used to evaluate the research hypothesis. Consistent changes across time served as the basis for evaluating whether the data pattern supported a causal relationship between the independent and dependent variables. A change in trend comparing behavior during baseline to intervention phase and intervention phase to return to baseline was also examined. Visual inspection served as a filter, allowing only especially potent interventions, significant effect sizes to be detected (Kazdin, 1982).

Nonoverlapping data as an indicator of performance differences between phases of SSD is frequently used to calculate effect size in SSD and support visual analysis of the data. PND and PEM are calculated with few errors on un-crowded graphs providing important information about effect size (Parker, Vannest, & Davis, 2011). Nonparametric effect size has advantages in SSD including providing an index of the strength of association between the intervention and outcome and not being systematically affected by sample size, potentially allowing a strong effect discernible within short data series (Brossart, Parker, Olson & Mahadevan, 2006).

Statistical analysis was also performed to supplement visual inspection. Friedman’s ANOVA is a nonparametric analysis of variance program that compares ranked values with
expected values in a chi-square analysis. Statistical analysis is more likely to detect subtle or minor effect changes in behaviors and identify effects of variables as significant that might be rejected through visual analysis (Kazdin, 1982). Data was entered in the SPSS database and backed up nightly on the Nemours Children’s Clinic Local Area Network.

The ABA design is the simplest of the true single-subject experimental designs. If targeted behaviors improved during the intervention phase and were reversed when medication was discontinued and placebo was introduced, the changes would be associated with the introduction and withdrawal of the intervention (Tervo, Estrem, Bryson-Brockmann, & Symons, 2003). While the experiment ended in the no-intervention phase, continued psychiatric services were offered to the subjects, including the opportunity to reinitiate pharmacotherapy.
Table 3-1. Single-subject experimental design for the evaluation of Abilify® in treating disruptive behaviors in children with ASDs

<table>
<thead>
<tr>
<th>Participants</th>
<th>N = 6; n = 3 children; n = 3 parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measures</td>
<td>Behavioral observations, ABC-I, PSI, CGI (severity of illness only), Autism Diagnostic Interview</td>
</tr>
<tr>
<td></td>
<td>Behavioral observations, ABC-I, CGI (severity of illness, global improvement)</td>
</tr>
<tr>
<td></td>
<td>Behavioral observations, ABC-I, CGI (severity of illness, global improvement and medication effect)</td>
</tr>
<tr>
<td></td>
<td>Behavioral observations, ABC-I, CGI (severity of illness, global improvement and medication effect)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Visits Weeks 1-2</th>
<th>Week 3</th>
<th>Week 5</th>
<th>Week 7</th>
<th>Week 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>O x 4-5 X1</td>
<td>X1 O x 3</td>
<td>X1 O x 3 (medication discontinued at end of week 7)</td>
<td>O x 3 (restart medication if indicated)</td>
<td></td>
</tr>
</tbody>
</table>

X1 = Abilify®, O = Observation, ABC-I = Aberrant Behavioral Checklist-Irritability Subscale, CGI = Clinical Global Impressions Scale, PSI = Parenting Stress Index, AIMS = Abnormal Involuntary Movement Scale
CHAPTER 4
RESULTS

Three subjects and their parents were enrolled in the research study. The first subject was a ten-year-old biracial female with severe irritability and poor impulse control, often breaking free of her caregiver (parent, grandparents and teacher) and running away when agitated, placing herself at serious risk of harm. The second subject was an eleven-year-old Caucasian male with severe acting out behaviors, including hitting, biting, punching others, yelling, and crying when not given his own way. The third subject was a seven-year-old minimally verbal Caucasian male who, like subject 1, was a flight risk and experienced severe irritability and aggression.

In this research, three child behaviors (tantrums, self-injury, and aggression) were visually analyzed and evaluated. Tantrums were defined as any clearly audible crying sounds emitted by the child, associated with kicking and/or flailing arms (and bounded by a 5-second pause). Self-injurious behaviors were defined as any behavior initiated by the child with intent to hurt self, including head banging, biting, scratching, or hitting self or attempting to hurt self with use of a foreign object. The final observed behavior, aggression, was defined as striking, pinching or kicking another person, pulling hair or biting another person. A copy of the coding manual can be found in Appendix A.

Direct observation of child behavior was video recorded by the researcher during in-home sessions. The 15-minute videotaped sessions allowed a 5-minute “settling in” (not coded period) followed by 10 minutes of taping that was coded for tantrums, self-injurious behaviors and aggression. Coding and analysis of target behaviors was facilitated by the widely used computerized Observer Program by Noldus. To evaluate for possible rater drift throughout the course of this research, a second rater coded 25% of videotaped sessions. If inter-rater agreement fell below 80%, practice sessions would have be re-instituted until 90% criterion level
was met. Inter-rater reliability remained high throughout the course of this research and coding practice sessions were not necessary (see Appendix B).

Behavioral observations were graphed and visually analyzed as well as compared using Friedman’s ANOVA. Effect size was calculated using several nonparametric approaches, the percentage of non-overlapping data (PND), the percentage of data points exceeding the median (PEM) and mean baseline reduction (MBLR). Non-overlapping statistical tests help defend visual analysis in single-subject research (Parker, Vannest & Davis, 2011). The number of tantrums, self-injury, and aggression were recorded during baseline, weeks 5, and 7 (intervention), and week 9 (return to baseline). Behaviors are visually demonstrated in Figures 4-1 through 4-3. Effect sizes are summarized in Table 4-1 and Table 4-2, and mean frequency of behaviors are summarized in Table 4-3. Summaries of results using the ABC-I, PSI and CGI-I are displayed in Tables 4-4, 4-5, and 4-6 respectively. Table 4-7 provides level of significance for each observed behavior, calculated using Friedman’s ANOVA. Blood pressure, heart rate, weigh, height and body mass index (BMI) were recorded during each clinic visit and are reported in Tables 4-8, 4-9, 4-10 and 4-11. The AIMS test was administered during each clinic visit. Scores for all three subjects throughout their participation in the research study were zero indicating no evidence of dystonia or tardive dyskinesia. During enrollment in the study, families were provided with a patient information sheet regarding Abilify®. During each follow up visit, parent(s) were asked about any observable side effects listed in this information sheet. Based upon parent subjective report and research observations during home and clinic visits, there were no reported side effects other than minimal weight gain in two of the three subjects. A copy of the Abilify® information sheet can be reviewed in Appendix C.
Research Subject 1

Measures

For Subject 1, a ten-year-old biracial female, five baseline observations were completed during a two-week period prior to the introduction of the intervention, Abilify®. Behaviors were observed during the intervention in weeks 5 and 7 on three occasions during each week. After the placebo was introduced and the intervention withdrawn (weeks 8 and 9), three observations were completed during week 9 (see Figure 4-1).

Baseline. In the baseline condition, measures indicated frequent tantrums, occasional aggressive outbursts and self-injurious behaviors. Aggression was towards the mother and the self-injurious behaviors involved Subject 1 biting herself. During initial observations, Subject 1 perseverated about wanting to eat and yelled repeatedly, “I’m hungry.” Self-soothing behaviors were also observed including spinning, sucking her thumb and sucking on her toes. There were frequent tantrums observed, n = 9 to 18 during baseline measures with an average duration of 15 seconds. During tantrums, Subject 1 yelled repeatedly at her mother, cried, and flailed her arms and legs. Aggression varied during baseline from 1 to 8 occurrences and entailed kicking and hitting her mother. Self-injurious behavior occurred 1 to 2 times during four of the observations.

During baseline, the Aberrant Behavior Checklist (ABC) and Parenting Stress Index short form (PSI/SF) were completed by Subject 1’s mother. The raw score on the ABC irritability subscale was 25, T-score = 68, placing Subject 1 in the 96% for irritability, agitation, and tantrums. The PSI/SF total stress score was 90, indicating the level of stress experienced within the role of parenting as 89%. High scores are considered to be scores at or above the 85th percentile (Abidin, 1995).
**Intervention.** The intervention was introduced at Week 3. Behavioral observations were completed on three occasions each week during weeks 5 and 7. During the intervention phase, no tantrums, aggression or self-injury were observed.

At Week 5, the ABC irritability subscale score was 7, T-score = 56, placing Subject 1 in the 73% for irritability, agitation, and tantrums. In week 7, the ABC irritability subscale score dropped further to 4, T-score = 54, placing Subject 1 in the 65% for irritability, agitation, and tantrums. The PSI score during week 5 was 64, which placed the level of stress within the role of parenting at 35%. The score was unchanged during Week 7 which indicated a significant decrease in total stress as it relates to parental distress, stress derived from the parent’s interaction with the child, and stresses resulting from the child’s behavioral characteristics. The Clinical Global Impressions Scale, Global Improvement (CGI-I), assessed by the researcher during clinic visits, indicated much improved behavior during week 5 (CGI-I = 2), and very much improved behavior during week 7 (CGI-I = 1).

During weeks 5 and 7, observations included Subject 1 helping to make a sandwich, accepting redirection, playing quietly with toys (generally ordering rituals – lining up such toys as animals or cars) and sitting quietly while her mother read a book out loud. Subject 1’s mother observed that social interactions were improving. She reported an incident after church during week 6, when Subject 1 observed another child crying and for the first time that her mother could recall, responded with concern and empathy, asking what was wrong with the other child and could something be done to help. The significance of this observation is discussed in greater detail in Chapter 5. Her mother also reported complete cessation of daytime enuresis from Week 5 through Week 7, also discussed further in Chapter 5.
**Return to baseline.** Medication was withdrawn during weeks 8 and 9. A placebo was given daily during this phase of the study. Tantrums were observed during the three final observations ranging from 1-2 each observation. No self-injurious behaviors were observed and one aggressive outburst towards mom was observed during the last videotaping session. During Week 9, the ABC irritability subscale score was 25, T-score = 68, placing Subject 1 in the 96% for irritability, agitation, and tantrums. The PSI/SF total stress score was 82, which indicated that the level of stress experienced within the role of parenting was 80%. Based upon the ABC irritability subscale, disruptive behaviors returned to baseline measurements once the intervention was withdrawn and parental stress increased after withdraw of the intervention to levels near baseline measurement. The CGI-I was 4 during Week 9 which indicated no change in Subject 1’s condition compared to baseline.

During the last three video-taping sessions, Subject 1’s behavior was increasingly oppositional. For example, Subject 1 refused to eat in the kitchen and regressed to behaviors observed during baseline, sucking her thumb and toes. Stereotypic movements such as twirling also increased. Her mother also reported frustration regarding a reoccurrence of daytime enuresis both at home and school.

**Effect Size**

The effect size of the behavioral observations for Subject 1 was calculated using Percentage of Non-Overlapping Data (PND), Percentage of Data Points Exceeding the Median (PEM) and Mean Baseline Reduction (MBLR). During treatment phase observations, weeks 5 and 7, the number of occurrences of tantrums, self-injurious behaviors (SIB) and aggression was zero. During the last observation in Week 9 (placebo phase), tantrums and aggression were increasing while self-injurious behaviors remained at zero.
The baseline-intervention PND for tantrums and aggression = 6/6 = 100%. The baseline-intervention PND for SIB was not able to be calculated due to data reaching the floor level (zero). Intervention-return to baseline PND for tantrums, aggression and SIB also were not able to be calculated due to some of the data reaching zero (Ma, 2006).

The baseline-intervention PEM for tantrums and aggression = 6/6 = 1 and baseline-intervention PEM for SIB = 0. Intervention-return to baseline PEM for tantrums and aggression respectively = 3/3 = 1. Intervention-return to baseline PEM for SIB was zero.

The baseline-intervention MBLR for tantrums, aggression and self-injurious behaviors was 100%. Intervention-return to baseline MBLR for tantrums and aggression = 100%. Intervention-return to baseline MBLR for self-injurious behaviors = 0 (see Table 4-1 and Table 4-2).

**Research Subject 2**

**Measures**

For Subject 2, an eleven-year-old Caucasian male, four baseline observations were completed during a two-week period prior to the introduction of the intervention, Abilify®. A fifth baseline observation was not needed for Subject 2 since the trend of the first four baseline observations was stable (Janosky et al., 2009). Behaviors were observed during the intervention in weeks 5 and 7 on three occasions during each week. The placebo was introduced and the intervention withdrawn (weeks 8 and 9). Three observations were completed during Week 9 (see Figure 4-2).

**Baseline.** In the baseline condition, measures indicated frequent tantrums, no self-injurious behaviors and one aggressive outburst when Subject 2 began hitting his father, demanding that dad get up from the couch to begin their father-son Saturday morning ritual of running errands. Tantrums were severe and ranged from 4 to 5 occurrences during each
observation with an average duration of 22 seconds. Aggression occurred on one occasion during the fourth baseline observation with Subject 2 hitting his father in frustration over their routine Saturday morning outing to the store being postponed.

During baseline, the Aberrant Behavior Checklist (ABC) and Parenting Stress Index short form (PSI/SF) were completed by Subject 2’s mother. The raw score on the ABC irritability subscale was 23, T-score = 62, which placed subject 2 in the 87% for irritability, agitation, and tantrums. The PSI/SF total stress score was 109, which indicated that the level of stress experienced within the role of parenting was 98%. Scores above 90% are considered clinically significant (Abidin, 1995).

**Intervention.** The intervention was introduced at Week 3. Behavioral observations were completed on three occasions each week during weeks 5 and 7. During the intervention phase, no tantrums, aggression or self-injurious behavior were observed. Observations during Week 5 included Subject 2 initiating conversations with his mother and attempting to problem solve when his father announced a change in the usual Saturday errand routine. Subject 2 was less rigid regarding the timing of errands. As Subject 2 problem solved with his mother, he considered the possibility of letting his father take a nap and then running errands together. Changes in routine were very difficult for Subject 2. While he was moderately restless and pacing due to the proposed change, he displayed an increase in flexibility regarding his schedule and an improved ability to handle frustration.

During Week 7 observations, both parents observed that their son had begun initiating interactions with them and was more accepting of redirection. For example, when told that the computer would need to be turned off in 5 minutes, Subject 2 did not have a temper tantrum, as
observed during baseline measures. He was able to transition without difficulty to the next activity, playing store, with his mother.

For Week 5, the ABC irritability subscale score was 7, T-score = 53, placing Subject 2 in the 60% for irritability, agitation, and tantrums. In week 7, the ABC irritability subscale score rose slightly to 10, T-score = 55, placing subject 2 in the 70% for irritability, agitation, and tantrums. The PSI score during week 5 was 82, which placed parental stress within a normal range at 80%. The score rose to 90 in week 7, placing parental stress in the 89th percentile.

Completion of all instruments occurred during office visits. During Week 7’s follow-up appointment, Subject 2 heard an announcement over the loud speaker to disregard all fire alarms, the system was being tested. His thoughts perseverated on the possibility of a fire alarm, the loud sound that the fire alarm would make, and the possibility of evacuating the building. He interrupted conversation between his parents and the researcher frequently and paced during most of his appointment. His increased agitation during the follow-up appointment may have increased parent stress and affected his mother’s answers in the PSI. The Clinical Global Impressions Scale, Global Improvement (CGI-I), assessed by the researcher during clinic visits, indicated much improved behavior during week 5 (CGI-I = 2), and very much improved behavior during week 7 (CGI-I = 1).

**Return to baseline.** Medication was withdrawn during weeks 8 and 9. A placebo was given daily during this phase of the study. Tantrums were observed on one occasion during the last in-home behavioral observation. No self-injurious behaviors were observed. Six aggressive outbursts occurred during the final in-home observation in the context of slapping at his mother when being told no regarding an activity. Other disruptive behaviors were observed during all three of the Week 9 home visits including refusing to follow directions, arguing with parents,
behaviors did not meet criteria for inclusion. During the last clinic visit, the mother reported that Subject 2’s behavior had deteriorating at school with negative behavioral reports being sent home by his teacher daily citing that Subject 2 was refusing to follow directions, cursing and pushing another student.

During Week 9, the ABC irritability subscale score was 19, T score = 59, which placed Subject 2 in the 84% for irritability, agitation, and tantrums. The PSI/SF total stress score was 110, which indicated that the level of stress experienced within the role of parenting was 98%. Based upon the ABC irritability subscale, disruptive behaviors were nearing baseline measurements once the intervention was withdrawn and parenting stress also increased after withdraw of the intervention to baseline measurement. The CGI-I was 3 during Week 9 indicated minimal improvement in Subject 2’s condition compared to his condition at admission to the study.

**Effect Size**

The effect size of the behavioral observations for Subject 2 was calculated using Percentage of Non-Overlapping Data (PND), Percentage of Data Points Exceeding the Median (PEM) and Mean Baseline Reduction (MBLR) (see Table 4-1 and Table 4-2). During treatment phase observations, weeks 5 and 7, the number of occurrences of tantrums, self-injurious behaviors (SIB) and aggression was zero. During the last observation in Week 9, tantrums and aggression were increasing (placebo phase).

The baseline-intervention PND for tantrums = 6/6 = 100%. The baseline-intervention PND for aggression and SIB were not able to be calculated due to data reaching the floor level (zero). Intervention-return to baseline PND for tantrums, aggression and SIB also were not able to be calculated due to some of the data reaching zero (Ma, 2006).
The baseline-intervention PEM for tantrums = 6/6 = 1, baseline-intervention PEM for aggression = 6/6 = 1 and baseline-intervention PEM for SIB = 0. Intervention-return to baseline PEM for tantrums and aggression respectively = 3/3 = 1. Intervention-return to baseline PEM for SIB was zero.

The baseline-intervention MBLR for tantrums and aggression was 100%. Since there was no SIB, MBLR = 0. Intervention-return to baseline MBLR for tantrums, aggression and self-injurious behavior = 100%.

**Research Subject 3**

**Measures**

For Subject 3, a seven year-old Caucasian male, four baseline observations were completed during a two-week period prior to the introduction of the intervention, Abilify®. A fifth baseline observation was not needed for Subject 3 since the trend of the first four baseline observations was stable (Janosky et al., 2009). Behaviors were observed during the intervention in weeks 5 and 7 on three occasions during each week. After the placebo was introduced and the intervention withdrawn (weeks 8 and 9), three observations were completed during week 9 (see Figure 4-3).

**Baseline.** In the baseline condition, there were frequent severe tantrums ranging from 4 to 8 occurrences during each observation with a mean duration of 28 seconds. Aggression occurred during 3 of the baseline observations, ranging from 1 to 3 occurrences including hitting and kicking his mother, pulling his mother away from a light switch which the parent had turned off. Subject 3 became very agitated if the background noise from the television was turned down or off or if any lights were turned off. Self-injurious behaviors ranged from 2-6 occurrences during baseline observations, as Subject 3’s frustration increased, he bit himself.
During the second baseline behavioral observation, the father was also present and talking during the videotaping regarding the stages parents experience when their child is diagnosed with autism. The father reflected on first blaming himself, “what did I do wrong?” The next stage was focused on “fixing” his son, “how can I fix it?” and the third stage was, “we have to get on with life.

During baseline, the Aberrant Behavior Checklist (ABC) and Parenting Stress Index short form (PSI/SF) were completed by Subject 3’s parents conferring together. The raw score on the ABC irritability subscale was 39, T-score = 71, which placed Subject 3 in the 98% for irritability, agitation, and tantrums. The PSI/SF total stress score was 127, which indicated that the level of stress experienced within the role of parenting was 99%. Total stress raw scores of 112 or above place the parental stress level at 99+ percentile.

**Intervention.** The intervention was introduced at Week 3. Behavioral observations were completed on three occasions each week during weeks 5 and 7. During the intervention phase, no tantrums, aggression or self-injury were observed. Observations included an increase in attempts to use sign language and verbal communication to make needs known to parents. Subject 3 began saying, “O” for go and “uhh” for up. Attention was observed to be sustained as Subject 3 worked with his mother on identifying objects and placing them in puzzles. Parents reported that tantrums were still occurring but, “the tantrums are fewer and of shorter duration.” Subject 3 was described during weeks 5 and 7 by his parents as being “more content.” Parents also reported resolution of daytime enuresis during the intervention phase.

At Week 5, the ABC irritability subscale score was 24, T-score = 64, which placed Subject 3 in the 90% for irritability, agitation, and tantrums. In Week 7, the ABC irritability subscale score dropped to 19, T-score = 60, which placed Subject 3 in the 85% for irritability,
agitation, and tantrums. The PSI score during week 5 was 127, which indicated that the level of stress within the role of parenting was 99%, unchanged from baseline. The score decreased to 107, in week 7, indicating the level of stress within the role of parenting as 97%. The Clinical Global Impressions Scale, Global Improvement (CGI-I), assessed by the researcher during clinic visits, indicated minimally improved behavior during week 5 (CGI-I = 3), and much improved behavior during week 7 (CGI-I = 2).

**Return to baseline.** Medication was withdrawn during weeks 8 and 9. A placebo was taken daily during this phase of the study. Behavioral observations during Week 9 did not support a return to baseline in disruptive behaviors. No tantrums were observed, although self-injurious behaviors began to return and were observed during the last two home visits ranging from 2 to 3 episodes of hand biting as well as two aggressive outbursts towards mom during the last videotaping session, hitting, pushing and slapping. Subject 3 was observed to be uncooperative, yelling, hyperactive and engaging in an increased amount of self-stimulating behaviors during Week 9. Observations included twirling and jumping off the couch, rolling, climbing and jumping again. However, due to coding definitions, these behaviors were not recorded.

During his last clinic visit, the mother reported that Subject 3’s behavior had deteriorated at school with negative behavioral reports being sent home by his teacher citing that Subject 3 was an elopement risk and was increasingly aggressive towards other students. Additionally, subject 3 had achieved daytime dryness during weeks 5 through 8. During Week 9, multiple episodes of enuresis occurred both at home and school.

During week 9, the ABC irritability subscale score was 28, T-score = 67, which placed Subject 3 in the 96% for irritability, agitation, and tantrums. Based upon the ABC irritability
subscale, disruptive behaviors were nearing baseline measurements once the intervention was withdrawn. The PSI/SF total stress score was 120, climbing back towards the baseline score (127), which placed the level of stress experienced within the role of parenting at 99%. The CGI-I was 5 during Week 9 indicating minimally worse condition compared to Subject 3’s condition upon admission to the study.

**Effect Size**

The effect size for Subject 3’s behavioral observations was calculated using Percentage of Non-Overlapping Data (PND), Percentage of Data Points Exceeding the Median (PEM) and Mean Baseline Reduction (MBLR) (see Table 4-1 and Table 4-2). During treatment phase observations, weeks 5 and 7, the number of occurrences of tantrums, self-injurious behaviors (SIB) and aggression was zero. During Week 9 (placebo phase) self-injurious behaviors and aggression were increasing.

The baseline-intervention PND for tantrums was 6/6 = 100%, baseline-intervention PND for SIB was 6/6 = 100%. For aggression, PND was not able to be calculated due to data reaching the floor level (zero). Intervention-return to baseline PND for tantrums, aggression and SIB also were not able to be calculated due to some of the data reaching zero (Ma, 2006).

The baseline-intervention PEM for tantrums was 6/6 = 1, baseline-intervention PEM for aggression was 6/6 = 1 and baseline-intervention PEM for SIB was 6/6 = 1. Intervention-return to baseline PEM for tantrums was 0 while intervention-return to baseline PEM for aggression was 3/3 = 1, and for SIB, PEM was 3/3 = 1.

The baseline-intervention MBLR for tantrums, aggression and self-injurious behavior = 100%. Intervention-return to baseline MBLR for aggression and self-injurious behavior = 100%. Since there were no observed tantrums during intervention or return to baseline, the MBLR for tantrums = 0.
Inferential statistics using Friedman’s ANOVA were also applied to behavioral data analyses. Statistical analysis with this nonparametric test lacked the power to detect a difference in this research with an n = 3. The distribution of mean number of tantrums across treatment phase approached significance (see Table 4-7).

Two of the subjects gained weight during the study. Subject 1 was underweight at the initiation of the study. Her weight increased by 0.73 kg but remained within a healthy percentile. Subject 2, likewise, experienced an increase in his weight of 0.69 kg. He was overweight at the initiation of the study and remained overweight. Subject 3 lost 1.4 kg from study initiation to endpoint, although his BMI percentile remained within a healthy range (see Table 4-8 through Table 4-11).
### Table 4-1. Baseline-intervention effect size using Percentage of Non-Overlapping Data (PND), Percentage of Data Points Exceeding the Median (PEM) and Mean Baseline Reduction (MBLR)

<table>
<thead>
<tr>
<th></th>
<th>S1T</th>
<th>S2T</th>
<th>S3T</th>
<th>S1A</th>
<th>S2A</th>
<th>S3A</th>
<th>S1SIB</th>
<th>S2SIB</th>
<th>S3SIB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PND</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>100%</td>
</tr>
<tr>
<td><strong>PEM</strong></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
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<tr>
<td><strong>MBLR</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<td>100%</td>
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<td>100%</td>
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</table>

*S = subject, T = tantrums, A = aggression, SIB = self-injurious behaviors, * = unable to calculate PND due to baseline measures having a zero point.*

### Table 4-2. Intervention-return to baseline effect size using Percentage of Non-Overlapping Data (PND), Percentage of Data Points Exceeding the Median (PEM) and Mean Baseline Reduction (MBLR)

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<th>S2T</th>
<th>S3T</th>
<th>S1A</th>
<th>S2A</th>
<th>S3A</th>
<th>S1SIB</th>
<th>S2SIB</th>
<th>S3SIB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PND</strong></td>
<td>100%</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><strong>PEM</strong></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>MBLR</strong></td>
<td>100%</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*S = subject, T = tantrums, A = aggression, SIB = self-injurious behaviors, * = unable to calculate PND due to return to baseline measures having a zero point.*
Table 4.3. Mean frequency of tantrums, self-injurious behavior (SIB) and aggression for each phase

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline</th>
<th>Intervention</th>
<th>Return-to-baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Tantrums</td>
<td>14.8</td>
<td>0</td>
<td>1.66</td>
</tr>
<tr>
<td>1-SIB</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1-Aggression</td>
<td>3.8</td>
<td>0</td>
<td>0.33</td>
</tr>
<tr>
<td>2-Tantrums</td>
<td>4.25</td>
<td>0</td>
<td>0.33</td>
</tr>
<tr>
<td>2-SIB</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-Aggression</td>
<td>0.33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3-Tantrums</td>
<td>5.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3-SIB</td>
<td>4.25</td>
<td>0</td>
<td>1.67</td>
</tr>
<tr>
<td>3-Aggression</td>
<td>1</td>
<td>0</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Table 4.4. Aberrant Behavior Checklist-Irritability subscale scores and percentiles

<table>
<thead>
<tr>
<th>Time of Assessment</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Week 1</td>
<td>Week 5</td>
<td>Week 7</td>
</tr>
<tr>
<td>1</td>
<td>25(96%)</td>
<td>7(73%)</td>
<td>4(65%)</td>
</tr>
<tr>
<td>2</td>
<td>23(87%)</td>
<td>7(60%)</td>
<td>10(70%)</td>
</tr>
<tr>
<td>3</td>
<td>39(98%)</td>
<td>24(90%)</td>
<td>19(85%)</td>
</tr>
<tr>
<td>Mean</td>
<td>29</td>
<td>12.67</td>
<td>11*</td>
</tr>
</tbody>
</table>

NOTE: *Positive response on ABC-I is defined as ≥25% reduction in score from baseline to Week 7. The mean difference is 18 representing a 38% reduction from baseline.
Table 4-5. Parenting Stress Index scores and percentiles

<table>
<thead>
<tr>
<th>Participants</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 5</td>
<td>Week 7</td>
</tr>
<tr>
<td>1</td>
<td>90(89%)</td>
<td>64(35%)</td>
<td>64(35%)</td>
</tr>
<tr>
<td>2</td>
<td>109(98%)</td>
<td>82(80%)</td>
<td>90(89%)</td>
</tr>
<tr>
<td>3</td>
<td>127(99%)</td>
<td>127(99%)</td>
<td>107(97%)</td>
</tr>
<tr>
<td>Mean</td>
<td>108.67</td>
<td>91</td>
<td>87*</td>
</tr>
</tbody>
</table>

NOTE: *Positive response on PSI is defined as a score decrease between baseline and treatment of 5.7(SD: 0.33). The mean difference is 21.67.

Table 4-6. Clinical Global Impression – Improvement scores

<table>
<thead>
<tr>
<th>Participant</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 5</td>
<td>Week 7</td>
<td>Week 9</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Mean</td>
<td>2.33</td>
<td>1.33*</td>
<td>4</td>
</tr>
</tbody>
</table>

NOTE: *Positive response on CGI considered a score of 1-2 at Week 7.

Table 4-7. Friedman’s Two-Way Analysis of Variance

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Tantrums</th>
<th>Aggression</th>
<th>Self-Injurious Behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Statistic ( )</td>
<td>5.636</td>
<td>3.2</td>
<td>3.714</td>
</tr>
<tr>
<td>Significance (p)</td>
<td>0.06</td>
<td>0.202</td>
<td>0.156</td>
</tr>
</tbody>
</table>
### Table 4-8. Subject 1’s vital signs

<table>
<thead>
<tr>
<th>Week</th>
<th>Heart Rate</th>
<th>Blood Pressure</th>
<th>Height</th>
<th>Weight</th>
<th>Body Mass Index (BMI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>93</td>
<td>97/63</td>
<td>1.35 m</td>
<td>25.6 kg</td>
<td>14.07 kg/m²</td>
</tr>
<tr>
<td>Week 5</td>
<td>105</td>
<td>106/69</td>
<td>1.36 m</td>
<td>25.7 kg</td>
<td>13.9 kg/m²</td>
</tr>
<tr>
<td>Week 7</td>
<td>101</td>
<td>110/63</td>
<td>1.36 m</td>
<td>27.6 kg</td>
<td>15.2 kg/m²</td>
</tr>
<tr>
<td>Week 9</td>
<td>94</td>
<td>103/59</td>
<td>1.36 m</td>
<td>28.1 kg</td>
<td>15.8 kg/m²</td>
</tr>
</tbody>
</table>

### Table 4-9. Subject 2’s vital signs

<table>
<thead>
<tr>
<th>Week</th>
<th>Heart Rate</th>
<th>Blood Pressure</th>
<th>Height</th>
<th>Weight</th>
<th>Body Mass Index (BMI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>91</td>
<td>100/57</td>
<td>1.35 m</td>
<td>42.87 kg</td>
<td>23.24 kg/m²</td>
</tr>
<tr>
<td>Week 5</td>
<td>93</td>
<td>105/64</td>
<td>1.36 m</td>
<td>43.38 kg</td>
<td>24.1 kg/m²</td>
</tr>
<tr>
<td>Week 7</td>
<td>90</td>
<td>100/62</td>
<td>1.37 m</td>
<td>44.45 kg</td>
<td>23.68 kg/m²</td>
</tr>
<tr>
<td>Week 9</td>
<td>81</td>
<td>104/61</td>
<td>1.37 m</td>
<td>44.9 kg</td>
<td>23.93 kg/m²</td>
</tr>
</tbody>
</table>

### Table 4-10. Subject 3’s vital signs

<table>
<thead>
<tr>
<th>Week</th>
<th>Heart Rate</th>
<th>Blood Pressure</th>
<th>Height</th>
<th>Weight</th>
<th>Body Mass Index (BMI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>106</td>
<td>94/54</td>
<td>1.22 m</td>
<td>24.22 kg</td>
<td>16.3 kg/m²</td>
</tr>
<tr>
<td>Week 5</td>
<td>104</td>
<td>100/55</td>
<td>1.23 m</td>
<td>24.2 kg</td>
<td>16.0 kg/m²</td>
</tr>
<tr>
<td>Week 7</td>
<td>100</td>
<td>102/50</td>
<td>1.25 m</td>
<td>24.5 kg</td>
<td>15.7 kg/m²</td>
</tr>
<tr>
<td>Week 9</td>
<td>110</td>
<td>108/60</td>
<td>1.29 m</td>
<td>24.9 kg</td>
<td>14.9 kg/m²</td>
</tr>
</tbody>
</table>
Table 4-11. Comparison of Body Mass Index and percentile ranking

<table>
<thead>
<tr>
<th>Week</th>
<th>Subject 1 – BMI</th>
<th>Subject 1 – % Ranking</th>
<th>Subject 2 – BMI</th>
<th>Subject 2 – % Ranking</th>
<th>Subject 3 – BMI</th>
<th>Subject 3 – % Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.1 kg/m²</td>
<td>5%</td>
<td>23.2 kg/m²</td>
<td>94%</td>
<td>16.3 kg/m²</td>
<td>65%</td>
</tr>
<tr>
<td>5</td>
<td>13.9 kg/m²</td>
<td>3%</td>
<td>24.1 kg/m²</td>
<td>95%</td>
<td>16.0 kg/m²</td>
<td>59%</td>
</tr>
<tr>
<td>7</td>
<td>15.2 kg/m²</td>
<td>18%</td>
<td>23.7 kg/m²</td>
<td>95%</td>
<td>15.7 kg/m²</td>
<td>51%</td>
</tr>
<tr>
<td>9</td>
<td>15.8 kg/m²</td>
<td>27%</td>
<td>23.9 kg/m²</td>
<td>95%</td>
<td>14.9 kg/m²</td>
<td>31%</td>
</tr>
</tbody>
</table>

The percentile indicates the relative position of a child’s BMI number among children of the same sex and age. Percentile rank is used for children and teens due to the amount of body fat changing with age and the amount of body fat differing between girls and boys. A percentile range between the 5th percentile through the 84th percentile is considered to be a healthy weight for children (Center for Disease Control and Prevention, 2011).
Figure 4-1. Subject 1 behavior observations. Dashed lines illustrate PEM (tantrums), dotted lines illustrate PND (tantrums & aggression – baseline only)
Figure 4-2. Subject 2 behavior observations. Dotted lines illustrate PEM and dashed lines illustrate PND.
Figure 4-3. Subject 3 behavior observations. Dashed lines illustrate PND and dotted lines illustrate PEM.
CHAPTER 5
DISCUSSION

King’s conceptual framework provided the theoretical perspective for this research. Children with developmental delays or disabilities function within a family system (Keen & Knox, 2004). Each of the families interested in participating in the Abilify® study had tried numerous alternative interventions including various forms of behavioral therapy, gluten/casein free diets, nutritional supplements and medications, such as alpha agonists (with fewer associated side effects compared to atypical antipsychotics) to treat disruptive behaviors. Due to poor response to other treatment modalities, and escalating disruptive behaviors, parents were willing to consider treatment with an atypical antipsychotic for their child. The interaction between nurse researcher and parents/child occurred because the parents identified a behavioral health concern in their child and sought a psychiatric evaluation resulting in interactions and transactions where information was shared and mutually set goals were agreed upon. The primary goal of both the nurse researcher and the parents was to improve the child’s behavioral health, consistent with King’s (1981) theory of goal attainment.

Parenting stress related to caring for their child with autism and severe disruptive behaviors was high, as evidenced by parent self-report during baseline evaluation. This can be viewed logically through King’s systems framework, which as described in detail in chapter 1, consists of three dynamic interacting systems: (1) personal systems, (2) interpersonal systems, and (3) social system. Since the systems are dynamic and interrelated, changes in one system affect the other systems. As a child’s behavior became increasingly disruptive, parent stress likewise increased. During the treatment phase of this study, as disruptive behaviors improved, parent stress decreased, followed by an increase once again during the placebo phase associated with parent reports on the ABC-I of disruptive behaviors increasing. Scores on the PSI and

88
ABC-I were nearing return to baseline levels during the placebo phase of the study further supporting the dynamic, interactive nature of systems.

**Comparison of Subjects, Limitations, and Strengths**

Results from this study indicate significant improvement of disruptive behaviors and decrease in parent stress during the intervention phase, with administration of low dose Abilify®. Behavioral observations during week 9, the placebo phase, in this A-B-A single subject design, did not indicate a return to baseline behaviors although disruptive behaviors did begin to increase compared to the zero tantrums, self-injury and aggression during behavioral observations in weeks 5 and 7. The PSI and ABC-I completed during week 9 by parents, in all instances, indicated scores nearing or returning to baseline measures. Additionally, the clinician completed Clinical Global Impressions-Improvement week 9 scores indicated an increase in disruptive behaviors further supporting observed improvements in behavior during treatment phase and worsening of behavior during the placebo phase.

Several different nonparametric methods were used to calculate effect size for comparison purposes. The percentage of non-overlapping data (PND) indicated scores > 90% for all behaviors that could be compared using this method, in other words, highly effective treatment. In many cases, such as SIB in Subject 1, baseline through intervention phase, this method was not effective due to the baseline containing a data point of zero. Floor effects in the baseline or return to baseline data automatically render 0 PND (Schlosser, Lee & Wendt, 2008).

The percentage of data points exceeding the median (PEM) resulted in scores of 1 for all subjects with the exception of SIB from baseline through treatment phase for Subject 2, SIB from treatment through return to baseline for Subjects 1 and 2 and tantrums in Subject 3, from treatment through return to baseline. PEM scores ranging from 0.9-1 reflect highly effective
treatment (Ma, 2006). Findings using MBLR supported data obtained using PEM. Nonparametric measures of effect size support visual analysis of data for Subjects 1, 2, and 3.

The discrepancy between Week 9 behavioral observations and scores on the PSI, ABC-I and CGI-I is a limitation of this study. In retrospect, the study design, ending with observations during Week 9 may have introduced a limitation. That is, because Abilify® has a long half-life (75 hours) and takes two weeks to achieve steady state or inactive state upon withdraw of the medication (Otsuka Pharmaceutical Company, 2008) some residual therapeutic effects of the medication may have remained. While clinically, carryover effects resulting in improved behavior are not problematic, experimental carryover effects may limit the inferences one can draw about the controlling effects of the treatment procedure administered (Barlow, Nock & Hersen, 2009). Extending the study to ten weeks would have allowed for behavioral observations to occur in the absence of any potential lingering medication effects. While return to baseline (RTB) behaviors did not reach the magnitude of behaviors observed during baseline, RTB observations for all three subjects increased as Week 9 observations progressed supporting a trend in the data regarding a rise in disruptive behaviors once the intervention was withdrawn. Additionally, parent stress increased significantly and scores of the ABC-I were nearing baseline scores during Week 9 indicating that parents were observing higher levels of disruptive behaviors than recorded by the researcher during home observations, further supporting the efficacy of treatment with low-dose Abilify®.

The lack of a return in baseline observations during Week 9 may have also be indicative of a form of habituation. One characteristic of children with autism is difficulty with new situations or changes in their routine (Konstantareas and Stewart, 2006). Johnson and Bolstad (1975) defined subject reactivity as the subject’s knowledge that he is being observed.
According to Elder (1999) while subjects may initially be camera-conscious, repeated observations (three to four sessions) are believed to minimize reactivity effects as the subject becomes accustomed or habituated to the observations and/or cameras. Possibly, the children became habituated to the presence of the researcher at their home during the 15 minute videotaping increments and associated this presence with an increase in attention from parents, responding with a decrease in disruptive behaviors in the presence of the researcher. Well-controlled clinical trials are needed to empirically evaluate the influence of videotaping on autistic subjects’ behavior over time.

Another limitation of the study may have been the narrow scope of behaviors that were counted. Other disruptive behaviors which were not identified as target behaviors for this study included arguing, defiance, self-stimulating, and yelling. These behaviors were observed to increase during Week 9 and may be additional behaviors to quantify in a future study.

Several interesting findings warrant further discussion. Both Subjects 1 and 3 had a history of daytime enuresis. During the intervention phase of the study, both experienced complete cessation of daytime enuresis and a return of their daytime enuresis during the placebo phase of the study. This may be clinically relevant to note particularly when considering a trial of an atypical antipsychotic in children with ASDs who have a history of diurnal enuresis or in children who are being treated with risperidone for their disruptive behaviors and experience enuresis as a result of treatment, a side effect reported to occur in 5% of children treated with risperidone (Gold Standard, Inc., n.d.). Further research is needed to assess the effects of Abilify® on enuresis in a larger sample population to establish generalizability.

In the case of all three research subjects, parents reported an improvement in social reciprocity and communication during the intervention phase of the study. This finding is
particularly relevant due to gross and sustained impairment in reciprocal social interaction and a marked and sustained impairment in communication being diagnostic features of ASDs (American Psychiatric Association, 2000). Subject 1 was observed to act empathetically towards another child while Subject 2 began initiating interactions with his parents. Subject 3, the most severely impaired child in this study, increased his efforts to communicate using sign language and single words, behaviors that were reported to be observed both at home and at school. Including behavioral observations of children with ASDs initiating social interaction and communication, both through sign language and speech are important behaviors to include in a future study evaluating the effects of Abilify® on children with ASDs.

Diversity among the subjects in this SSE was a strength of this study. Subject 1 was a 10 year-old biracial female with high functioning autism. Subject 2 was a 12 year-old Caucasian male with Asperger Syndrome. Subject 3 was a seven year-old, minimally verbal, Caucasian male with severe autism. In all subjects, significant behavioral improvement was observed during treatment phase. The heterogeneity of this subject population improves the generalizability of the research findings. The study would be further strengthened by replication with an additional SSE. A change in methods to an A-B-A-B design is recommended which would allow confirmation of the effects of the independent variable.

In previous studies involving doses of Abilify® ranging from 5-15 mg daily, fatigue and somnolence were the most commonly reported symptoms occurring in a dose-response relationship (Blankenship et al., 2010; Owen et al., 2009). There were no reports of fatigue or somnolence among subjects in this 2 mg. Abilify® study. Weight gain occurred in Subjects 1 and 2 while Subject 3 lost weight. Notably, Subject 1’s weight at enrollment in the study and through Week 5 was border-line to low, ending in Week 9 within a healthy range. Subject 2 was
overweight at the study initiation with a BMI of 23.24 kg/m² (94%) and at week 9 his BMI was 23.93 kg/m² (95%). Subject 2 clearly would benefit from nutritional counseling and dietary modification. Subject 3’s BMI and percentile rank decreased from study initiation to endpoint but remained within a healthy range.

For Subject 1, her mother reported improved appetite, a willingness to try a wider variety of food and fewer food aversions related to texture. Subject 2 and 3’s parents did not report observing any changes in their child’s appetite. The medication was well-tolerated. The mean weight gain for Subjects 1, 2, and 3 was 0.4 kg. This is significantly less than the mean weight gain reported in larger clinical trials and may indicate that lower doses of Abilify® are associated with less weight gain in children. The mean weight gain in children reported in double blind clinical trials of Abilify® varied between 1.3 to 2 kg and the mean BMI change was +0.7 (Marcus et al., 2009; Owen et al., 2009). Without any reports of percentile range in the randomized controlled clinical trials, it is difficult to ascertain whether the weight gain in those study participants represented improved weight in children of low-weight to a healthy range, weight gain remaining within a healthy range or unhealthy weight gain raising concerns regarding obesity. Further studies are needed regarding the effects of Abilify® on children’s weight.

The short-term nature of this study does not provide conclusions regarding longer-term effects of a low dose of Abilify® on irritability in children with autism. Current study findings should be viewed as heuristic, prompting further research regarding the efficacy of low doses of Abilify® as well as other atypical antipsychotics in treating disruptive behaviors in children with autism. Confirmation of research findings in a larger sample is advised.
Implications for Nursing Practice

A unique aspect of this research was that it represents a clinical trial of a psychotropic medication initiated by an advanced practice registered nurse. The study question resulted from observations in clinical practice of patients’ positive responses to treatment on lower doses of Abilify® than recommended and approved by the FDA. This study represents a problem-solving approach to improving patient care and the delivery of clinical care through research in clinical practice. The best evidence from well-designed studies along with the clinician/researcher’s expertise and a spirit of inquiry led to the development of the research question. With the completion of this study, now provides additional evidence based research data (Banning, 2005).

Evidence based research provides the underpinning for evidence based practice. The case for EBP is supported by research. Patient outcomes are 28% better when clinical care is based upon evidence (Melnyk & Small, 2007). The implementation of EBP leads not only to improved patient outcomes but also to decreased healthcare costs and higher quality of care (Melnyk & Fineout-Overholt, 2012). There are gaps in research focused on developing and testing interventions to guide evidence-based care in children and adolescents. Improving mental and physical health in childhood provides the foundation for a productive society and healthy adult life (Melnyk & Small, 2007).

In a review of the literature, every study published to date evaluating the efficacy of Abilify® in treating disruptive behaviors in children, included investigators acting as consultants and/or receiving grant support from Bristol-Myers Squibb (Marcus et al., 2009; Marcus et al., 2011; Owen et al., 2009; Stigler et al., 2009; Stigler et al., 2004). Systematic reviews have documented that pharmaceutical industry sponsorship of drug studies is associated with findings that are favorable towards the sponsoring company’s product. Most pharmacotherapy studies are
either conducted in-house by the pharmaceutical company or externally by consultants who are paid for by the company (Lundh, Lexchin, Sismondo, Busuioc, & Bero, 2011). The research findings reported in this study are the result of independent research. The study investigators had no affiliation to the manufacturer of Abilify®. This is important to note due to the significance and importance of research in clinical practice being a unique opportunity to add to the research findings previously reported in large, pharmaceutically supported drug studies. The findings from this study support previous reports regarding the safety and efficacy in treating disruptive behaviors in children with ASDs with Abilify® and add to the body of knowledge suggesting that lower doses of Abilify® than previously studied can be effective in controlling disruptive behaviors and better tolerated than higher doses of Abilify® in the health care professions, this is a time of transformation. More than a quarter million nurses are advanced practice registered nurses (APRNs or ARNPs) having passed national certification exams with master’s or doctoral degrees. In 2008, the Robert Wood Johnson Foundation (RWJF) and the Institute of Medicine (IOM) launched a two-year initiative to respond to the need to assess and transform the nursing profession (Institute of Medicine, 2010). This research study is a testament to the recommendations from RWJF and IOM. At Nemours Children’s Clinic, Jacksonville, (NCC-J), the primary investigator of this study, was for the first time in the history of the clinic, a nurse. The research proposal was initially presented to the Institutional Review Board at NCC-J with a medical doctor as the primary investigator and the nurse researcher, a PhD student at the University of Florida as the co-investigator. The study was approved with several modifications including the following recommendation: “The IRB also inquired about why Tina D’Alessandro is not listed as PI on this study rather than Dr. De La Hunt. While having a qualified MD as a co-investigator is necessary for this study, the IRB feels that Ms. D’Alessandro is qualified to
serve as PI and should be so listed on the protocol and Parental Permission and Informed Consent for Participation in a Research Study.” (Nemours Office of Human Subjects Protection, 2010).

The Institute of Medicine’s 2020 goal is that 90% of clinical decisions be evidence based (IOM, 2010). This research study provides a model for clinical trials in individual practice settings that adds to our body of knowledge, answers a clinically relevant question and improves patient care and outcomes. As the nursing profession strives to implement the IOM’s future of nursing recommendations, the scope of nursing research will continue to evolve as advanced practice nursing privileges move in the direction of allowing nurses to practice to the full extent of their education and training.
APPENDIX A
CHILD BEHAVIORAL CODING BOOK

General instructions for coders: View the 15 minute segment of videotape. Begin regarding behaviors for the last 10 minutes of the videotape. Record no more than 2 behaviors at a time. Once you have coded the initial 1-2 behaviors, proceed to the next behavior. Continue coding in this manner until all target behaviors are coded. Frequently occurring behaviors may need to be coded individually. Use the definitions that are provided on this page.

Subject #______  Tape #______  Coder ID______  Date______

<table>
<thead>
<tr>
<th>Child Behaviors</th>
<th># of Occurrences in 10 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. tantrums</td>
<td></td>
</tr>
<tr>
<td>b. self-injurious behaviors</td>
<td></td>
</tr>
<tr>
<td>c. aggression</td>
<td></td>
</tr>
<tr>
<td>Total a &amp; b &amp; c</td>
<td></td>
</tr>
</tbody>
</table>

a. Tantrum- Any clearly audible crying sounds emitted by the child, associated with kicking and/or flailing arms (and bounded by a 5-second pause).

b. Self-injurious Behaviors- any behavior initiated by the child with intent to hurt self including head banging, biting, scratching, or hitting self or attempting to hurt self with use of a foreign object.

c. Aggression- striking, pinching or kicking another person, pulling another person’s hair or biting another person.

ADDITIONAL COMMENTS:
APPENDIX B
INTER-RATER RELIABILITY FOR OBSERVED BEHAVIORS

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tantrums</td>
<td>.94</td>
<td>.91</td>
<td>1.00</td>
</tr>
<tr>
<td>Aggression</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Self-Injury</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

NOTE: Coefficients were determined by calculating the investigator’s ratings and an average of 25% of the total number of videotaped sessions (randomly chosen) and ratings by Rater 1. The formula used for obtaining the coefficient was: #agreements/#agreements+disagreements (Portney & Watkins, 2000, p. 233).
Trade Name: Abilify®

What is this medicine?
Aripiprazole (ay ri PIP ray sole) is an atypical antipsychotic. It is used to treat schizophrenia and bipolar disorder, also known as manic-depression, and to treat some symptoms of autism. This medicine may also be used in combination with antidepressants to treat major depressive disorder.

What should I tell my health care provider before I take this medicine?
They need to know if your child has any of these conditions: * dehydration * diabetes * heart disease * history of a brain tumor, head injury or stroke * seizures * suicidal thoughts, plans or attempt * a previous suicide attempt by your child or a family member * an unusual or allergic reaction to aripiprazole, other medicines, foods, dyes, or preservatives.

How should I use this medicine?
Take this medicine by mouth with a glass of water. Follow the directions on the prescription label. Your child can take this medicine with or without food. Take one dose daily. Do not take the medication more often than directed. Overdosage: If you think your child has taken too much of this medicine, contact a poison control center or emergency room at once. NOTE: this medicine is only for your child. Do not share this medicine with others.

What if my child misses a dose?
If your child misses a dose, give it as soon as you can during the same day. Do not take double or extra doses.

What side effects may occur when taking this medicine?
Side effects that you should report to your health care provider as soon as possible include: * allergic reactions like skin rash, itching or hives, swelling of the face, lips, or tongue; * breathing problems; * confusion; * feeling faint or lightheaded, falls; * fever, chills or sore throat; * increased hunger or thirst; * increased urination; * joint pain, muscle pain, spasms; * problems with balance, talking, walking; * restlessness or need to keep moving; * seizures; * suicidal thoughts or other mood changes; * trouble swallowing; * uncontrollable head, mouth, neck, arm, or leg movements; * unusually weak or tired; * blurred vision; * constipation; * headaches; * nausea, vomiting; * trouble sleeping; * weight gain

Call the research investigator for medical advice about side effects, you may report side effects to the FDA at 1-800-FDA-1088.

What should I watch for while my child is using this medicine?
It may be several weeks before you see the full effects of this medicine. Do not suddenly stop taking this medicine. Patients and their families should watch out for depression or thoughts of suicide. Also watch out for sudden changes in feelings such as feeling anxious, agitated, panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and
hyperactive, or not being able to sleep. If this happens, call the research investigator. Your child may get dizzy or drowsy. This medicine can reduce the response of your child’s body to heat or cold. Try not to let your child get overheated or dehydrated from exercise. If you notice an increased hunger or thirst, different from your child’s normal hunger or thirst, or you find that your child has to urinate more frequently, you should let the research investigator know this. This medicine may cause changes in blood sugar levels. Your child will receive blood work to check blood sugar before beginning this medication and again after three months of treatment and periodically throughout treatment to monitor blood sugar and other lab values.

Where should I keep medication?
Keep out of reach of children. Store this medication at room temperature between 15 and 30 degrees C (59 and 86 degrees F).
LIST OF REFERENCES


King, I. (1990, July). Speech presented at the Wayne State University College of Nursing Summer Research Conference, Detroit, MI


BIOGRAPHICAL SKETCH

Tina Marie Malcolm D’Alessandro is a psychiatric nurse practitioner at Nemours Children’s Clinic where she is active in shared governance and serves as the Chairperson for the Research Council. She received the Florida Nurse of the Year Award in 2012 at the Nemours Children’s Clinic in Jacksonville, Florida, recognizing her involvement in nursing research initiatives, advocacy efforts, leadership, and mentoring.

Tina graduated cum laude from Duke University in 1983. She was class president from 1982-1983 and inducted into Sigma Theta Tau, the national nursing honor society. She completed her Master of Science in nursing at the University of Florida in December 2000 and a post master’s at the University of Florida in psychiatric nursing in December 2006. Tina received her Doctor of Philosophy from the University of Florida in December 2012. She is board certified by the American Nurses Credentialing Center as a Family Nurse Practitioner and a Family Psychiatric Nurse Practitioner.

Tina has traveled abroad teaching nursing to baccalaureate students in Cambodia. She plans on continuing clinical practice, research initiatives and teaching both nationally and internationally.