Therapies Used in Children with Autism Spectrum Disorders: a Pilot Study of Caregivers' Perspective

By

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Abstract

Autism Spectrum Disorders (ASD) management is challenging. This pilot study investigated parents/caregivers' perception of therapies and other interventions in their ASD children. Information for children attending NDS department of MATC in Winnipeg was collected from participants through questionnaire-guided interviews. Mixed quantitative/qualitative methods were employed to analyze data. A total of 12 participants completed the study and data from14 children were collected. All children attended school, 88% were males, and more than 50% reported eating/sleeping difficulties. ADHD comorbidity was reported in 69%. The prescription drug most commonly tried was risperidone 56%, which found effective in controlling aggressive behaviours. Melatonin mostly tried in children for sleep. Behavioural therapy was rated as the most effective intervention, but was often limited by coverage and waiting period's issues. Common concerns voiced by participants were the lack of trained professionals, the limited understanding of ASD children's needs and the uncertainty for the future of their children (financial/service support at older age). Future studies should be conducted in a larger population and a longer observation time to document the changing needs of ASD children.

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List of Abbreviation

ABA: Applied Behavior Analysis

ABC: Aberrant Behavior Checklist

ABC-C: Aberrant Behavior Checklist-Community

ABC-I: Aberrant Behavior Checklist –Irritability

ADHD: Attention-Deficit Hyperactivity Disorder

ADI-R: Autism Diagnostic Interview Revised

ADHD-RS: ADHD Rating Scale

ADOS: Autism Diagnostic Observation Schedule

AHRQ: Agency for Healthcare Research and Quality

APA: American Psychiatric Association

ASD: Autistic Spectrum Disorders

ATN: Autism Treatment Network

CADDRA: Canadian Attention Deficit Hyperactivity Disorder Resource Alliance

CAIRN: Canadian Autism Intervention Research Network

CAM: Complementary and Alternative Medicine

CASDA: Canadian Autism Spectrum Disorders Alliance

CBT: cognitive behavioral therapy

CDC: Centers for Disease Control and Prevention

CGI-I: Clinical Global Impression of ADHD-Improvement

CTRS-R.S: Conners Teacher Rating Scale-Revised: Short Form

CYBOCS-PDD: Children's Yale- Brown Obsessive Compulsion Scale-Modified for Pervasive Developmental Disorders

DBC: Developmental Behavior Checklist

DSM: Diagnostic and Statistical Manual of Mental Disorders

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision

DTT: Discrete Trial Training

EIBI: Early Intensive Behavioral Intervention

EA: Education Assistant

EPS: Extrapyramidal Symptoms

HREB: Health Research Ethic Board

HRQOL: Health-Related Quality of Life

ICD-10: International Classification of Diseases

ID: Intellectual Disabilities

IPSA: Interdivisional Program for Students with Autism

MATC: Manitoba Adolescent Treatment Centre

NEDSAC: The National Epidemiologic Database for the Study of Autism in Canada

NDS: Neurodevelopmental Services department

NIHB: Non-Insured Health Benefits

OT: Occupational Therapy

OTC: Over the Counter

RBS-R: Repetitive Behaviors Scale

RCT: Randomized Clinical Trial

RUPP: The Research Units on Pediatric Psychopharmacology

SOL: Sleep Onset Latency

SCQ: Social Communication Questionnaire

SRS: Social Responsiveness Scale

SSRI: Selective Serotonin Reuptake Inhibitors

PREMISE

Autism Spectrum Disorders (ASD) represents a group of developmental disorders that include autism, Asperger syndrome, Pervasive Developmental Disorders (PDD), and Childhood Disintegrative Disorder (CDD). ASD involves impairments in social interaction, communication and behavioral functioning such as repetitive and stereotyped behaviors (APA 2000). ASD is one of the most common neurocognitive disorders of childhood and the latest estimate of ASD prevalence in the US is 1 in every 68 children (Centre for Disease Control (CDC) report 2014). Diagnosis of ASD has been based upon the Diagnostic and Statistical Manual (DSM) and the International Classification of Diseases (ICD) guidelines. There is no cure for ASD but many therapeutic approaches have been tried to address specific symptoms with variable results. There is still a high need to improve the understanding of the condition, its diagnosis, and the effectiveness of available therapies. The ultimate goal of therapy in children affected by ASD is to control their symptoms and improve their quality of life. The perspective of caregivers is important in the evaluation of the effectiveness of therapies and services. Our study contributes to the understanding of how an ASD diagnosis and its management affects children and their families.

BACKGROUND

Definition of ASD

According to the 2010 edition of the ICD (ICD-10), ASD is defined as a type of PDD, characterized by (a) the presence of abnormal or impaired development that manifests before the age of three years, and (b) the characteristic type of abnormal functioning in all the three areas of psychopathology: reciprocal social interaction, communication, and restricted, stereotyped, repetitive behavior. An updated version of the definition is expected in the ICD-11, still in the revision process, to be released in 2018.

In the DSM-4 (released in 1994), ASD included four separate disorders: Autistic Disorder (autism), Asperger's Disorder, Childhood Disintegrative Disorder (CDD) and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). In the current DSM-5 (released in May 2013), all four conditions are considered as a single condition, ASD.

Prevalence

According to the CDC, autism rates had increased in the US from 1 in 200 by the late 1990s, to 1 in 68 children by 2014 (ADDM, 2014). This estimate did not represent the entire population of children in the United States, but was based on a population of 8-year-old children living in 11 communities. The new 2014 CDC estimate is about 30% higher than the estimate for 2008 (1 in 88), 60% higher than the estimate for 2006 (1 in 110), and approximately 120% higher than the estimates for 2002 and 2000 (1 in 150) (ADDM, 2014). ASD is four to five times more common in males than in females (Fombonne E et al., 2009; CDC Mar 2014).

In 2001, a National Epidemiologic Database for the Study of Autism in Canada (NEDSAC) was established and funded by the Canadian Institutes of Health Research (CIHR). The main goal was to track the proportion of children with ASD in various regions of the country in order to determine

whether the prevalence of ASD was changing over time. Unfortunately, funding for NEDSAC ended in 2012 and data for this project are no longer being collected; nevertheless, valuable reports on ASD prevalence in certain regions and provinces became available for Alberta, British Columbia, Newfoundland and Labrador, Prince Edward Island, Manitoba and Southeastern Ontario. According to NEDSAC data, the prevalence of ASD in Manitoba among children 0-14 years of age was (1 in 252) in 2007. In contrast, data from the Manitoba Centre for Health Policy (MCHP) supported a prevalence of ASD children of (1 in 126) in the same year and in the same age group. A reason for the difference was seen in the fact that data collected by NEDSAC were based on children identified through the Children's Special Services, a provincial program that serves children with special needs throughout the province (excluding those living on reserves), while MCHP offers larger population-based databases (Ouellette H et al., report 2011). In southeastern Ontario, ASD prevalence was (1 in 77) among children 2-14 years of age in 2010 (Ouellette H et al., 2011).

In 2014, the Autism Society Canada's estimated that, based on the CDC report of the same year, approximately 515,000 Canadians were living with ASD (Please refer to Appendix I); however, the exact prevalence of ASD in Canada is currently unknown. Health Canada has initiated an ASD surveillance program within their current epidemiological surveillance system to address this question. The first step taken toward constructing a national surveillance system for ASD was an environmental scan. The next step will be to implement a series of pilot studies based on the environmental scan in order to explore optimal surveillance options. (Please check Health Canada website/ Building an autism spectrum disorders surveillance system for Canada).

Symptoms of ASD

According to the DSM-V, ASD symptoms present two major characteristics:

1) they must be present at childhood and 2) they must impair and limit everyday functioning. Any child who was diagnosed according to DSM-IV diagnostic criteria would still meet the ASD criteria of the new DSM-V.

Symptoms are divided into two major domains (A) and (B) and total 7 criteria (A1, A2, A3, B1, B2, B3 and B4). Minimum criteria required are 5.

(A) Social communication and social interaction under which further subgroups and criteria are included:

A1 - Problems with social initiation and response; for example, unusual social initiations like intrusive touching, licking of other persons, failure to conduct a normal back and forth conversation and/or showing no pleasure in social interactions, or failure to share enjoyment, excitement or achievements with others.

A2 - Problems with non-verbal communication; for example, the child does not make eye contact and does not understand body postures (e.g., facing away from the listener) and/or the child lacks coordinated verbal and non-verbal communication (e.g., inability to coordinate eye contact or body language with words).

A3 - Problems with social awareness and insight, as well as with the broader concept of social relationship: the child has difficulties to adjust behavior to suit social contexts; for example, the child does not notice another person's lack of interest in an activity, and/or has difficulties in making friends (e.g., does not try to establish friendships or does not have preferred friends).

(B) Restricted, repetitive interests and activities; this can be further sub-grouped into

B1-Atypical speech, movement and palsy: stereotyped or repetitive speech, the child sometimes reverses the use of pronouns (e.g., “You” for “I”) or refers to self by own name, or mixing up gender “he” for “she”.

B2- Rituals and resistance to change: adherence to certain routine or unusual routines, repetitive use of certain objects, inability to understand humor, difficulty in transitions, excessively rigid and inflexible.

B3- Preoccupation with objects or topics: the child focuses on the same few objects (line up toys), repetitively opens and closes doors, has unusual fears (e.g., afraid of people wearing earrings).

B4- Atypical sensory behavior: high tolerance for pain (self-injurious behavior such as self-biting), becoming extremely distressed by atypical sounds, and unusual squinting of eyes or looking at objects/ people out of corner of the eye.

(Carpenter L, 2013) (Please refer to Appendix II for details described in the DSM-V).

Assessment and diagnostic tools for ASD

In addition to the DSM diagnostic list, other diagnostic measures can be used, such as the Autism Diagnostic Interview (ADI), the Autism Diagnostic Interview-Revised (ADI-R), the Autism Diagnostic Observation Schedule (ADOS), the Social Responsiveness Scale (SRS), Social Communication Questionnaire (SCQ), and the Childhood Autism Behavior Scales (CABS) (please refer to Appendix III).

The Canadian Autism Intervention Research Network (CAIRN) suggests conducting also general physical examinations, which include questions about sleep and bowel/bladder function. A full neurological examination is recommended for children with ASD and co-existing medical

problems, and for children who have unusual symptoms (e.g., seizures). Children presenting with a high degree of language or learning disabilities in addition to ASD should undergo genetic testing, such as karyotyping to look for chromosomal abnormalities, and molecular testing to look for Fragile X syndrome (Harrington JW et al., 2014, CAIRN and Autism Canada Foundation).

ASD and DSM-V changes

Major changes regarding ASD included in the DSM-V compared to the previous

DSM-IV are:

(1) as previously mentioned, all four subtypes of PDD such as autistic disorder, Asperger's disorder, childhood disintegrative disorder and PDD-NOS are included in one new category called Autism Spectrum Disorders (ASD), (Grant R et al., 2013; Halfon N et al., 2013; Turygin N et al., 2013).

(2) DSM-IV had 3 diagnostic domains for autism: a) social interaction, b) social communication, and c) restricted, stereotyped, repetitive behavior, while in DSM-V both social interaction and social communication fall into one domain. In addition, in DSM-V the number of requirements for deficits under each diagnosing domain has changed in some instances (Halfon N et al., 2013, Mayes SD et al., 2013 and Geneva Center for Autism).

(3) DSM-V eliminated the age restriction for ASD diagnosis: symptoms must be presented at an early age (but not strictly before age 3) (Halfon N et al., 2013).

(4) The co-occurrence of Attention Deficit Hyperactivity Disorder (ADHD) and ASD is recognized. DSM-IV precluded the diagnosis of both disorders in the same child and specified that the presence of ASD symptoms were an exclusion criterion for ADHD.

It is expected that these changes will significantly affect diagnosis and treatment of ASD and comorbid ADHD+ASD. There is currently some controversy among researchers about the

implications of such changes on ASD prevalence, clinical practice, health services and children's lives (APA 2013; Grant R et al., 2013; Halfon N et al., 2013; Mayes SD et al., 2013; Turygin N et al., 2013).

Comorbidity of ASD and ADHD

It has been clear, however, that even before the publication of the DSM-V, the co-occurrence of ASD and ADHD was clinically recognized; in fact, high rates have been reported together with evidence of clinical, neuropsychological and genetic overlap (Rommelse N et al., 2011).

Both ADHD and ASD are diagnosed based upon behavioral symptoms. The level of ADHD symptoms, mainly inattention, hyperactivity and impulsivity, is increased in children with ASD (Murray MJ et al., 2010; Mahajan R et al., 2012); as well, there is an increased level of ASD symptoms, such as impairments in social functioning, communication and behavior problems, in ADHD children (Lee DO et al., 2016; Mahajan R et al., 2012).

The prevalence of ADHD symptoms (hyperactivity and impulsivity with or without inattention) in children with ASD has been assessed in retrospective chart review studies with variable results (from 30% to 78%) (Goldstein S et al, 2004; Gadow D et al, 2004, 2005 and 2006). On the other hand, there are no conclusive statistics on the prevalence of autistic traits in ADHD (Kochhar P et al., 2011; Kroger A et al., 2011).

Studies conducted to evaluate the co-occurrence of ASD and ADHD comprised different aspects (genetic, neurophysiological, social), and further subcategorized children to ASD only (children with typically developing autism), ADHD only (children with typically developing ADHD) and ASD+ADHD. However, the interaction and mode of ASD and ADHD co-occurrence is still not completely understood (Taurines R et al., 2012).

One study (Tye C et al, 2012) aimed to compare the Event-Related Potentials (ERPs) abnormalities

in children with ASD, ADHD and comorbid ASD + ADHD. ERP is a tool used to investigate different temporal stages of information processing by observing face and gaze. Children were individually assessed using screening questionnaires and diagnostic interviews to confirm ASD or ADHD, or both diagnoses. Each child from each group was given colour images of three female faces with direct or averted gaze (looking right or left); images were presented in upright or inverted orientation on grey background. Children's responses were recorded and analyzed using Electroencephalography (EEG). The study found that children with ASD have specific abnormalities in gaze processing and altered neural specialization, while children with ADHD show abnormalities at early visual attention stages. Children with ASD + ADHD have an additive co-occurrence with deficits of both disorders (Tye C et al, 2012).

Risk Factors

The pathogenesis and etiology of ASD is not completely understood; however, several risk factors (genetic, neurobiological, environmental and perinatal) have been identified.

Genetic risk factors

There is increasing evidence for the role of genetic factors in the etiology of ASD (Muhle R et al., 2004). In fact, ASD is considered a highly genetically determined disorder with heritability around 90% (Freitag CM et al., 2007). The high prevalence of ASD in males (XY chromosome) compared to females (XX chromosome) is consistent with this role of genetics in ASD (Muhle R et al., 2004), increased possibility of ASD occurrence in siblings/ relatives of ASD children compared to others (Sandin S et al., 2014), and 36 to 96% occurrence in monozygotic twins (Colvert E et al., 2015). The epigenetic theory was supported by several studies (Baron-Cohen S 2006; Lopez-Rangel E et al., 2006; Samaco RC et al., 2004), which explained how an abnormal gene is turned "on" early in fetal development stages and affects the expression of other genes that are not mutated themselves;

this leads to changes in the brain development, affecting social and communication development leading to restricted interests and repetitive behavior. Genetic studies of ASD include investigations on neuronal migration, growth, and dendritic spine development as well as excitatory and inhibitory neurotransmission (Freitag CM et al., 2012; Freitag CM et al., 2010).

Neurobiological risk factors

Brain abnormalities were proposed from neuroimaging and autopsy studies (Volkmar FR et al., 2003; Boddaert N et al., 2009). Brain abnormalities such as differences in total and regional gray and white matter volumes, brain chemical concentration variations, changes in cortical structure and organizational/cognitive processing have been identified in individuals diagnosed with ASD (Baron-Cohen S et al., 1999 and Tang G et al., 2014). An increased overall brain size by 2-10%, which could be further explained by an increased number of neurons in the prefrontal cortex (Courchesne E et al., 2011; Piven J et al., 1996 and 1995), supports the presence of brain abnormalities in ASD children. Furthermore, MRI studies showed that individuals with ASD use different patterns of connectivity, cognitive strategies, and brain areas to process information during tasks requiring social interaction or response to visual or auditory stimuli (Williams JH et al., 2006; Dalton KM et al., 2005; Piven J et al., 1995). In addition, brain electrophysiology studies explained that ASD children process information about faces differently and seem to have a marked delay in the neural system processing eye gaze (Bailey AJ et al., 2005; McPartland J et al., 2004).

Environmental and perinatal risk factors

There is correlation between environmental and perinatal risk factors, and ASD. An increased paternal age seems to be a factor, in fact, offspring of fathers ≥ 50 years old were 2.2 times more likely to have autism than offspring of men aged ≤ 29 years (Hultman CM et al., 2011). Also pre-

term birth seems to have influence: babies born at <26 weeks of gestation were three times more likely to have a psychiatric disorder, including ASD, than their classmates (Johnson S et al., 2010). Many studies were conducted on the maternal use of psychotropic medications and found an association with a diagnosis of ASD in their children (e.g., valproic acid, selective serotonin reuptake inhibitors (SSRIs)) (Williams G et al., 2001; Croen LA et al., 2011). Autoimmune diseases (e.g., psoriasis) during pregnancy (Croen LA et al., 2005) have also been associated with ASD diagnosis. Nevertheless, the exact mechanisms of how the environmental and perinatal risk factors influence the probability of having children with ASD need to be further investigated.

Therapeutic Options for ASD

While there is no cure for ASD, a comprehensive treatment plan that addresses patients' needs is important. Treatments for ASD should be individualized according to age, comorbid conditions, therapies previously tried, degree of impairment in social and behavioral function, and special needs of the child and his/her family (Maglione MA et al., 2012). The major goal of an ASD management plan is to maximize the child's independence, functioning and quality of life (Maglione MA et al., 2012, Myers SM et al., 2009).

Overall, ASD therapies should (a) improve communication skills, (b) enhance social functioning, (c) improve adaptive skills, (d) reduce negative behaviors, and (e) strengthen academic functioning and cognition (Lai MC et al., 2014; Maglione MA et al., 2012; Myers SM et al., 2009).

Current treatments for ASD falls into two major categories: (1) the non-pharmacological (e.g., behavioural interventions) and (2) the pharmacological (medical management) interventions.

(1) Non- Pharmacological Therapies

Non-pharmacological therapies include behavioral and educational interventions, occupational and/or massage therapy, and complementary or alternative therapies (e.g., homeopathic medicine,

dietary restriction “special diets”, and traditional Chinese medicine) (Maglione MA et al., 2012; Myers SM et al., 2007 and 2009).

(a) Behavioural and educational interventions

Behavioural and educational interventions target the core symptoms of autism and help achieve major treatment objectives for ASD (Myers SM et al., 2007 and 2009). The most recommended non-drug therapies are the “intensive behavioral interventions”, which include, but are not limited to applied behaviour analysis (ABA), early intensive behavioural intervention (EIBI) and discrete trial training (DTT) (Myers SM et al., 2007, 2009; LeBlanc LA et al., 2012).

The National Research Council (Washington, DC 2001) and the New York State Department of Health Early Intervention Program have recommended initiating educational services and intensive behavioral interventions as soon as a child is suspected of having ASD. In fact, evidence from many observational studies showed that maximum benefit could be obtained with early intervention (Maglione MA et al., 2012; Myers SM et al., 2007 and 2009; National Research Council, Washington, DC 2001). In addition, in order to maximize success of an intensive behavioral program, low student-to-therapist ratio is recommended (National Autism Center's National Standards Report, Randolph, MA, 2009). Intensive behavioral programs could be delivered in a variety of settings (e.g., home, inclusive classroom, and community) (Levy SE et al., 2009).

ABA is defined as the application of the principles and procedures from the science of behaviour analysis (learning) to socially significant behaviour (LeBlanc LA et al., 2012). ABA is a psycho-educational treatment considered to be an efficacious intervention for ASD. The ABA approach is to teach social, motor, and verbal behaviours as well as reasoning skills (Rogers SJ et al., 2008). ABA aims at increasing desirable behaviors and decreasing undesirable ones by using repeated

reward-based skills. ABA establishes relationships between the behaviour and the environment, and subsequently designs methods to change that behaviour and systematically applies these methods to improve behaviour in everyday activities. There are 7 dimensions of ABA (applied, behavioural, analytic, technological, conceptual systems, effective and generality) identified by Bayer, Wolff, and Risely in 1968 (ABA educational series provided by Geneva Center for Autism, ON).

EIBI is defined as a behavioural treatment, based on the principles of ABA, that is delivered early (before the age of 5 years) and intensively (25–40 hours per week) usually over a span of 2–3 years. Currently, EIBI is the only well-established treatment that produces positive outcomes for children with ASD (LeBlanc LA et al., 2012). The purpose of EIBI is to increase intellectual (i.e., communication, cognitive, academic) skills and adaptive functioning (i.e., social skills, self-care skills, safety) in order to prepare children with ASD to learn and succeed in typical home and school environments with the lowest possible support (Howlin P et al., 2009; Lovaas OI et al., 1987). In a Cochrane systematic review of EIBI studies, the author found that EIBI is an effective behavioral treatment for some children with ASD and found that children receiving EIBI treatment performed better on tests of adaptive behavior than children in the comparison groups after about two years of treatment (Reichow B et al., 2012).

DTT sometimes is referred to as “Lovaas therapy” from the psychiatrist who developed it. DTT is a highly structured teaching strategy commonly used in EIBI (Lovaas OI et al., 1987; Levy SE et al., 2009; Orinstein AJ et al., 2014). It is implemented in a one-to-one setting and is often used to teach specific behaviors or skills necessary for learning more complex ones (LeBlanc LA et al., 2012). The discrete trial method has four distinct parts: (1) the trainer's presentation (e.g., clear instructions about a desired behavior “pick up a paper”), (2) the child's response (e.g., child

respond correctly), (3) the consequence (e.g., the behaviour is reinforced), and (4) a short pause between the consequence and the next instruction (between interval trials) (Anderson et al., 1996). Most educational and behavioral intervention studies focused on the treatment of preschool and school aged children; little information is available about behavioural and educational interventions therapies in adolescents and children younger than two years (Zwaigenbaum L et al, 2009).

Observational studies and systematic reviews (Howlin P et al., 2009; Maglione MA et al., 2012; Myers SM et al., 2007) pointed out the characteristics of successful and beneficial educational programs for ASD children, which may include, but are not limited to (a) individualized programming, (b) teachers with special expertise in working with children with ASD, (c) highly supportive teaching environment, (d) family involvement, (e) close monitoring and modification as per child's needs and changes (National Research Council, Washington DC 2001; New York State Department of Health Early Intervention Program, Publication No.4217, Albany, NY 1999; Orinstein AJ et al., 2014).

Two reports by the Vanderbilt Evidence-based Practice Center (Nashville, TN) for the Agency for Healthcare Research and Quality (AHRQ) of the U.S. Department of Health and Human Services reviewed the effectiveness of behavioural therapies in the context of other interventions: the overall results were that behavioural therapies are associated with positive outcomes for children with ASD, but that it is important to deepen our understanding and isolate elements or components of interventions most commonly associated with beneficial effects in specific children (Warren Z et al., 2011; Weitlauf AS et al., 2014)

(b) Occupational therapy

Occupational therapy (OT) addresses all areas of the occupational domain to support patients'

health and their participation to everyday activities (American Occupational Therapy Association, 2008). OT services can be provided for ASD children in schools or in clinical settings. The primary occupations of children generally include play, learning, social participation, and self-care (Provost B et al., 2009). Occupational therapists are known for their ability to use the sensory integration approach (over respond, under respond or/and sensory-motor problems) (Ayres AJ 1972, 1978, 1989); children with ASD often show atypical sensory responses, poor motor skills, weakness, clumsiness, and/or decreased independence with daily activities (Jasmin E et al., 2009). OT bridges the gap between sensory integration and occupation, and helps ASD children participate in activities that require rich and meaningful sensorimotor skills. OT improves child's independence with daily living skills (Jasmin E et al., 2009; Manning-Courtney P et al., 2013; Roseann C et al., 2005).

As stated by Ayres [1972], "*A sensory integrative approach to treating learning disorders differs from many other approaches in that it does not teach specific skills. . . Rather, the objective is to enhance the brain's . . . capacity to perceive, remember, and motor plan as a basis for learning. . . Therapy is considered a supplement, not a substitute to formal classroom instruction."* (Ayres AJ, 1972; Roseann C et al., 2005)

(c) Complementary and alternative therapies

The medical literature on complementary and alternative medicine (CAM) for ASD is limited and their effectiveness is uncertain (Levy SE et al., 2008; Carbone PS et al., 2010). There are many reasons why ASD children parents/caregivers would try complementary and alternative therapies. Parents of children with difficult disorders, who do not respond well to available therapies, tend to explore alternatives in order to help their children; in addition they might have concerns about prescribed medications' safety and side effects and might considered alternative approaches

somewhat safer. Parents might learn about these therapies from magazines, or the television or the internet. Culture and family traditions also play a role. Most complementary and alternative therapies for ASD are normally not recorded in medical charts and parents/caregivers often do not volunteer such information to clinicians. It is therefore advisable for health care providers to ask parents/caregivers specific questions regarding the use of any complementary and/or alternative therapies (National Center for Complementary and Alternative Medicine, 2000; Wong HH et al., 2006; Hanson E et al., 2007; Levy SE et al., 2008; Perrin JM et al., 2012). CAM may include but is not limited to homeopathic medicine, dietary restriction, "special diets", traditional Chinese medicine, horse riding, and music therapy (Maglione MA et al., 2012; Myers SM et al., 2007 and 2009).

(2) Pharmacological Therapies

There are no currently available pharmacologic agents with proven efficacy to treat ASD core symptoms, therefore, they should be considered only after educational and behavioral interventions have been used (Towbin KE et al., 2003). Pharmacological options for ASD are generally chosen to treat specific symptoms and behaviours such as attention deficit, hyperactivity and irritability, obsessive or compulsive behaviors, repetitive behavior, anxiety, depression, and sleeping disorders. Psychotropic medications (antipsychotics, stimulants, antidepressants, alpha agonists, anxiolytics, and anticonvulsants) are most commonly used (Dove D et al., 2012; Doyle CA et al., 2012; Posey DJ et al., 2000). Other options include natural and over-the-counter products (e.g., melatonin, omega-3 fatty acids and multivitamins) and other medications such as secretin, naloxone, N-acetylcysteine (Canitano R et al., 2011; Doyle CA et al., 2012).

Pharmacological treatments do not treat the underlying ASD symptoms alone, but they could improve the child's functioning and the ability to participate in behavioral interventions. In fact, if

pharmacological treatments are to be tried, they should be used in conjunction with appropriate behavioral and environmental interventions (Canitano R et al., 2011; Carbone PS et al., 2010; Doyle CA et al., 2012).

(a) Psychopharmacological medications

Psychotropic medications need to be prescribed by specialists (e.g., child psychiatrists or developmental-behavioural pediatricians) since the use of these medications needs to be monitored for safety and doses need often to be adjusted according to autistic symptoms or any other comorbid condition. Each ASD child is a unique case and response may vary, therefore medication choices should be individualized. A team of health care providers is usually needed to monitor progress, evaluate therapy effectiveness, and recommend behavioral and educational programs and/or activities. In addition to child psychiatrists or developmental-behavioral pediatricians, the team may in fact include speech and language specialists, occupational therapists, genetic counselors, nurses and social workers (Aman MG et al., 2004; Carbone PS et al., 2010).

Consideration should be given to selecting the appropriate dose (e.g., start at lower dose and increase slowly), to determining formulation availability, cost, insurance coverage and to monitoring requirements (which may include child's weight and growth, and laboratory tests such as glycemia, lipidemia, liver enzymes, EKG) (Myers SM et al., 2007). It is important to consider that children with ASD seem to be more sensitive to psychopharmacotherapy and more likely to experience adverse effects than children without ASD (Matson JL et al., 2011; Farmer CA et al., 2008; Aman MG et al., 2004; Aman MG et al., 2003).

The use of psychotropic medications has increased over the past two decades (Lake JK et al., 2014) and multi-psychotropic medication use (polypharmacy) has been noticed in children with ASD,

despite minimal evidence of its effectiveness (Spencer D et al., 2013; Coury DL et al., 2012; Matson J. L et al., 2011)

(i) Antipsychotics

Second generation antipsychotics, SGA, (e.g., risperidone, aripiprazole, paliperidone) seem to be the most efficacious drug class for the treatment of irritability and aggression in children with autism (Politte LC et al., 2014). Improvement has been observed also in stereotypical behaviour and hyperactivity (Doyle CA et al., 2012)

Risperidone is the most studied antipsychotic agent in autism (Canitano R et al., 2011; Williamson E. D et al., 2012) and it has been shown to be useful in the treatment of maladaptive behaviors, such as irritability, aggression and self-injury symptoms; it also appears to be well tolerated (Canitano R et al., 2008; McCracken J et al., 2002; Robb AS et al., 2010; RUPPAN: Research Units on Pediatric Psychopharmacology Autism Network, 2005b).

Evidence from two large randomized controlled trials suggested that aripiprazole could also be effective in treating maladaptive behaviors in children and adolescents with ASD. It was found to be safe and well tolerated and to produce less irritability, hyperactivity, and stereotype behaviors (such as repetitive and purposeless actions) (Ching H. et al., 2012; Marcus RN et al., 2009; Owen R et al., 2009).

Paliperidone, a risperidone metabolite, has also proven to be effective for the treatment of irritability and was well tolerated in individuals with autism (adolescents and young adults, age group 12-21 years); however, more studies are needed to support these results (Stigler A et al., 2012).

Other SGAs such as quetiapine and ziprasidone have been tried in clinical practice in children with ASD, with no favorable results (Corson AH et al., 2004; Findling RL et al., 2004; Malone RP et

al., 2007). More studies are required to support the use of these agents (Canitano R et al., 2011).

FDA approved antipsychotics for the treatment of irritability in ASD children. Risperidone was approved in 2006 for children ages 5-16 years old and aripiprazole in 2009 for children ages 6-17 years old (Politte, L. C et al., 2014). In contrast, Health Canada has not approved the use of antipsychotics in children, and stated that their safety and efficacy in children under the age of 18 have not been established (Health Canada, Drugs and Health Products 2015). The only recent exception is aripiprazole, which is indicated for adolescents with schizophrenia (15 – 17 years of age) or adolescents in a manic or mixed episode of bipolar I disorder (13 – 17 years of age), but not for autism (Health Canada, Drugs and Health Products, 2015). However, antipsychotics are generally used off-label for children with ASD in Canada (Alessi-Severini S et al., 2012). Parents/caregivers should be informed about the medications that are being prescribed off-label to their children.

SGAs present an array of adverse effects, which include increased appetite (weight gain), constipation, fatigue, drowsiness, and increased lipid, prolactin, and blood glucose levels (Matson JL et al., 2011).

Older generation antipsychotics (e.g., haloperidol and phenothiazines) demonstrated efficacy but their use has been limited in children because of their significant risk of extra-pyramidal side effects (EPS) (Canitano R et al., 2011; Doyle CA et al., 2012)

(ii) ADHD medications

ADHD medications may be useful to control symptoms of hyperactivity and short attention span (Jahromi LB et al., 2009; RUPPAN: Research Units on Pediatric Psychopharmacology Autism Network, 2005a). Psychostimulants such as methylphenidate (MPH) demonstrated some benefit but their overall efficacy is low and they seem to produce more side effects (e.g., irritability) in

ASD children compared to typically developing children with ADHD (Doyle CA et al., 2012). Studies on other stimulants such as amphetamines (e.g., dextroamphetamine, lisdexamfetamine) used for attention deficit and hyperactivity in children with ASD are still limited (Hazell P, 2007). A study on the effects of extended-release MPH for the treatment of ADHD and associated behaviours in ASD (Pearson D.A et al., 2013) found that MPH treatment was associated with significant declines in hyperactive and impulsive behaviour both at home and at school. Parents noted significant declines in inattentive and oppositional behaviour, together with improvements in social skills. No exacerbation of stereotypical behaviours was noted, and side effects were similar to those seen in typically developing children with ADHD. Dose response was primarily linear in the dose range studied (Pearson DA et al., 2013).

Adverse events of stimulants may include irritability, insomnia, cardiovascular side effects (increased heart rate) and decreased appetite (CPS monographs, 2015).

Studies of atomoxetine (a selective norepinephrine reuptake inhibitor), a non-stimulant ADHD medication, in children with ASD with associated ADHD symptoms suggested a favorable response in at least half of treated patients, with mild to moderate side effects (Arnold LE et al., 2006). In one double-blind RCT, atomoxetine was superior to placebo in controlling ADHD symptoms after a treatment period of 8 weeks and was generally well tolerated (non-severe adverse effects were gastrointestinal upsets, sleep problems, and fatigue) (Harfterkamp M et al., 2012). Other adverse effects of atomoxetine may include mood swing, dizziness, irritability, decreased appetite and suicidal ideation (CPS monographs, 2015).

(iii) Antidepressants

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and fluvoxamine, have been used in clinical practice to treat repetitive behaviors in children with ASD based on their

effectiveness in obsessive-compulsive disorder (OCD). They are also used to treat comorbid depression or/and anxiety (Canitano R et al., 2011), even though clinical trials had not shown convincing results. SSRIs have low effectiveness in the treatment of interfering and repetitive behaviours in autistic individuals and are poorly tolerated in children with autism compared to adults (Kolevzon A et al., 2006; Soorya L et al., 2008). Fewer studies have been conducted with other antidepressants (such as clomipramine), with no significant results (Remington G et al., 2001). Citalopram is sometimes used in clinical practice for anxiety in ASD children but it has been shown not to be effective for repetitive behaviours in ASD children and it seems to be associated with side effects (particularly increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, and dry skin or pruritus) (King BH et al., 2009; Ipser JC et al., 2009; Stein DJ et al., 2009). It has to be recognized that most studies of antidepressants in ASD have been of low quality and showed mostly unfavorable results (Canitano R et al., 2011; Doyle CA et al., 2012). Overall, SSRI adverse effects may include anorexia, agitation, tremor, insomnia and gastrointestinal side effects (CPS monographs, 2015).

(iv) Alpha agonists

Alpha-two adrenergic agonist (clonidine) and a selective alpha-two adrenergic receptor agonist (guanfacine) are used to target certain symptoms of inattention, impulsivity and hyperactivity in children who do not respond to / or experience adverse events from psychostimulants (Aman MG et al., 2008; Hazell P et al., 2007; Leskovec TJ et al., 2008; Posey DJ et al., 2004; Scahill L et al., 2006). In two small trials, clonidine showed an effect in decreasing irritability, stereotypy, inappropriate speech and oppositional behaviour (Fankhauser MP et al., 1992; Jaselskis CA et al., 1992). However, evidence of effectiveness is still limited. A retrospective analysis of guanfacine therapy use in ASD children (N=80) found it to be well tolerated with response rates of 27% for

symptoms of hyperactivity and 21 % for inattention (Posey DJ et al., 2004). Adverse effects for alpha-adrenergic agonists may include sedation, dry mouth, hypotension, and dizziness (CPS monographs, 2015).

(v) Anticonvulsants (antiepileptics)

Anticonvulsant drugs (such as carbamazepine, lithium, and valproate) have been used as mood stabilizer in ASD children and remain attractive because of the common co-occurrence of epilepsy/seizures and autism. Benefits have been demonstrated in several studies (Canitano R et al., 2011; Doyle CA et al., 2012). The use of valproate to treat repetitive behaviors in children with ASD has been supported by results of RCTs (Hollander E et al., 2006; Hellings JA et al., 2005; Hollander E et al., 2005b; Hollander E et al., 2010). Side effects may include weight gain, aggression, dizziness and gastrointestinal side effects (nausea, vomiting) (CPS monographs, 2015).

(vi) Anxiolytics

Anxiety is common in ASD children, and it may lead to aggressive or self-injurious behaviors. Therapies used in children with anxiety only (e.g., SSRIs) are applied to ASD children (White SW et al., 2009); however, the number of studies that evaluate anxiolytic therapies in ASD children is still limited, more RCTs would be required (Doyle CA et al., 2012). Buspirone has been used to treat anxiety in ASD children; in one open-label study, buspirone was well-tolerated and showed improvement in anxiety symptoms (Buitella JK et al., 1998).

Table 1: Summary of common psychotropic medications used in children with ASD

Class	***Subclass***	***Drug Names***	***Benefits for ASD symptoms***	***Side Effects***	***Comments***
Antipsychotics	Atypical (SGA)	Risperidone Aripiprazole Paliperidone	Maladaptive behaviors (irritability, aggression and self-injury symptoms)	weight gain, constipation, fatigue, drowsiness, elevated lipid, prolactin and blood sugar levels	FDA approved risperidone and aripiprazole for treatment of irritability in children with autism. Health Canada has not approved the use of antipsychotics in children with autism.
	Typical (FGA)	Haloperidol	Irritability and aggression	EPS, weight gain, elevated lipid, prolactin and blood sugar levels	Their use has been limited in children because of the significant risk of EPS side effects.
ADHD medications	Stimulants	Methylphenidate Amphetamines salts	Hyperactivity and short attention span	irritability, insomnia, C.V. side effects and decreased appetite	They demonstrated some benefit but their overall efficacy is low and they produce more side effects in ASD children compared to typically developing ADHD children.
	Non-Stimulants	Atomoxetine	Hyperactivity and inattention	G.I. symptoms, mood swings, dizziness, irritability, sleep problems, fatigue and decreased appetite	Atomoxetine showed favorable responses in at least half of treated ASD patients, with mild to moderate side effects.

Continue Table 1

Class	***Subclass***	***Drug Names***	***Benefits for ASD symptoms***	***Side Effects***	***Comments***
Alpha Agonists		Guanfacine Clonidine	inattention, impulsivity and hyperactivity	sedation, dry mouth, hypotension, and dizziness	Used in children who do not respond/or have adverse events from stimulants. Showed benefits but evidence of effectiveness is still limited.
Antidepressants	SSRIs	Citalopram Fluoxetine Fluvoxamine	Repetitive behaviors, comorbid depression and anxiety	anorexia, agitation, tremor, insomnia and G.I. adverse events.	Did not show remarkable results, these agents have lower effectiveness in the treatment of repetitive behaviors in ASD children and are poorly tolerated.
	Others	Clomipramine Amitriptyline	Repetitive behaviors and comorbid depression	constipation, urinary retention, blurred vision, dizziness	Limited number of studies, no significant results.
Anticonvulsants Mood Stabilizers		Lithium Valproic acid	Co-occurrence of epilepsy/ seizures, used as mood stabilizer and to target repetitive behaviors in ASD children	weight gain, aggression, dizziness and G.I. side effects	Valproate to treat repetitive behaviors in children with ASD was supported by results from randomized controlled trials.

ADHD: attention deficit hyperactivity disorder. **ASD**: autism spectrum disorders. **C.V**: cardiovascular. **EPS**: extra-pyramidal side effects. **G.I**: gastrointestinal. **SGA**: second generation antipsychotic. **SSRI:** selective serotonin reuptake inhibitors

(b) Natural products and over-the-counter medications

Natural products and over-the-counter (OTC) medications have been tried in ASD children to treat common comorbid conditions, such as sleeping disturbances, gastrointestinal irregularities G.I (e.g., constipation, diarrhea), appetite abnormalities (e.g., overeating -"not feeling full" or poor appetite - "picky eaters") (Hyman SL et al., 2012; Soden SE et al., 2012). These comorbid problems have been recognized in children with a typical ASD diagnosis but they could be also side effects of their medications (e.g., ADHD and antipsychotics) (Johnson KP et al., 2009; McElhanon BO et al., 2014; Brimacombe M et al., 2008). Some natural products and OTC medications used in ASD include melatonin, omega-3 fatty acids, vitamin B6 and magnesium, other vitamins and supplements (Hyman SL et al., 2012; Soden SE et al., 2012).

(i) Melatonin has shown benefits in treating sleep disturbances in children with ASD have been evaluated in several types of studies such as observational, open-label studies, small-randomized placebo-controlled crossover trials and meta-analyses (Guénolé F et al., 2011; Giannotti F et al., 2006; Garstang J et al., 2006; Rossignol DA et al., 2011; Wasdell MB et al., 2008; Wright B et al., 2011). Overall, melatonin was found to be effective in helping ASD children with sleeping disturbances (e.g., they fall asleep more easily or sleep longer) (Appleton RE et al., 2013; Appleton RE et al., 2012; Andersen IM et al., 2008). Side effects may include daytime sleepiness, enuresis and difficulty waking (Paavonen EJ et al., 2003). No prescription is required for melatonin. There are no dosing guidelines of melatonin for ASD children (Appleton RE et al., 2013; Appleton RE et al., 2012; Andersen IM et al., 2008; Paavonen EJ et al., 2003, Wirojanan J et al., 2009). Melatonin is available in the Canadian market in the 3mg, 5mg, 10mg strengths as tablets, capsules, chewable tablets and/or sublingual tablet forms.

(ii) Omega-3 fatty acids are also OTC products. The hypothesis of nutritional imbalance (caused

by several causes such as G.I irregularities, poor absorption, imbalance diet) in ASD children prompted the use of omega-3 fatty acids and other vitamins and minerals (Sliwinski S et al., 2006). Fatty acid deficiencies or imbalances have been associated with childhood neurodevelopmental disorders (such as ASD) (Richardson AJ, 2004 and 2005). Some studies suggest that plasma omega-3 fatty acid concentrations in children with ASD are low (Vancassel S et al., 2001). It is believed that omega-3 fatty acids improve general health, sleeping patterns, cognitive and motor skills, concentration, eye contact, and sociability, as well as reduce irritability, aggression and hyperactivity (Bell JG et al., 2004). However, results from various studies and recent systematic reviews, including a Cochrane review failed to show clear benefits of the use of omega-3 fatty acids in improving ASD symptoms (Amminger GP et al., 2007; Bent S et al., 2009 and 2011; James S et al., 2011). In fact, no guidelines for omega-3 fatty acid use in children with ASD are available. Common side effects of omega-3 supplementation are nausea and diarrhea.

(iii) Other vitamins and minerals

Other vitamins and minerals tried, used or studied in ASD children (Adams J.B et al., 2011, Levy SE et al., 2008) may include the following

B6/magnesium has been tried in children with ASD based on an old theory that implied benefits in mental health disorders (magnesium was added to reduce B6 side effects, which may happen at high doses, such as nausea, stomach pain and tingling); however, no B6/magnesium benefit was demonstrated in children with ASD (Nye C et al., 2005).

Vitamin C and other anti-oxidant therapies (e.g., methylcobalamin and folinic acid) have been tried in ASD children to address metabolic abnormalities (Al-Gadani Y et al., 2009; James SJ et al., 2004). There is some evidence of benefits in ASD children but not a strong enough evidence for a therapeutic recommendation (Dolske MC et al., 1993; Main PA et al., 2010; Parr J, 2008).

Zinc and digestive enzymes have not been evaluated in controlled trials and there is no strong evidence of their benefits in ASD (Levy SE et al., 2008; Weber W et al., 2007).

(iv) Probiotics have been tried in children with ASD, based on the G.I abnormalities hypothesis, to restore the intestinal microbic balance (Myers SM et al., 2007). No strong evidence is available to support their use (Parr J, 2008; Srinivasjois R et al., 2015).

(c) Other pharmacological therapies

Other pharmacological therapies include the following:

N-Acetylcysteine (NAC): in one study a significant decrease only in the Aberrant Behavioral Checklist (ABC) irritability subscale was observed compared to placebo. NAC was overall well tolerated and the conclusion was that it might be helpful in targeting irritability in children with autism. However, several methodological limitations were observed in this study and the level of reduced irritability was lower compared to that reported for aripiprazole and risperidone (Ardan AY et al., 2012) (please refer to Table 2).

Secretin: a hormone (available as intravenous dosage form) that controls the environment in the duodenum by regulating the secretions of the stomach and pancreas has been tried in ASD children based on the gastrointestinal disturbances theory. A systematic review of studies concluded that this agent does not provide any therapeutic benefit in children with ASD (Krishnaswami S et al., 2011; Williams K et al., 2012).

Conclusion

ASD is a chronic neuropsychiatric condition characterized by impairment in two major domains: (a) deficit in social communication and social interaction and (b) restricted repetitive behavior. ASD needs a comprehensive treatment plan. Therapy choices need to be individualized. The main objective in ASD management is to maximize child's functioning, independence and quality of

life. Although there is no cure for ASD, early educational and intensive behavioral therapies are considered to be the gold standard to treat ASD core symptoms. Pharmacological therapies could be prescribed to target certain symptoms (hyperactivity, irritability, anxiety, sleep disturbances), but they are not treating ASD core symptoms. More studies are required to understand ASD diagnosis and management, to evaluate current ASD therapies and to address the unmet needs of children with ASD and those of their families.

Table 2: Recent studies on ASD pharmacotherapies (2012-2015)*

Title ***Author/Year*** ***Study Design***	***No. of population*** ***Length of study***	***Intervention***	***Measures***	***Results***	***Comments***
Use of psychotropic medication in children and adolescents with autism spectrum disorders. Coury DL et al **2012** Observational study	2853 children aged 2 to 17 years with diagnoses of ASD. Sample, derived from the Autism Treatment Network registry (all children enrolled in the ATN Registry from December 2007 to the end of April 2011).	No intervention. The study examined variations in medication use by psychiatric comorbidities and other medical comorbidities.	Assessments include DSM-IV-TR criteria and administration of the Autism Diagnostic Observation Schedule.	Of the 2853, 763 (27%) were prescribed 1 psychotropic medication; 15% received ≥1 medication, 7.4% received 2 medications, and 4.5% reported receiving ≥3.	The use of psychotropic medications (SSRIs, stimulants, antipsychotic and α-adrenergic agents) increased over the last 2 decades. Use of antipsychotic agents highly related to comorbid psychiatric disorder, race, ethnicity and older age.
A retrospective study of amitriptyline (AMI) in youth with autism spectrum disorders Bhatti I. et al., **2012** Retrospective Chart Review	Data of AMI treatment duration, dose and adverse events were systematically extracted from 50 outpatient charts of ASD children males and females age 4-18 years. 40 were males and 10 females.	No intervention, data extracted included: age at AMI treatment initiation; gender, diagnoses, including ASD subtype; intellectual disability level and seizure history. Number of prior ADHD medication trials was recorded as an indicator of treatment resistance. AMI treatment duration, final AMI dose, comorbid conditions, starting and final blood pressure, pulse, height, weight, and any adverse events (AEs) elicited by clinical questioning were recorded. Based on the observed high rates of aggression and self-injury in these youth, these symptoms were also extracted in order to inform readers and researchers regarding co-occurrence with ADHD-like symptoms in youth with ASD and possible impulsive underpinnings.	All met DSM-IV criteria for an ASD and presented with ADHD symptoms of hyperactivity and impulsivity. Primary outcome was measured using the Clinical Global Impressions-Improvement scale (CGI-I).	Mean age was 9.4 years (4.6–17.9); 30 % had failed atomoxetine and 40 % had failed ≥ 3 ADHD medications. Mean dose was 1.3 ± 0.6 mg/kg/day, mean trough level 114.1 ± 50.5 ng/ml, mean duration 3.4 years. CGI-I was ≤ 2 in 60% of patients at the final visit, and in 82 % of patients with at least 50 % of follow-up.	Cautious use of low dose AMI shows promise for treatment-resistant youth with ASD accompanied by hyperactivity, impulsivity, aggression and self-injury.

Title ***Author/Year*** ***Study Design***	***No. of population*** ***Length of study***	***Intervention***	***Measures***	***Results***	***Comments***
Paliperidone for irritability in adolescents and young adults with autistic disorder. Stigler A et al., **2012** Open Label study	8 weeks open-label study of paliperidone in 25 adolescents and young adults with autism; age 12-21 years.	Paliperidone dose range:3-12 mg/day (the mean final dosage was 7.1 mg/ day).	Primary outcome measures included the CGI-I Scale and the Irritability subscale of the Aberrant Behavior Checklist (ABC-I).	84% (21 out of 25 subject) responded to paliperidone (very much or much improved using CGI-I scale), and ≥ 25% improvement on the ABC-I. S.E: mild to moderate EPS in 4 subjects, weight gain of 2.2 ± 2.6 kg, increased serum prolactin from 5.3-41.4 ng/ml.	Significant improvement in symptoms of irritability (e.g. aggression and self injury) from using paliperidone, but several factors could potentially limit the reliability and validity of these findings. The open-label nature of the study limits conclusions that may be drawn regarding the efficacy and tolerability of paliperidone and may bias effect sizes. The sample size was small, and the study was of relatively short duration.
Aripiprazole for autism spectrum disorders (ASD). Ching H, et al., **2012** Meta analysis of 2 RCTs with similar methodology	Most of the studies included >300 children with ASD, evaluated the use of aripiprazole for duration of eight weeks, only studies in children and youths were found.	RCT using oral administration of aripiprazole vs. placebo. Out of 19 RCT for aripiprazole, only two studies were included. Meta-analysis for primary and secondary outcomes.	Diagnoses of ASD in trial participants were corroborated by the administration of a standardized instrument such as the Autism Diagnostic Interview-Revised. ABC scales	Meta-analysis of study results revealed a mean improvement of 6.17 points on the ABC irritability subscale, 7.93 points on the ABC hyperactivity subscale, and 2.66 points in the stereotypy subscale in children treated with aripiprazole relative to children treated with a placebo. In terms of adverse side effects, children treated with aripiprazole had a greater increase in weight with a mean increase of 1.13 kg relative to placebo, and had a higher risk ratio for sedation (RR 4.28) and tremor (RR 10.26).	Evidence from two RCT suggests that aripiprazole can be effective in treating some behavioral aspects of ASD in children. After treatment with aripiprazole, children showed less irritability, hyperactivity, and stereotypies (repetitive, purposeless actions). However, notable side effects must be considered, such as weight gain, sedation, drooling, and tremor. Longer studies of aripiprazole in individuals with ASD would be useful to gain information on long-term safety and efficacy.

Title ***Author/Year*** ***Study Design***	***No. of population*** ***Length of study***	***Intervention***	***Measures***	***Results***	***Comments***
Risperidone or aripiprazole in children and adolescents with autism and/or intellectual disability: a Bayesian meta-analysis of efficacy and secondary effects. Cohen, D et al., **2012** Bayesian meta-analysis	Bayesian meta-analysis on 41 short-term controlled studies (93 arms) with children and adolescents (N=4015) treated with SGA	To assess the most common short-term adverse effects for each SGA, a meta-analysis of the relevant short-term, controlled studies published between 1980 and 2009. Medline and EMBASE, FDA and EMEA databases for complementary information and synopses of unpublished trials databases were searched for articles describing controlled trials of SGAs in children and adolescents.	Bayesian meta-analysis method was used.	41 short-term studies were found from 1972 to 2010 (3- to 12-week). Controlled studies that assessed the secondary effects of SGAs in children and adolescents. Among these studies, 8 trials investigated SGA for behavioral disturbances in children and adolescents with autism and/or ID. In total, the meta-analysis consisted of 18 arms, including 782 children and adolescents who received aripiprazole (4 arms, N = 213), risperidone (6 arms, N = 226), or placebo (8 arms, N = 343).	Meta analysis concluded that the short-term efficacy of risperidone and aripiprazole are similar for behavioral disturbances associated with autism and/or ID, and that secondary effects are frequent.
Controlled-release (CR) melatonin, singly and combined with cognitive behavioural therapy (CBT), for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial Cortesi F et al., **2012** Randomized control trial (RCT)	Age 4-10 years, for 12 weeks of treatment.	Orally given 3-mg controlled-release (CR) dose of melatonin administered at approximately 21:00 h. Dose changes were not permitted. CBT Melatonin combined with CBT	Sleep behavior was assessed using the Children's Sleep Habits Questionnaire (CSHQ)	Sleep onset latency (SOL) reduction by 50% at the 12 weeks assessment was 39.29% for the melatonin group and 10.34% for the CBT group. For the combination group it was 84.62%	It was noted that melatonin therapy alone was more effective than CBT alone in improving bedtime resistance, sleep onset delay, night-waking and sleep duration. CBT alone seemed to be slightly more effective in reducing sleep anxiety. The effect sizes for all significant comparisons fell into the medium–high range. From covariance analysis, it appeared that neither gender nor age influenced sleep significantly. However, combining CBT and CR-melatonin produced additional improvement.

Title ***Author/Year*** ***Study Design***	***No. of population*** ***Length of study***	***Intervention***	***Measures***	***Results***	***Comments***
A randomized controlled pilot trial of oral N-Acetylcysteine (NAC) in children with autism. Ardan AY et al., **2012** Randomized control trial (RCT)	33 randomized in the study (31 male subjects, 2 female subjects; aged 3.2–10.7 y). Duration 12 weeks.	NAC were initiated at 900 mg daily for 4 weeks, then 900 mg twice daily for 4 weeks and 900 mg three times daily for 4 weeks.	ABC irritability subscale and safety measures were performed at baseline and 4, 8, and 12 weeks. Secondary measures included the ABC stereotypy subscale, Repetitive Behavior Scale-Revised, and Social Responsiveness Scale.	Oral NAC was well tolerated with limited side effects. Compared with placebo, NAC resulted in significant improvements on only ABC irritability subscale.	A significant decrease only in the ABC irritability subscale was observed in the active group compared to placebo. However, this study had a few limitations: small sample size, narrow age range, most subjects were using psychotropic medications and behavioral intervention.
A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. Harfterkamp M *et al* **2012** Randomized control trial	97 patients aged 6 to 17 years with ADHD and ASD were randomly assigned to double-blind treatment.	Participants were given orally 1.2 mg/kg/day atomoxetine or placebo for 8 weeks.	Primary endpoint was the (ADHD-RS) score; secondary endpoints were (CGI-I) and (CTRS-R:S) score.	ADHD-RS scores for atomoxetine vs placebo were 40.7 and 38.6 after 8 weeks. The CTRS-R:S hyperactivity subscore improved significantly but not the other subscores, CGI-I there were not significantly more patients on atomoxetine 20.9% improved much vs. placebo (8.7%, p=0.14)	Findings indicate that atomoxetine is superior to placebo after a treatment period of 8 weeks and is generally well tolerated. There were no serious adverse events.
Placebo-controlled pilot trial of mecamylamine for treatment of autism spectrum disorders. Arnold, L. E **2012** Placebo-controlled pilot trial	Twenty children with ASD age 4–12 years were randomly assigned for 14 weeks	Placebo (n = 8) or mecamylamine (n = 12) were given ascending fixed doses: 0.5 mg/day for 6 weeks, 2.5 mg for 2 weeks, then 5 mg/day for 6 weeks. Because of small sample, data analysis was descriptive.	The outcome measures used included: the Ohio Autism Clinical Impressions Scale, the Repetitive Behavior Scale, ABC, the Social Responsiveness Scale and target symptom assessment.	18 participants (10 mecamylamine, 8 placebo) completed the study. All doses were well tolerated; the only side effect of note was constipation 3 children had clinically nonsignificant electrocardiographic QT prolongation. Of the 4 in active treatment that showed sustained improvement, 3 had a maximum dose of 0.13–0.15 mg/kg/day, while those who regressed had doses ‡ 0.18 mg/kg/day. Better outcome suggested with lower mg/kg and longer medication duration.	Mecamylamine appeared to be safe, but not very effective in autism. The suggestion of better results at lower doses and longer exposure warrants consideration for future trials. The authors suggested to explore varenicline, which is a more specific a4b2 nAChR agonist.

Title ***Author/Year*** ***Study Design***	***No. of population*** ***Length of study***	***Intervention***	***Measures***	***Results***	***Comments***
Effect of aripiprazole 2 to 15 mg/d on health-related quality of life in the treatment of irritability associated with autistic disorder in children: a post hoc analysis of two controlled trials. Varni JW et al., **2012** Analysis of 2 controlled trials	316 pediatric patients (aged 6 –17 years) with autistic disorder. Duration: 2-8 weeks.	Evaluation of the impact of aripiprazole on health-related quality of life (HRQOL) in the treatment of irritability in pediatric patients using fixed dose 5,10 and 15 mg/day.	HRQOL was assessed at baseline and at week 8 using 3 Pediatric Quality of life Inventory (PedsQL) scales	Compared to placebo, aripiprazole was associated with a clinically significant improvement in (PedsQL combined-scales total score) odds ratio [OR] =1.9; 95% CI, 1.0 –3.3; $P < 0.05$), Emotional Functioning scale (OR =2.2; 95% CI, 1.2– 4.0; $P < 0.05$) and Social Functioning scale (OR =2.2; 95% CI, 1.2– 4.1; $P < 0.05$). Patients were significantly less likely to experience deterioration (OR: 0.3, 95% CI: 0.1–0.8; $P < 0.05$).	Aripiprazole was associated with improvment in HRQOL, as assessed using 3 PedsQOL scales, in pediatric patients with irritability associated with autistic disorder. Specifically, clinically meaningful improvements were observed in aspects of emotional and social functioning.
Celecoxib as adjunctive treatment to risperidone in children with autistic disorder: A randomized, double-blind, placebo-controlled trial. Asadabadi M et al., **2013** Randomized control trial (RCT)	40 outpatient children with ASD. Duration: 10 weeks.	Subjects were randomly allocated to celecoxib plus risperidone or placebo plus risperidone. The dose of risperidone and celecoxib were titrated up to 3 and 300 mg/day, respectively,	Patients were assessed at baseline and after 2, 4, 6, and 10 weeks of starting medication using the ABC-community rating scale.	By week 10, patients in the celecoxib group showed significantly greater improvement in the Irritability ($P < 0.001$), Lethargy/Social Withdrawal ($P < 0.001$), and Stereotypic Behavior ($P < 0.00$) but not in Hyperactivity/ Noncompliance (P 0 0.202) and Inappropriate Speech (P 0 0.802) subscales than the placebo group. Complete response was achieved by four (20 %) patients in the placebo group and 11 (55 %) patients in the placebo group (P= 0 0.022).	Combination of risperidone and celecoxib was superior to risperidone alone in treating irritability, social withdrawal, and stereotypy of children with autism. Limitation: short follow-up.

Title ***Author/Year*** ***Study Design***	***No. of population*** ***Length of study***	***Intervention***	***Measures***	***Results***	***Comments***
Memantine as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial. Ghaleiha A et al., **2013** Randomized control trial (RCT)	40 ASD age 4-12 years old, randomly allocated to risperidone plus memantine or placebo plus risperidone for 10 weeks	Risperidone dose (0.5 mg tablet) was titrated up to 2 or 3 mg/d based on child's weight and memantine was titrated to 20 mg/d. Children were assessed at baseline and after 2, 4, 6, 8 and 10 weeks of starting medication protocol.	Primary outcome measure was the irritability subscale of ABC-C.	Difference between the two treatment arms was significant as the group that received memantine+ risperidone had a greater reduction in ABC-C subscale scores for irritability, stereotypic behaviour and hyperactivity compared to the group who received risperidone with placebo.	The study suggested that memantine may be a potential adjunctive treatment strategy for autism and it was generally well tolerated.
A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder Findling R. L et al., **2014** Randomized control trial (RCT)	Multicenter, double-blind, randomized, placebo- controlled, relapse-prevention trial that enrolled 215 ASD children age 6–17 years. Phase 1 single blind stabilization for 13-26 weeks and phase 2 double blind randomization for 16 weeks.	In phase 1, aripiprazole was flexibly dosed (2–15 mg/d) for 13–26 weeks. Patients with a stable response of ≥ 25% decrease in ABC-Irritability subscale score and a rating of "much improved" or "very much improved" on CGI-I scale for 12 consecutive weeks were randomized into phase continue aripiprazole (same dose) or switch to placebo. Treatment was continued until relapse or up to 16 weeks.	Primary outcome measures were ABC-I and CGI-I scales. Primary end point was time from randomization to relapse. Efficacy assessment used the Kaplan-Meier relapse rates.	85 patients were randomized in phase 2. The difference in time to relapse between aripiprazole and placebo was not statistically significant (*P* = .097). Kaplan-Meier relapse rates at week 16 were 35% for aripiprazole and 52% for placebo (hazard ratio [HR] = 0.57; number needed to treat [NNT] = 6). The most common adverse events during phase 1 were weight increase (25.2%), somnolence (14.8%), and vomiting (14.2%); during phase 2 (aripiprazole vs placebo), they were upper respiratory tract infection (10.3% vs 2.3%), constipation (5.1% vs 0%), and movement disorder (5.1% vs 0%).	There was no statistically significant difference between aripiprazole and placebo in time to relapse during maintenance therapy.

Title ***Author/Year*** ***Study Design***	***No. of population*** ***Length of study***	***Intervention***	***Measures***	***Results***	***Comments***
A randomized double-blind placebo-controlled clinical trial of adjuvant buspirone for irritability in autism. Ghanizadeh A et al., **2015** Randomized control trial (RCT)	40 outpatient children and adolescents with autism. Duration: 8 weeks	Two groups were given either oral buspirone twice daily plus risperidone or risperidone plus placebo over the 8 weeks. The dose of risperidone was up to 2 mg/day for children weighing less than 40 kg and up to 3 mg/day for children weighing more than 40 kg. The dose of buspirone was up to 10 mg/day for children weighing less than 40 kg and up to 20 mg/day for patients weighing more than 40 kg. The dosage was increased to this target dose from week 1 to week 2 considering the side effects.	Primary outcome measure was the irritability subscale of Aberrant Behavior Checklist (ABC)	18 patients in the placebo group and 16 patients in the buspirone group completed this trial. The mean dose of buspirone was 6.7 (SD 2.7) mg/day. Irritability subscale score significantly decreased during this trial in both groups (buspirone group: declined from 25.7 [SD 5.7] to 16.3 [SD 8.5]; placebo group: declined from 24.7 [SD 7.6] to 18.2 [SD 7.7]). 13 (81.2%) of 16 patients in the buspirone group and 7 (38.9%) of 18 patients in the placebo group showed ≥ 30% decline in irritability score. The relative risk for treatment was 2.1. There were no serious adverse effects. The most common adverse effects in the buspirone group were increased appetite, drowsiness, and fatigue.	This clinical trial supports that low dose buspirone plus risperidone is more effective than risperidone plus placebo for treating irritability in individual with autism.
N-Acetylcysteine as an adjunctive therapy to risperidone for treatment of irritability in autism: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety. Nikoo M et al., **2015** Randomized control trial (RCT)	A total number of 50 ASD children were equally randomized to the NAC or the placebo group. Age 4-12 years old. Duration: 10 weeks. 40 children completed the study.	One group received risperidone plus NAC, and the other group received risperidone plus placebo. The dose of risperidone was titrated between 1 and 2.0 mg/d, and the dose of NAC was 600 to 900 mg/d.	The main outcome was mean decrease in the ABC-C irritability subscale score from baseline at 5 and 10 weeks. Changes in other subscales were considered as secondary outcome measures.	Repeated-measures analysis showed significant effect for time × treatment interaction in irritability (P = 0.01) and hyperactivity/noncompliance (P = 0.02) subscales. By week 10, the NAC group showed significantly more reduction in irritability (P = 0.02) and hyperactivity/noncompliance (P = 0.01) subscales scores.	NAC can be considered as an adjuvant therapy for ADs with beneficial therapeutic outcomes.

Title *Author/Year* *Study Design*	*No. of population* *Length of study*	*Intervention*	*Measures*	*Results*	*Comments*
The effect of oxytocin nasal spray on social interaction deficits observed in young children with autism. Yatawara C. J et al., **2015** Randomized clinical crossover trial	31 children with ASD age between 3 and 8 completed the study. Total duration: 14 weeks (phase1: 5 weeks, washout period: 4 weeks, and phase 2: 5 weeks).	ASD children enrolled in the study received 12 International Units (IU) of oxytocin and placebo nasal spray, morning and night (24 IU per day). All participants were stabilized on psychotropic medication for 8 weeks before commencement of the trial, and no changes to dose were made for the duration of the trial.	Caregiver-rated Social Responsiveness Scale (SRS-P).	Caregiver-rated Social Responsiveness Scale (SRS-P) showed significant improvement. SRS-P scores were: 0.42 from first administration of oxytocin compared to 0.21 with placebo, and 1.17 from second administration of oxytocin compared to 0.02 with placebo.	Oxytocin was well tolerated, with minor S.E reported: increased urination, thirst and constipation. Limitations for this study include, small sample size, children were stabilized on psychotropic before starting the trail, and reliance on caregivers to measure the main outcomes.

*** Only the most relevant papers have been summarized. Not a systematic review.**

ABC= Aberrant Behavior Checklist. **ABC-C** =Aberrant Behavior Checklist-Community. **ABC-I** =Aberrant Behavior Checklist –Irritability. **ADHD**=Attention Deficit Hyperactivity Disorder. **ADI-R**=Autism Diagnostic Interview Revised. **ADHD-RS**= ADHD Rating Scale. **ADOS**= Autism Diagnostic Observation Schedule. **AE**= adverse events. **AMI**=Amitriptyline. **ATN**=Autism Treatment Network. **ASD**= Autism Spectrum Disorder. **CBT**=cognitive behavioral therapy. **CGI-I**= The Clinical Global Impression of ADHD-Improvement. **CYBOCS-PDD** =Children's Yale-Brown Obsessive Compulsion Scale-Modified for Pervasive Developmental Disorders. **CTRS-R.S**= The Conners Teacher Rating Scale-Revised: Short Form. **DBC-P**= Developmental Behavior Checklist/parents-caregivers. **DSM-IV-TR**= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. **EPS**=extrapyramidal symptoms. **HRQOL**=health-related quality of life. **ID**= intellectual disabilities**. NAC**= *N*-Acetylcysteine. **PedsQL**=Pediatric Quality of life Inventory**. RCTs**= randomized controlled trials. **RBS-R**= Repetitive Behaviors Scale. **S.E**= side effects. **SOL**= sleep onset latency. **SRS-P**= the caregiver-rated Social Responsiveness Scale. **SSRI**=selective serotonin reuptake inhibitors.

Parents/caregivers' perspective in the management of children with ASD

The struggles and needs of children with ASD and the perspectives of those who care for them have not been fully addressed in the literature. Studies have looked at coping strategies, "likes and dislikes", delivering of services, the effect of receiving a diagnosis of ADS and the perception of ASD etiology (please refer to Table 3 for details of the most relevant studies). These studies utilized various qualitative methods, including phenomenology, discourse analysis and grounded theory with the use of questionnaires or interviews (Creswell J, 2009; Hennink M, 2007; Starks H et al., 2007).

No comprehensive survey has been dedicated to the complexity of assessing in a naturalistic setting parents/caregivers' perspective of the effects of therapies on their children and at the same time collect qualitative data on their needs in terms of support at school and in the community.

Table 3: Studies conducted on Parents/Caregivers of children with ASD

Title ***Description***	***Author/*** ***Year published***	***No. of participants*** ***Duration***	***Measures***	***Results***
"A qualitative study of coping in mothers of children with an autism spectrum disorder" Interviews based study/ a phenomenological qualitative approach was used to study ASD mothers' experience	Kuhaneck, H et al., **2010**	11 mothers from suburban, affluent community in the north- eastern United States. (Data collected in 2010)	This study aimed to explore mothers' perceptions of effective coping strategies for their parenting stressors with their ASD children.	Six themes emerged from the data analysis related to maternal coping: (a) "me time," (b) planning, (c) sharing the load, (d) knowledge is power, (e) lifting the restraints of labels, and (f) recognizing the joys. In this study, the mothers of ASD children experienced multiple difficulties, but they reported a series of strategies they used to deal with each of these difficulties. Service providers and the community need to understand the experiences of being a mother of a child with autism in order to best support the mother, the child, and their family.
"What do you like/dislike about the treatments you're currently ysing?" A web-based (questionnaire), qualitative study of parents of children with ASD	Mackintosh,V H et al., **2012**	486 parents Families lived in the United States, Canada, Australia, New Zealand, England, and Ireland. (Conducted between Aug 2002 and Feb 2004)	Families' perspective: "dislikes" versus "likes" about their ASD child treatments.	Six themes emerged and were discussed: effectiveness of treatments, relationships with professionals, access to treatments, costs, medication concerns, and stress. The majority of parents 70.6% expressed at least one "dislike" regarding treatments, and 47.3% made at least one positive comment about their children's therapies.
"Communicating a diagnosis of autism spectrum disorder - a qualitative study of parents' experiences" Interview-based study, using inductive approach	Abbott, M et al., **2013**	9 families attending the Child and Adolescent Mental Health Service (CAMHS) in North East England. (Jun 2008 to Feb 2009)	This study aimed to explore the experiences of the 'feedback session' for ASD parents (experience of disclosure of an ASD diagnosis)	Twenty-one clusters of themes were identified and from these four key themes emerged: 1. Parents' emotional state and reactions to the diagnosis 2. Amount and clarity of information 3. Structure of session 4. Consultation style and relationships with clinician(s). The feedback session had been of huge significance to the parents, and they were generally very positive about the feedback session and the professionals involved.

Title ***Description***	***Author/*** ***Year published***	***No. of participants*** ***Duration***	***Measures***	***Results***
"Parents' and professionals' perceptions of family-centered care for children with autism spectrum disorder across service sectors" Measure of Processes of Care (MPOC) questionnaire and interview based study (MPOC-20 for families and MPOC-SP for service providers)	Hodgetts, S et al., **2013**	152 parents with children with ASD completed the MPOC-20, while 146 professionals working with persons with ASD completed the MPOC-SP; additionally, in-depth interviews were conducted in a sub-sample of 19 parents. (Data collected in 2011 in Alberta, Canada)	The goal of this study was to increase knowledge and understanding of how families with children with ASD experience family-centered care (FCC) in Alberta, Canada. Quantitative data were analyzed using descriptive and inferential statistics, and qualitative data (interviews) were analyzed using grounded theory. MPOC-20 domains measured were 1-enabling and partnership, 2-coordinated and comprehensive care, 3-respectful and supportive care 4-providing general information and 5-providing specific information. MPOC-SP domains were measured, 1-showing interpersonal sensitivity, 2-treating people respectfully, 3-providing general information and 4-communicating specific information Themes were collected from the interview: the fight, the roles and restrictions of care and the therapeutic rapport.	Overall there were no statistically significant differences in FCC scores across service sectors, but statistically significant differences in FCC scores between parents' and professionals' were found. Qualitative data revealed positive experiences and perceptions of receiving FCC from professionals "on the ground" across sectors, but negative experiences and perceptions of FCC at the systems level (i.e., administration, funders).
"Difficulties in everyday life: Young persons with attention-deficit/hyperactivity disorder and autism spectrum disorders perspectives" Internet-based chat logs with ADHD and ASD young adults	Ahlstrom, B. H et al., **2014**	Data were collected from 12 chat logs, produced interactively by the participants and the coaches. The study took place in the south of Sweden. (2008 to 2010)	The aim of this study was to describe how young persons with ADHD and ASD function and how they manage their everyday life.	The findings revealed two themes: (1) ''fighting against an everyday life lived in vulnerability'' with the following subthemes: ''difficult things,'' ''stress and rest,'' and ''when feelings and thoughts are a concern''; and (2)''struggling to find a life of one's own'' with the following subthemes: ''decide and carry out,'' ''making life choices,'' and ''taking care of oneself.'' The findings show that those who participated in the study had their everyday life affected by serious, problematic situations. Strengths were recognized in the wish to find adequate solutions and a role in society.

Title ***Description***	***Author/*** ***Year published***	***No. of participants*** ***Duration***	***Measures***	***Results***
"Emergence of autism spectrum disorder in children from Simplex families: relations to parental perceptions of etiology" Using an ASD- adapted version of Revised Illness Perception Questionnaire (IPQ-R) to assess parents' beliefs about causes of ASD	Goin-Kochel, R. P et al., **2015**	148 families of ASD children were included in the Simons Simplex Collection (SSC) (specifically at the Baylor College of Medicine, BCM, site). SSC is a North American repository.	One of the goals of this study was to describe parental attributions to their children's ASD diagnosis and to examine parents' beliefs about the causes of their children's ASD. This study hypothesized that parents of children who displayed regression without prior delays pattern would be more likely to attribute their children's ASD to external factors.	The most commonly reported factor was "genetics/heredity'' 42.6 %, followed by ''external factors'' 22.1 %, which included responses to vaccines, toxins, diet, pollutions, allergies, and viruses. In the second category, ''external factors'' the majority (76.5 %) specifically cited toxins found in vaccines as the most likely cause of their child's ASD.

Significance

This pilot study was designed to investigate parents/caregivers' perspective and preferences on various aspects of their children treatment and well-being and to collect in depth information on therapies and strategies not usually reported in the medical records or captured in clinical trials. By using questionnaire-based interviews (combined with a chart-review design), this study explored the real world effects of ASD treatments and the gaps in the understanding of the changing needs of children with ASD and their families.

Objectives

The objectives of this pilot study included

- the assessment of parents/caregivers' perspective on the effect of tried and current ASD therapies on their children's quality of life,
- the assessment of ADHD-associated symptoms in ASD population,
- the description of therapies used in clinical practice in children with ASD and comorbid ADHD symptoms,
- the identification of unmet needs in this population in terms of services and support.

Methods

Research Design

This was an observational pilot study based on information collected through questionnaires guided interviews with parents/caregivers and medical chart reviews to collect data about therapies used in children with ASD.

Ethical Consideration and Approvals

Ethics approval was obtained from the Health Research Ethics Board (HREB) at the University of Manitoba (H2014:392) (Please refer to Appendix IV).

Approvals were also obtained from the Quality, Research and Evaluation Committee of the Manitoba Adolescent Treatment Centre (MATC) in Winnipeg and the Neurodevelopmental Services (NDS) department.

Why MATC clinic?

MATC falls under the jurisdiction of the Winnipeg Regional Health Authority Mental Health Program - Child & Adolescent Mental Services, and is governed by a Board of Directors appointed by the Minister of Health. MATC provides a range of mental health services to children and adolescents, who experience psychiatric and/or emotional disorders, and their families. The Neurodevelopmental Services (NDS) department of MATC, in particular, provides psychiatric support for children 5–18 years of age with complex neurodevelopmental issues such as ASD. These services include assessment, education, consultation and support to families and caregivers who are involved with school-aged children with ASD (more detailed information about the ASD population served, referral process, services and contacts is available from MATC website, (http://www.matc.ca).

Recruitment

Health care professionals at NDS approached parents/caregivers of children and youth (5-17 years of age) diagnosed with ASD (newly diagnosed or returning to the clinic for follow-up) to determine if they were interested in participating in the study. Permission to contact consent forms were provided and signed by the parents/caregivers who accepted to be know more about the study. Interested parents/caregivers were contacted by e-mail or by phone. We explained the purpose of the study and described the study protocol, which included two interviews (one at the time of enrolment and a second one to take place four months after the initial interview). The interview format was designed to facilitate response to the questionnaires. All participants signed informed consents (please refer to Appendix V). The informed consent included permission to access children's charts at the clinic. Both consent forms (permission to contact consent form, research participants information and consent form) have been stored in a locked cabinet in a locked room at the University of Manitoba.

Interviews were scheduled at participant's convenience and conducted either by phone or in person at the participant's preferred location. Data collected was de-identified and stored in password-protected computer and files. No identifying information was recorded (e.g., no name, date of birth or address). Each child was given a code. A master file that connect parent/ caregiver name with the child code has been kept in a password-protected computer**.** Participants were offered a $50 honorarium as compensation for their time. The project was conducted with minimal disruption to the operations at MATC.

Data Collection

The first interview (questionnaire number one) (please refer to Appendix VI) was designed to collect: (1) demographic information (e.g., age, sex, area of residence, and primary caregiver), (2) information regarding child's symptoms (with special attention to ADHD symptoms, as per Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA) guidelines (CADDRA, 2011), (3) parameters of quality of life "general well being " (e.g., eating, sleeping patterns and school attendance), (4) therapies previously tried and currently used, which included (i) pharmacological therapies (prescribed and non prescribed medications, e.g., stimulants, antipsychotics, over the counter, supplement and herbal remedies) and (ii) non-pharmacological (e.g., behavioral, occupational, speech therapy), (5) miscellaneous questions about physicians visits and support (school, family and financial), (6) a section for comments was also included.

In addition, each child's chart available at MATC was accessed to complement the information obtained from participants. In the follow-up interview (second questionnaire, please refer to Appendix VII), specific questions regarding improvement of symptoms and quality of life parameters were asked and any change in therapy (stop or add new agent, reason, and comments) was recorded. Data were collected between February 2015 and November 2015.

Specific questions were designed to stimulate comments and suggestions. This helped in categorizing common themes.

Data Analysis

Mixed quantitative/qualitative methods were employed to analyze data after conducting all the interviews and collecting all data. Data obtained from the interviews were categorized into two parts: (A) quantitative data obtained from close-ended questions (e.g., sex, age, number of antipsychotic medications, number of physician visits and others) and analyzed by descriptive

statistics, (B) qualitative data obtained from open-ended questions (parents/ caregivers' comments) were analyzed by thematic analysis and coded into theme categories (symptoms, therapies, service/support, school).

Qualitative Data Analysis

The advantage of having qualitative data complement quantitative results is the opportunity to interpret complex issues (Young TK, 2005). The steps of qualitative data analysis followed in this study were: (a) organizing the entire parents/caregivers' comments (open–ended questions), (b) reading the comments accurately, (c) identifying common themes, (d) collecting common sentences from all transcripts, (e) segmenting them into manageable parts under each topic theme (category), and (f) interpreting and describing the meaning of the extracted themes (discussion/conclusion). Several ways can be adopted to improve analytical reading, interpret qualitative data collected and develop major topic themes (Hennink MM 2007; Rubin H and Rubin I., 1995 and 2005). In this study, we combined (i) an in-depth knowledge of the ASD condition (e.g., diagnosis, prevalence, therapies), (ii) an understanding of previous studies of caregivers' perspective on other topics (please refer to Table 3), (iii) a complete assessment through questionnaire/interviews.

What is a theme?

Theme is an idea, concept, issue or commonly occurring observations extracted from textual data (interviews, opinion, survey) (Hennink MM, 2007; Rubin H and Rubin I., 1995 and 2005). There are several approaches in identifying themes based on the qualitative study strategy (Hennink MM, 2007).

Thematic Analysis

It is one of the most common qualitative methods (Guest G, 2012); it identifies (situation/issue), examines (interview/questionnaire), and records (themes). Data provided by the participants are analyzed and interpreted into meaningful outcomes (Guest G, 2012; Braun V et al., 2006). Thematic analysis is performed through the process of coding in six phases to create established, meaningful themes. These phases are: familiarization with data, generating initial codes, searching for themes among codes, reviewing themes, defining and naming themes, and producing the final report (Braun V et al., 2006; Fereday J et al., 2006; Daly K et al., 1997).

Results

Sample

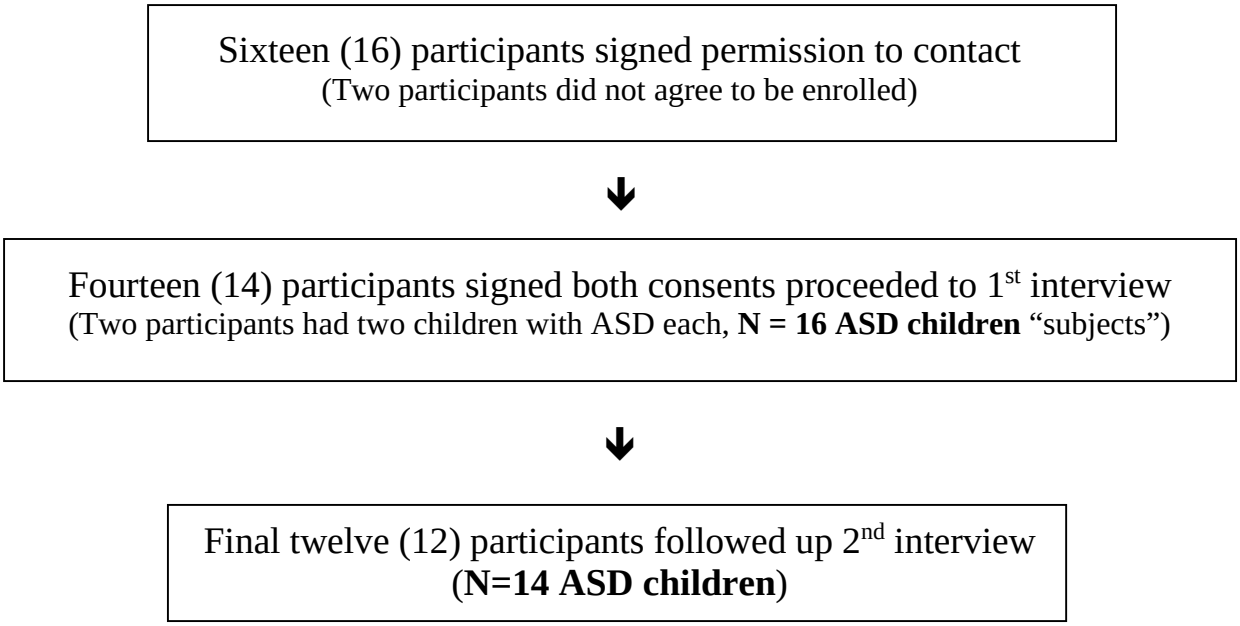
Sixteen (16) parents/caregivers (participants) signed the permission to contact consent form. All (16) individuals were contacted; however, two individuals did not agree to be enrolled; as a result, after the study was explained to them, a total of fourteen (14) participants signed the research participant's information consent form and proceeded to the first interview. Two of the fourteen (14) participants had two children with ASD each, therefore the total number of subjects (children with ASD) for whom we collected information was sixteen (16). However, two of the fourteen (14) participants dropped out of the study after filling out the first questionnaire and did not fill the second questionnaire. Twelve (12) participants completed the study, which resulted in 14 children with a complete follow-up (please refer to Figure 1).

Subjects' characteristics

In our sample 87.5% were males and 12.5% females (Table 4) and their ages at enrolment ranged form 8 to 15 years. All children in our sample were attending school (grade ranged from grade 2 to grade 9). Regarding the school support question, we further categorized the (Yes) answers to specify if they were receiving education assistant (EA) full-time or part-time. ASD16 said (Yes) for general school support but no EA was specified as such support was not available in the rural area where they lived. Some changes in coverage for EA were observed and documented in the second questionnaire, which included changes in coverage for education assistance: (a) satisfied parents' response for ASD03 and ASD04 because of full-time EA coverage was obtained (b) unsatisfied parents' response for ASD05, ASD08 and ASD11 because no funding/ approval for EA. There was no follow up with ASD12 or ASD13 after four months (parents did not complete the second questionnaire). Mothers of subjects ASD11 and ASD08 were hoping to see school staff

trained and certified with ABA in the future. While all children had a diagnosis of ASD, the range of co-morbid conditions varied among subjects from 0 to 7 (please refer to Table 5 for details).

Figure 1



- Participant= parent/caregiver of ASD child
- Subject= ASD child
- Data were collected between Feb 2015-Nov 2015

Table 4: Demographic Questions
Results from first questionnaire. Number of ASD Children =16.

Variable	Results
Sex, N (%)	
Male	14 (87.5)
Female	2 (12.5)
Area of Residence, N (%)	
Urban	14 (87.5)
Rural	2 (12.5)
Primary caregiver, N (%)	
Both Parents	10 (62.5)
Mother only	5 (31.3)
Foster family	1 (6.3)
Current Age	
(Mean ± SD, Range)	10.8±1.9, (8-15)
Age at ASD Diagnosis	
(Mean ± SD, Range)	4.4±1.9 (1-8)
Comorbid Conditions	
Yes N (%), Range	15 (93.8), R 1 -6
No, N (%)	1 (6.3)
Comorbid conditions include ADHD? N (%)	
Yes	11 (68.8)
No	5 (31.3)
School attendance N (%)	
Yes	16 (100)
No	0
School Grade	
Range	2-9
School support N (%)	
Yes	14 (87.5)
No	2 (12.5)
School support (Yes answers only N=14), N (%)	
EA.FT	8 (57.1)
EA.PT	5 (35.7)
None	1 (7.1)
Number of siblings	
Range	1-4
Siblings with comorbid ASD or ADHD, N (%)	
ADHD	6 (37.5)
ASD	4 (25)

EA.FT= education assistant full time. EA.PT=education assistant part time
Age= current age at the time of first interview. Grade= current grade at the time of first interview

Table 5: List of comorbid conditions

Code. No	Comorbid Conditions List	Code. No	Comorbid Conditions List
ASD01*	Tourette's disorder, anxiety disorder, expressive language disorder	**ASD09**	Anxiety disorder, language disorder, primary enuresis and primary encopresis
ASD02	ADHD and fatty liver and pancreas	**ASD10**	ADHD
ASD03	None	**ASD11**	ADHD, anxiety disorder and asthma
ASD04	ADHD, nocturnal enuresis, repetitive expressive language disorder and social skills deficit	**ASD12**	ADHD
ASD05	ADHD	**ASD13**	ADHD
ASD06	Language disorder, anxiety disorder, primary enuresis and primary encopresis	**ASD14****	ADHD, receptive-expressive language delay, sensory sensitivity, stereotypical behaviors, insomnia, social anxiety disorder.
ASD07*	ADHD and asthma	**ASD15****	Anxiety disorder, primary enuresis, primary encopresis, receptive-expressive language delay, sensory sensitivity and insomnia.
ASD08	ADHD and anxiety disorder	**ASD16**	ADHD

*Siblings
**Siblings

ADHD symptoms

By cheking medical charts, it was found that 11 children out of 16 had a diagnosis of ADHD according to the DSM-IV diagnostic criteria in addition to have ASD as a primary diagosis. The remaining 5 chidren were not diagnosed with ADHD, but their parents/caregivers' answers to the question regarding ADHD-associated symptoms showed possible comorbidity. Results from the first questionnaire (Table 6) showed that 62.5% of our participants said (stongly agree) for question number 3 ("My child loses his/her things (toys, books..etc) and is forgetful in daily activities)". Also, 62.5% of our participants said (agree) to question number 7, ("My child avoids direct eye contact or seems to not listen when spoken to directly"). Four month later, the second questionnaire (14 subjects followed up) captured if the symptoms were (same, improved, worsened); it was found that 92.9% said (same) for question number 3 and only 7.1% said (improved) for the same question, while 64.3% said (same) for question number 7, 28.6% said (improved) and 7.1% said (worsened) (please refer to Tables 6 and 7 for further details).

Table 6: ADHD associated symptoms

Results from first questionnaire. Number of ASD Children =16. Results N (%)

Questions	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Don't Know
1-My child faces difficulties in giving close attention to details	7 (43.8)	7 (43.8)	1 (6.3)	1 (6.3)	-	-
2- My child faces difficulties in sustaining attention in play activities	5 (31.3)	9 (56.3)	1 (6.3)	1 (6.3)		-
3-My child looses his/her things (toys, books…etc.) and is forgetful in daily activities	**10 (62.5)**	5 (31.3)	-	-	1 (6.3)	-
4-My child fidgets with hands or feet	9 (56.3)	4 (25)	1 (6.3)	2 (12.5)	-	-
5-My child runs or jumps excessively / has difficulty to await his/her turn	5 (31.3)	6 (37.5)	3 (18.8)	1 (6.3)	1 (6.3)	-
6-My child has difficulties in playing quietly	5 (31.3)	3 (18.8)	4 (25)	2 (12.5)	2 (12.5)	-
7-My child avoids direct eye contact or seems to not listen when spoken directly	3 (18.8)	**10 (62.5)**	1 (6.3)	2 (12.5)	-	-
8-My child gets annoyed by others' requests; he/she argues and dislikes to obey orders	5 (31.3)	5 (31.3)	3 (18.8)	1 (6.3)	1 (6.3)	1 (6.3)
9-- My child deliberately does things that annoy other people	2 (12.5)	5 (31.3)	2 (12.5)	4 (25)	1 (6.3)	2 (12.5)
10- My child is often angry or vindictive	3 (18.8)	4 (25)	5 (31.3)	3 (18.8)	1 (6.3)	-

Table 7: ADHD associated symptoms Follow-up

Results from second questionnaire. Number of ASD children at follow-up=14. Results N (%)

Questions	Same	Improved	Worsened
1-My child faces difficulties in giving close attention to details	11 (78.6)	3 (21.4)	-
2-My child faces difficulties in sustaining attention in play activities	10 (71.4)	4 (28.8)	-
3-My child looses his/her things (toys, books…etc.) and is forgetful in daily activities	**13 (92.9)**	1 (7.1)	-
4-My child fidgets with hands or feet	12 (85.7)	2 (14.3)	-
5-My child runs or jumps excessively / has difficulty to await his/her turn	9 (64.3)	5 (35.7)	-
6-My child has difficulties in playing quietly	10 (71.4)	4 (28.8)	
7-My child avoids direct eye contact or seems to not listen when spoken directly	**9 (64.3)**	4 (28.6)	1 (7.1)
8-My child gets annoyed by others' requests; he/she argues and dislikes to obey orders	8 (57.1)	3 (21.4)	3 (21.4)
9-My child deliberately does things that annoy other people	11 (78.6)	2 (14.3)	1 (7.1)
10-My child is often angry or vindictive	8 (57.1)	3 (21.4)	3 (21.4)

General Well-Being

Children in our study were struggling with sleeping (Yes 50%), eating (Yes 56.3%) and gastrointestinal (G.I) irregularities (Yes 37.5%). Regarding eating difficulties, 56.3% responded (Yes) and 18.8% (Sometimes). As per parents' comments we could identify either overeating (e.g., " not feeling full"), or being a very picky eater ("self limiting diet", food sensitivity, "doesn't like to try new food", "not feeling hungry for days"). G.I problems are common in children affected by ASD; in our sample G.I irregularities were in fact identified (Yes 37.5% and 25% Sometimes). Out of the 10 (62.5%) parents/caregivers who responded (Yes/ Sometimes), 7 reported diarrhea, 2 reported constipation, and 1 did not specify.

In our sample children attended school regularly (93.8%) and were involved in extracurricular activities (68.8%).

Four months later, the same general well-being questions were asked in the second questionnaire (14 participants) in order to identify any change. Sleeping and eating symptoms improved in 42.9% of the cases. G.I issues had improved in 2 cases (ASD02 and ASD11), i.e., (14.3%) because of changes in diet and/or therapy. Please refer to Tables 8 and 9 for further details.

Table 8: General Well-Being

Results from first questionnaire. Number of ASD Children =16. Results N (%)

Questions	Yes	No	Sometimes
1-My child has difficulties in Sleeping	8 (50)	3 (18.8)	5 (31.3)
2-My child has difficulties with Eating	9 (56.3)	4 (25)	3 (18.8)
3-My child attends School Regularly	15 (93.8)	-	1 (6.3)
4-My child is involved in Extracurricular Activities	11 (68.8)	1 (6.3)	4 (25)
5-My child often has Gastro-Intestinal issues (diarrhea/constipation)	6 (37.5)	6 (37.5)	4 (25)

Table 9: General Well- Being Follow up

Number of ASD Children followed up =14. Results N (%)

Questions	Same	Improved Yes	Improved No
1-My child has difficulties in Sleeping	4 (28.6)	6 (42.9)	4 (28.6)
2-My child has difficulties with Eating	4 (28.6)	6 (42.9)	4 (28.6)
3-My child attends School Regularly	6 (42.9)	2 (14.3)	6 (42.9)
4-My child is involved in Extracurricular Activities	6 (42.9)	4 (28.6)	4 (28.6)
5-My child often has Gastro-Intestinal issues (diarrhea/constipation)	6 (42.9)	2 (14.3)	6 (42.9)

Pharmacological Therapies

Pharmacological therapies were divided into:

(A) Prescribed medications (Rx): (1) antipsychotics (2) ADHD medications (3) antidepressants/SSRI (4) other psychotropic medications.

(B) Non-prescription products: OTC, supplements and natural products (please refer to Table 10 and 11 for details).

Of note is that medical charts were also checked to complete the information provided by parents/caregivers regarding each child's tried/current medications.

(A) Prescribed medications (Rx) (results from the first questionnaire, Table 10)

(1) Risperidone was the most commonly used antipsychotic; 9 out of 16 children had tried risperidone, 6 were still on it, and, as per participants' perspective, it was used for sleeping, irritability and aggression.

(2) Of the ADHD medications, methylphenidate controlled-release (CR) (Biphentin®) was tried in 8 of the 16 children but none of them was currently on it. The reasons why this medication was discontinued, as reported by the participants, included unpleasant taste and/or texture, and negative side effects on sleeping and appetite. The second most common stimulant was short-acting methylphenidate (Ritalin®), which was tried by 7 out of 16 children and currently used by only 2 children.

(3) Of the antidepressants medications, citalopram was tried by 5 out of 16, but currently only 3 were still on it. The parents' perspective was that it was useful for anxiety, agitation and anger.

(4) Clonidine (centrally acting alpha 2 agonist) was tried in 7 out of 17 and 5 were still on it. The parents' perspective was that it was helpful for sleeping, agitation and to settle down at bedtime.

Four month later, (Table 11):

(1) Two cases (ASD01 and ASD09) were reported to have received dose increases for the current antipsychotic medication: ASD01 had risperidone dose increased from 1 mg once daily and 1 mg PRN (as needed) to 2 mg once daily. Risperidone dose was also increased for ASD09 from 2.5 mg or 3 mg daily (maximum) if needed to 2 mg twice daily (i.e., total 4 mg a day). Two cases (ASD08 and ASD09) add/stop new antipsychotic agents. Aripiprazole was added as a trial to ASD08 regimen to stabilize his mood and reduce his aggression, but, as per the parents, the opposite happened: "*….[ASD08] was lethargic and aggressive towards his teachers, the medication was stopped because of side effects*". Quetiapine was added to ASD09 regimen during the summer time to help him sleep after the mother who was away had returned and noticed that her child had become more aggressive with more sleeping difficulties. Overall, 57.1% answered the (Same) to the improvement question as a result of antipsychotic use in the second interview.

(2) Two cases (ASD08 and ASD16) reported dose changes in ADHD medications: methylphenidate ER (Concerta®) dose for ASD08 was decreased by the doctor from 45 mg to 36 mg once daily during the summer time, ("*may change it again when back to school*"). For ASD16, methylphenidate SR and IR (Ritalin®) doses were increased from 40 mg (20 mg SR morning and 20 mg IR evening) to 60 mg (2 tablet of 20 mg SR morning and one tablet of 20 mg IR evening). Two cases were reported to have added/stopped ADHD agents (ASD04 and ASD05). The psychiatrist stopped methylphenidate and added lisdexamfetamine (Vyvanse®) to ASD04 regimen, which, according to the parents, helped "*to have less hyperactivity and being more focused*". While the psychiatrist stopped lisdexamfetamine (Vyvanse®) for ASD05 "*because [it] was not so effective"*, according to the mother, and added atomoxetine (Strattera®) (non stimulant)

as a trial; 71.4% reported (Same) for the improvement question from ADHD medications at the time of second questionnaire.

(3) In four cases, doses of antidepressants were increased:

ASD01 sertraline dose increased from 100mg to 150mg

ASD03 paroxetine dose increased from 10mg to 15mg

ASD04 citalopram dose increased from 10mg to 20mg

ASD14 citalopram dose increased from 10mg to 20mg

No SSRI addition or discontinuation was reported in our sample and 64.3 % reported (Same) for improvement question.

(4) Other psychotropic medications*:* a dose change was reported in one case: clonidine dose for ASD14 was increased from 0.025 to 0.05 mg at bedtime to help with sleeping. In one case a new therapy was reported: guanfacin (Intuniv®), which was added to the regimen for ASD03 to reduce impulsivity, aggression and to help with sleeping.

(B) OTC, supplements and natural products (please refer to Table 10 and 11)

The most commonly used OTC product was melatonin. The reason for use was to help with sleeping difficulties; it was tried by 9 children out of 16 and 7 were still on it at the time of the first interview. The majority of our participants found it helpful.

In the second questionnaire, dose changes were reported in two cases: melatonin dose was Increased for ASD05 (2.5mg to 3.5mg) and ASD16 (1.5mg to 3mg).

Several agents were added or stopped (data captured after second questionnaire, Table 11):

Milk thistle for liver function was stopped by ASD02. As per ASD02 mother "*now he has been followed by a naturopath. ASD02 now follows a yeast free diet. It was discovered by the naturopath that ASD02 has sensitivity to eggs and dairy. Since ASD02 has been avoiding these products he*

seems less irritable, and seems slightly less likely to argue". ASD02 was using olive leaf (a natural product with antioxidant activity that could help in fighting internal infections), 2 capsules twice daily, and HMF Forte® (Probiotics), used for the same G.I issue,1 capsule twice daily; as per the mother's perspective both products were used for yeast overgrowth. On the other hand, ASD04 was currently using Theanine 100mg (OTC natural supplement and antioxidant), as per parents' perspective, it was for sleeping in addition to melatonin 1.5 mg. ASD08's parents stopped all OTCs, supplements and natural products for their son during the summer time, according to what they reported in the second interview. ASD11's parents realized that their son was experiencing G.I irregularities (diarrhea) in correlation with eating dairy; lactase enzyme product (Lacteeze®), 1 tablet before eating dairy products was added to ASD11. More details are discussed with the qualitative results (please refer the Parents/Caregivers Comments: Qualitative Results section and Appendix IX).

Table 10: Pharmacological Therapies

Prescribed (Rx), Over the Counter (OTC), supplements and Natural Products (NP)/Diet
Results from first questionnaire. Number of ASD Children =16

A- Rx Medications	Dose Range	No. Tried	No. Current
1-Antipsychotics			
Aripiprazole (Abilify®)	1-4 and 15-20 mg	8	3
Risperidone (Risperidal®)	0.5 -3 mg	9	6
Quetiapine (Seroquel®)	25-100 mg	4	3
Olanzapine (Zyprexa®)	5- 15 mg	1	0
2- ADHD medications			
***Stimulants**			
Amphetamine salt (Adderall®)	30 mg	1	0
Dextroamphetamine (Dexedrine®)	10 mg	2	1
lisdexamfetamine (Vyvanse®)	30-40 mg	3	2
Methylphenidate (Ritalin®)	5-40 mg	7	2
Methylphenidate CR (Biphentin®)	10-20 mg	8	0
Methylphenidate ER (Concerta®)	18-45 mg	6	3
***Non stimulants**			
Atomoxetine (Strattera®)	18-60 mg	2	1
3- Antidepressants/SSRI			
Citalopram (Celexa®)	5- 20 mg	5	3
Fluoxetine (Prozac®)	10-20 mg	4	2
Fluvoxamine (Luvox)	25 mg	1	0
Paroxetine (Paxil®)	10-30 mg	4	2
Sertraline (Zoloft®)	50-10 mg	1	1
4- Other Psychotropic			
Clonidine (Catapres®)	0.025-0.1 mg	7	5
Guanfacine (Intuniv®)	-	-	-
Valproic Acid (Depakene®)	?	1	0
5- Other Rx medications			
Salbutamol HFA (Ventolin®)	-	4	4
Fluticasone HFA (Flovent®)	-	1	1
Montelucast (Singulair®)	-	3	3
Ciclosonide inhaler (Alvesco®)	-	2	2
Epipen®	-	1	1

B- OTC/ Supplements	**Reason of using**		
Melatonin	Sleeping	9	7
Multivitamins	General well-being	4	4
Omega 3	Brain regulation	3	3
Probiotics	GI- irregularities	2	1
Vitamin C	General well-being	1	1
Vitamin D	General well-being	1	1
Vitamin B-complex/ Mg	General well-being	1	0
Dimenhydrinate (Gravol®)	Sleeping	1	0
Loratidine (Claritin®)	Allergy	1	1
C-Natural products/Diet modifications	**Reason of using**		
Gluten free diet	GI- irregularities	1	0
Hemp seed oil	Brain regulation/ clarity	1	1
Honey/ cinnamon mix	General well-being	1	1
Immune echinacea	Improve immunity/get less sick	1	1
Fish oil	Brain regulation	1	1
Milk Thistle	Assist liver function	1	1

Table 11: Pharmacological Therapies Follow up

Results from second questionnaire. Number of ASD Children followed up =14.

A- Rx Medications	**Dose Change** *Yes Increase Decrease No	**Add and/or Stop** *Add: name of new agent *Stop: name of stop agent and reason	**Improvement N (%)** Yes No Same
1-Antipsychotics	2 dose increase* 7	2 Aripiprazole*, Quetiapine * 1 Aripiprazole (S.E)*	5 (35.7) 1 (7.1) 8 (57.1)
2- ADHD medications	2 dose inc * /dose dec * 3	2 lisdexamfetamine*, Atomoxetine * 2 lisdexamfetamine *, Methylphenidate (S.E)*	3 (21.4) 1 (7.1) 10 (71.4)
3- Antidepressants/SSRI	4 dose increase * 4	- -	4 (28.6) 1 (7.1) 9 (64.3)
4- Other Psychotropic	1 dose increase * 3	1 Guanfacin * -	2 (14.3) - 12 (85.7)
5- Other Rx medications	- -	- -	1 (7.1) - 13 (92.9)
B- OTC/ Supplements	2 dose increase * 8	3 probiotic, theanine * 4 multivitamins, omega 3, Vit C & D *	6 (42.9) - 8 (57.1)
C-Natural products/Diet modifications	- -	4 Lacteeze®, olive leaf, Naturopath"/natural medicine"* 1 milk thistle (try new N.P Tx)	2 (14.3) - 12 (85.7)

Controlled Release (CR), Extended Release (ER), Prescribed (Rx), Over The Counter (OTC), supplements and Natural Products (NP)/Diet restriction. G.I= Gastro intestinal. SSRI= selective serotonin reuptake inhibitors. S.E= side effects. Tx= therapy. * See Pharmacological Therapies Results section.

Non-Pharmacological Therapies

Results from the first questionnaire (Table 12) showed that occupational therapy (OT) was the most "tried" and/or "currently used" therapy (10 children out of 16), followed by speech therapy (9 out of 16) and ABA (7 out of 16).

As it can be observed in Table 12, other non-pharmacological therapies also tried/used in our sample include support groups, chiropractic services, massage services, music, physiotherapy, acupuncture, and others. We collected information about coverage (Yes, No, Partial) and feedback from the participants as to whether they found these therapies helpful or not. Regarding the coverage question, it was found that some therapies were totally or partially covered through government, others were completely or partially covered through parents/caregivers' private insurance (i.e., through work).

Four month later, we captured the following changes regarding the non-pharmacological therapies: ASD03 was back to OT through school, the services were now covered. Parents stopped OT private sessions. Mother's comments regarding OT services provided through the school was "neutral, not so helpful". It seems that when the child was younger, OT private sessions were helpful. ASD09 was back to ABA therapy, as per the mother "*it is, unfortunately, not covered any more, fewer number of sessions and very hard for me to follow up because of divorce and full-time work"*. In addition to that, ASD09 was back to OT and speech therapy through school.

Unfortunately, ASD01, ASD07, ASD06, ASD4, ASD11 did not receive any non- pharmacological therapies (i.e., no ABA nor OT).

ASD11 and ASD08 mothers are hoping to see in the future school staff trained in ABA.

Improvement from non-pharmacological therapy reported in 8 out of 14 (57%) (Please refer to Table 13)

Table 12: Non-Pharmacological Therapies

Results from first questionnaire. Number of ASD Children =16.

Therapy Type / Name	**Number** Tried Current	**Covered** Yes No **Partial	**Comments** Helpful Not Helpful
ABA	7 1	7 -	6 1
OT	10 1	9 1	7 3
Speech Tx	9 3	7 2	7 2
Support Group (Through MATC)	5 -	5 -	4 1
Support Group (Through school, internet, others)	3 -	3 -	1 2
Chiropractic Tx	1 -	- 1	- 1
Massage Tx	2 1 *	1* - 1**	2 -
Music Tx	2 -	- 2	2 -
Physiotherapy	2 -	1 - 1**	2 -
Others (Acupuncture, Biofeedback, homeopathy, and Equestrianism= horseback riding)	1 -	- 1	- 1

Applied Behavior Analysis (ABA), Occupational Therapy (OT), Therapy= Tx,

* See Non-Pharmacological Therapies Results section ** Partial coverage: only part of this service or therapy was covered through private insurance

Table 13: Non-Pharmacological Therapies Follow up

Results from second questionnaire. Number of ASD children with follow up = 14.

Non Pharmacologic Therapies	Results
Change in coverage	
Yes	2*
No	12
Improvement	
Yes	8
No	3
Same	3

* Please see Non-Pharmacological Therapies Results section

Miscellaneous questions

Data regarding the number of physician (GP) and specialist visits, and school, family and financial support were collected in the first questionnaire (N =16) Table 14. Overall, school support was received by approximately 70% of the responders; regarding financial support, 81.3% had medication coverage (please refer to Tables 14 and 15 for details).

Table 14: Miscellaneous _Support Questions

Results from first questionnaire. Number of ASD children =16

Question		Results
1-Number of physician's (GP) visits per year	Range	0-24
2- Number of specialist's visits per year	Range	0-24
3-School Support, N (%) *		
a-My child's school meets his/her needs	Yes	11 (68.8)
	No	3 (18.8)
	Sometimes	2 (12.5)
b-My child's school helps the development of his/her skills	Yes	11 (68.8)
	No	2 (12.5)
	Sometimes	3 (18.8)
c- My child's school staff creates a supportive environment for my child	Yes	12 (75)
	No	1 (6.3)
	Sometimes	3 (18.8)
4-Family Support *		
a-Our Family/Friends understand my child's needs	Yes	6 (37.5)
	No	7 (43.8)
	Sometimes	3 (18.8)
b-Our Family/Friends offer the help and support	Yes	8 (50)
	No	4 (25)
	Sometimes	4 (25)

5-Financial Support *	
a-Our child's medications are covered by prescription insurance	
Yes	13 (81.3)
No	1 (6.3)
**Partial	2 (12.5)
b- All services for our child are covered	
Yes	7 (43.8)
No	6 (37.5)
Partial	3 (18.8)

** Partial coverage: only part of medications is covered through private insurance.
*See Qualitative Results and Appendix IX.
*See Support and Miscellaneous questions Results section.

Table 15: Miscellaneous _Support Questions, Follow-up*

Results from second questionnaire. Number of ASD Children followed up =14.

Changes in Physician's visits	
GP	14 All Same as before
Specialist	2 More visits 12 Same as before
Changes in Support *	
School Support	6 Yes 5 No 3 Same
Financial Support	7 Same 7 No

*See Qualitative Results section and Appendix IX

Parents/Caregivers Comments: Qualitative Results

Four common themes were identified in the interview response and were further analyzed using the thematic analysis approach. Themes in our study were identified using the explicit topic areas included in the questionnaire and through the discussions with parents/caregivers on these guided topics: symptoms comments, therapies feedback, services and support suggestions. Therefore our study themes were categorized based on these areas: (i) symptoms, (ii) therapies, (iii) services/support and (iv) school support. Select comments that best represent each theme were carefully curated to highlight the caregivers' satisfaction, dissatisfaction and suggestions with regards to interventions for ASD (please refer to Table 16 for a summary of each theme and comments. For a complete repertoire of interview response and caregivers' comments, please see Appendix IX).

Some comments could fit either under one theme or multiple themes; in fact, we found that many participants commented about ABA, which is a non-pharmacological therapy but it is also a service provided by certified staff as a government-covered or private service. Participants' own words and comments were used where appropriate, but minor modifications were made for clarity purposes. Any names or identifying information was removed from the transcript and only children's codes were used to refer to their parents/caregivers comments and suggestions.

(i) Symptoms

Several parents described their child's ASD **symptoms in relation to specific triggers**, as in the case of ASD02: "*my son can usually get angry if agitated. He typically is happy, but gets angry if doesn't get what he wants, or feels things are unfair*." More than one caregiver reported spatial and audio triggers for their children's ASD symptoms: "*he does not like to be around a lot of people, such as shopping places… he gets agitated when it gets cloudy*" (ASD06); "*he was*

uncomfortable in crowded places, and did not like noises"(ASD11); "*he doesn't like noises, crowded places and noisy people. These things make him agitated, overwhelmed and crying*"(ASD13). One parent identified alleviating factors "*he likes tight feeling, and deep pressure*" (ASD06) and tried interventions (i.e. massage therapy) that would help alleviating some of his symptoms.

Symptoms related to eating and diet were also frequently described; more than one caregiver reported that their children were not feeling full and had diarrhea, as in ASD01 case: "*not feeling full, not controlled appetite, he has often diarrhea, mother has to lock the fridge*"; "*has diarrhea often, because of overeating*" (ASD02); "*he does not seem to feel full"* (ASD08); " he eats a lot, but not showing, he is skinny" (ASD13). Other parents reported their children poor appetite, as in case ASD05: " *my daughter is extremely picky eater (not overeating) and it is very hard to convince her to try food. Any changes in food brand are not accepted"* (sensitive to texture); while ASD12 said "*my son is very picky eater, sensitive for food texture and has G.I irregularities (often constipation)*".

Difficulty with sleep was one of the huge issues remarked by most the participants. ASD13: "my son has sleeping issues". Also ASD03, ASD04, ASD05, ASD08, ASD09, ASD14, ASD15 and ASD16 reported sleeping difficulties. ASD12 described that her son was afraid to sleep by himself, but was getting better. As per participants' perspective, sleeping and eating difficulties were either from ASD symptoms before starting any therapy, or in some subjects these issues had improved with medications, others worsened with medications; for example, ASD03: " *my son had sleeping difficulties before meds, meds has improved his sleeping, but he has eating difficulties from meds*". More details for therapies will be discussed in the following section.

(ii) Therapies

Participants' comments about their ASD children's therapies were wide ranging. Some were satisfied and reported improvement in their children's symptoms (hyperactivity, sleeping, social deficit, speech delay) as an outcome of the therapies (pharmacological and non-pharmacological use). Others reported unsatisfied comments about their children's therapies such as adverse events (e.g., antipsychotics, ADHD medications), taste, texture, cost, coverage, and no access and long waiting list for non pharmacological therapies (e.g., ABA) (for more detailed comments, please refer to Table 16 and Appendix IX).

Many were the comments about the **effectiveness of pharmacological therapies** (e.g., prescribed, OTC and natural products). The mother of ASD01 and ASD07 (twins) noticed that risperidone had increased their appetite, their nipple size and weight, but she thought that the advantages of risperidone outweighed the disadvantages as it was very helpful for sleeping and agitation; she also found that melatonin was effective for his sleeping difficulties. Also the mother of ASD14 and ASD15 found that the combination of quatiapine and clonidine was very helpful: "*it seemed that without them my children would not sleep*"; ASD13: "*my son has sleeping issues, but controlled by risperidone*". ASD03: "*paroxetine has [made a] huge difference in reducing his anxiety at home"*. ASD08's mother reported that citalopram helped to stabilize her son's mood (less anxiety), so that he was performing better in school. She added that methylphenidate ER was used to improve his school performance; it seemed to increase his aggression, but with the combination of citalopram and methylphenidate ER, he seemed to be in a better mood and experienced fewer incidents at school. Melatonin was found to be helpful for sleeping, as per ASD01, ASD07, ASD08, and ASD16 feedback.

Comments about several therapies problems were reported:

(a) Issues with adherence, ASD01: "*he refused capsule form even when I used capsule ingredients and added it to his jam sandwich, still he could recognize it"*. Methylphenidate CR capsules were refused by all children in our sample because of taste and texture, as per ASD01, ASD03, ASD04 and ASD16, or because of side effects such as sleeping and eating disturbances, and irritability, as described by ASD05, ASD10, ASD11 and ASD12.

(b) Medication adverse events, such as increase or decrease appetite, weight gain, aggression, sleeping/ eating difficulties were described; in the case of ASD08, it was noticed that his appetite was reduced because of methylphenidate ER. ASD03's mother stated that they had tried many psychotropic medications, but because of side effects and poor response many were eventually stopped: citalopram, prescribed for anxiety and anger, had lead to an emergency visit and it was stopped; risperidone increased appetite and caused weight gain, it was stopped as well; fluvoxamine increased his anger and violent behavior; fluoxetine increased self-harm talk and anger; olanzapine increased his weight and cholesterol level, aripiprazole upset his stomach, they were all stopped. ASD14 mother's comments on her son's therapies were that paroxetine caused bruising of the skin and was not helpful, therefore it was discontinued; methylphenidate caused hyperactivity and aggression and the mother thought that this medication could have been responsible for speech delay "stop *talking*".

(c) Cost and coverage comments: in the case of ASD01, the mother stated that "*medications are covered through private insurance, but not everything is covered, coverage will run out, what will happen when children get older"*. ASD05's medications were covered through private insurance (father's work insurance), four month later ASD05 was switched to atomoxetine, which was not covered by insurance (parents had to pay out-of-pocket). The majority of our participants' children

medications were covered through their parents' work insurance, except two: one through the government [Manitoba provincial drug program (Pharmacare)] and one through the Non-Insured Health Benefits (NIHB).

Overall, **improvement from non-pharmacological therapies** (tried/currently used, such as ABA, OT, speech therapy, support groups, complimentary and alternative medicine) was highly recognized by the majority of our participants (follow-up questionnaire, Table 13): 8 out of 14 (57%) said Yes for improvement with non-pharmacological therapies, but coverage for older age children, accessibility, limited trained staff were the main challenges. ABA was the therapy that the majority found helpful, but not all could enroll their children or continue to have this therapy available to their children, mainly because of lack of coverage for children and lack of availability of sites with staff trained in ABA.

ASD08 and ASD10 hoped to see ABA-trained staff available in schools. ASD09's mother found ABA, speech, music and OT most helpful among several non-pharmacological interventions that they had tried. ASD03 parents found that OT therapy helped their son's sensory sensitivity (reduced his irritation caused by smells) but it was stopped, as it was hard to continue because of the school schedule (also the service was not covered by insurance); acupuncture therapy was tried but found not helpful. As per the second questionnaire, ASD03 was back to receiving OT services through the school (covered service), but the mother found it "neutral/not so helpful": "*apparently when the child was younger and had OT private sessions, those were helpful!"* ASD05's mother said that the physiotherapy sessions that her daughter received from the school's physiotherapist was helpful, however, ABA therapy was not provided. In the follow-up interview, ASD02's parents said they were trying dietary natural medicine (follow-up with a naturopath); the mother was giving her son olive leaf and HMF forte® "probiotic", both NP products were used for yeast

overgrowth; as per the mother's comments, her son was showing improvement and seemed less irritable.

(iii) Services/Support

We collected a variety of comments about services and support.

Positive comments from satisfied participants were reported: ASD06 feedback regarding services and support was *"good support"* and ASD08's mother found MATC services and support helpful; ASD02's mother appreciated Children Special Services and wished that she had contacted them earlier. ASD13's foster mother found that she had received services that were very good, but she had concerns about her foster son's future, especially when reaching the age of 18 (e.g., continue support, safe place and work), and she whished to see more support for foster families.

Unsatisfied comments included: needs for more support, service coverage, and understanding of ASD children and their families. In the case of ASD01, the mother stated that *"support is needed when attending a diagnostic lab to get blood work done"*, (her son cannot wait in turn, cannot stay in crowded places, he refuses needles), *there are no special lab services for ASD children.…visual aids should be available in the doctors' offices to inform children of what to expect during their visit. Respite – it is dreadfully challenging to find trained workers who know anything about ASD. Lab techs/pharmacists/secretarial staffs need to know more about ASD to support needs during visits. Need a center for ASD which provide special services and a trained team (lab tech, pharmacist, ..etc.) to understand their needs"*. Also ASD02's mother reported that *"we don't have a lot of support, no ABA because he was diagnosed after the age which qualifies him for ABA services, and behavioural therapies if started earlier would be more helpful"*. Other participants emphasized the fact of coverage approval difficulties for older children and high functioning ones (as described by ASD02, ASD03, ASD11 and ASD14).

Suggestions; some participants suggested having more cooperation among several service departments as described by ASD03's mother: *"it is difficult to manage all behaviours in an inclusive setting"*. She thought that *"programs like the Interdivisional Program for Students with Autism* (*IPSA) are needed for high functioning, verbal students"*. She also added that *"parents of ASD children need guidance on how to navigate the network of different services, it would be helpful if school staff would know what MATC is offering, – family services etc. More communication is required between different services and departments (schools/MATC/children special services …etc.)"*. Moreover, ASD10's parents mentioned the need to have easy accessible services, easy to obtain funding for ASD children and their families and a simplified process for parents to get services and school support (e.g., pamphlets, booklets…etc.). For more detailed comments, please refer to Table 16 and Appendix IX.

(iv) School support

Participants in our study elaborated on school support. Their perspective ranged between being "satisfied" about their children's school support and being "not satisfied" as they expected to have more support; some added suggestions about what they wished to see in the future.

Positive feedback examples **(satisfied)**: in the case of ASD01, the mother stated that "*the school has had to make many accommodation to support my son's daily functioning. They provide a quiet space for him and made adjustments to his routine to reduce sensory overload"*. Another positive feedback for school support was given by ASD06: "*his symptoms are improving; he does very well with staff and students. He is now involved with current school activities"*

Unsatisfied comments were about the lack of support as described by ASD02, ASD03, ASD14, and ASD15: not enough school support, hard to get approval for education assistant, transportation support for ASD children, and/or need improvement (ASD05, ASD11 and ASD12). ASD02

reported that "*the school system is not helpful for him*" and *"the school staff is bound to school protocol, they are patient with my son and they are understanding but they are restricted in what they can do by the school regulations"*. ASD07 comments, which could fit in both services/support and school support comments, were the following: "*children with ASD who are high functioning tend to fall through the cracks in the educational system. Schools do not see these children as having behavioural issues, therefore they do not implement necessary programming to support the social skill development required for future well-being. These children are at higher risk of depression and suicide later in life because they acknowledge their own limitations of "not fitting in". There is a lack of trained individuals available to provide respite to families"*.

Some **suggestions** for school support included the following: *"having* a *specialized school to support high functioning children with ASD is essential"*(ASD03); ASD05 wrote these suggestions: *"more services needing improvement include*: (1) *more EA support available in the school system,* (2) *more access to physiotherapists/occupational therapists,* (3) *more training for teachers about autism and teaching kids with ASD, (4) classroom programs for kids to teach about peers with ASD"*. ASD10 mentioned the need for more one-to-one support in the school system, and for clear, specific guidelines for school services (e.g., accessible transportations for special needs children): "*it would be useful to have a website to explain the school system in details to parents of children with ASD"*.

Summary of qualitative results and common themes

(Please refer to Table 16)

For the symptoms comments theme, our study participants were hoping to see more autism awareness in the community and a better understanding of their children's special needs and more general support.

Some participants were satisfied and reported improvement in their children symptoms (hyperactivity, sleeping, social deficit, speech delay) as an outcome of the therapies (pharmacological and non-pharmacological use) and support.

Other participants expressed their concerns about their children's symptoms, such as child's misbehaviours being triggered by noise, smell, crowd places and about their child having no friends, having issues with eating habits (not feeling full or being a picky eater), not accepting any changes in routine and not enjoying social events (e.g., birthdays parties or summer vacations).

Regarding the comments on therapies, participants found non-pharmacological therapies (e.g., ABA, OT, and speech therapy) more effective, but coverage for older children, more trained staff and accessible centers were required. On the other hand, pharmacological therapies (e.g., risperidone, clonidine and melatonin) were helping in ASD symptoms, but most participants emphasized the importance of facilitating the process for seeing specialists, and that family physicians should have a background in treating psychological disorder in children; also accelerating the process for getting refills and reassessing their children's medications would be helpful. In addition, having pharmacists' cooperation and support would also help on a number of issues from generic substitution to waiting time for prescriptions.

Regarding the services/support comments, our study participants pointed out their concerns about their children's future. It was stated that it was important to receive clear guidance on how to access services and that it was crucial that manageable services/support were provided also for older and high functioning ASD children who had a good chance to succeed. More coverage and simplified service/coverage applications and approval processes were also considered highly desirable.

Within the school comments theme, some of our study participants reported that their children received good school support; however, other participants found that school staff needed to be more understanding of their children special needs. Parents/caregivers were also hoping to see more transportation services (from and to school), more ABA, OT, and speech service through the school and to have more safety procedures in school. Some participants suggested that adopting one-to-one teaching methods and more creativity in teaching approaches would be helpful (not to be limited inside the “academic box”).

Table 16: Common Themes/ list of common sentence

Theme	Suggestions	Satisfied	Unsatisfied
1- Symptoms	• More ASD awareness • More understanding for ASD children needs • More visualized signs (Dr's office, hospital, pharmacy, lab) • DSM-IV vs. DSM-V changes	• Improvement in ASD symptoms by using Tx; pharm Tx and nonpharm Tx • Improvement in general well-being (sleeping, eating, GI) by using Tx • Improvement in ASD symptoms since get older • Improvement in ASD symptoms since having new sibling • My ASD child is responding to Tx • My child likes reading, high IQ, excellent school performance	• Agitation from changes • Seems not listening • Triggered from noise, smell, crowded places • Not feeling full (overeating) • Picky eater (eat only specific food) • Other general well being difficulties (sleeping and GI) • Doesn't like group activities (e.g. hockey) • Hard to predict or deal with next crisis • Hard time in summer, Christmas, and parties • Hard to convince, explain and communicate with ASD child • Social issues (no friends, not invited to other kids' parties, or play at their houses)
2-Therapies	• Non- pharm Tx (ABA, OT) more effective, but coverage for older age is required • Generic and Brand changes issues • More Coverage required • Follow up with Doctors and Refills Process • ASD Pharmacist awareness • More access to physiotherapy/OT for ASD • Record for alternative Tx in charts (natural, OTC, homeopathy and others) • Parents' compliance, stress, financial status is important for ASD Tx success	• Antipsychotic (risperidone and quetiapine) helping to sleep and reduce agitation • ADHD meds helped in improving attention/overall performance • Melatonin helping in sleeping • ABA very helpful • OT, speech, massage Tx helpful	• ADHD meds side effects (sleeping and appetite) • Antipsychotic increase child's weight • Med's taste, texture, S.E, cost, availability • Coverage by private insurance • ABA, OT, speech Tx not enough, need more session to get benefit • High functioning child not qualified for coverage (EA, OT, ABA and others) • Polypharmacy • Fluctuation in response • ASD children more sensitive for meds S.E

3-Services and support	• Concern for the child's future • Need lab/ pharmacy/ staff trained for ASD children • Clear guidance to access several services • Massage service to be covered for ASD children • Need easy accessible services • Simplify the process to receive funding, support and services • Ease the GP visit/refill Rx and GP need more knowledge for children mental illnesses	• Successful approval for EA • New coverage for ASD services	• Accessibility difficulties • Financial Barrier • Not covered for older ASD child • Not covered for high functioning ASD children • Not enough services and support • Cooperation between different departments is required • Significant lack of trained individuals for ASD children (doctors, nurses, pharmacists, Lab tech ..etc)
4- School support	• Safety • Transportation • More schools with ASD program • To have a website to explain school system in details for ASD children parents • Trained ASD staff • ABA trained school staff • Coverage for EA (even for high functioning children) • More EA required • Classroom programs to teach kids about peers with ASD • Need specialized schools back for special needs children (even for high functioning children)	• New school meets my child's needs • Supportive staff for my ASD child • My child like the school and has friends from his school	• No EA coverage for high functioning ASD child • No transportation services provided for my ASD child • High IQ, but not good in school performance • No one to one teaching services for ASD children • Poor programming outside the academic box • Poor safety measures for ASD children

Discussion

The characteristics of our study sample were similar to those reported in previous studies in the fact that majority of the sample were males. It has been recognized that ASD is four to five times more frequently diagnosed in boys than in girls (Fombonne et al 2009 and CDC Mar 2014 report). All children were attending school regularly and were receiving some sort of support. Our results show that ADHD comorbidity was present in 68.8% of the children. ADHD symptoms in ASD have been clinically recognized for some time and reported in previous chart review studies with a prevalence varying from 30% to 78% (Goldstein S et al, 2004; Gadow D et al, 2004, 2005 and 2006); however, it was included as an accepted comorbidity in the DSM-V only in 2013.

It was noted that the number of comorbid conditions documented in the medical charts varied from what was reported by some parents/caregivers; in fact, a few parents reported no comorbid conditions when many were recorded in the medical charts, probably because parents assumed that ADHD, anxiety or insomnia were included as ASD symptoms.

Our interview had a question regarding the number of siblings but not siblings' comorbid conditions; however, our participants voluntarily disclosed their other children's comorbid ASD or/and ADHD diagnoses. This type of information, which was not always captured in the medical charts, was valuable in assessing variation of medication effects.

We observed a wide variation in participants' perception of their children's response to pharmacological therapies, especially because individual responses can be influenced by many factors such as dose, side effects, combination with OTC medications, drug interactions, follow-up with doctors and refill processes (e.g., booking appointments, getting refills), and environmental changes (e.g., weather changes, holiday time, back-to-school time) that can deeply affect ASD children's moods and behaviours, a switch from a brand name product to its generic

alternative can be distressing for a child who is used to a certain shape or color. Our results regarding such factors are in line with what was shown in previous studies (Matson J. L et al., 2011; Farmer CA et al., 2008; Aman MG et al., 2004; Aman MG, and Towbin KE et al., 2003).

Children in our sample were prescribed medications that had been evaluated in clinical trials (e.g., antipsychotic and ADHD medications). This testifies to the appropriate use of medications; in fact none of the children had ever been treated with anxiolytics/hypnotics, such as benzodiazepines (e.g., alprazolam, lorazepam), buspirone, or zopiclone, drugs that are not fully evaluated for use in children.

The most commonly tried antipsychotic in our study subjects was risperidone. Similarly to what was found in other studies (Canitano R et al., 2008; McCracken J et al., 2002; Robb AS et al., 2010), most of the participants in our study thought that risperidone was beneficial for sleeping, irritability and aggression.

The most tried ADHD medication was the controlled release methylphenidate (Biphentin®) but none of our study subjects was still receiving this product. Reasons why this medication was discontinued included unpleasant taste and/or texture, and negative side effects on sleeping and appetite. The second most common stimulant that was tried was the short acting methylphenidate (Ritalin®). Overall, our study participants felt that ADHD medications were used to improve attention, school performance and reduce hyperactivity; however, stimulants have been shown to be less effective and to cause more side effects (such as irritability, sleeping and eating difficulties) in ASD children with comorbid ADHD symptoms compared to children with only a ADHD diagnosis (Cortese S et al, 2012; Doyle CA et al., 2012). This was in fact confirmed by one participant who had noticed that her older son with a primary diagnosis of ADHD (without ASD) was responding much better to methylphenidate compared to her other son who had ASD and

comorbid ADHD. In ASD children with comorbid ADHD dose adjustments of stimulants should be considered; as well, switching to long acting formulation or using non-stimulant ADHD therapy (e.g., atomoxetine) seem to be advisable (Pearson, D.A et al 2013; Arnold LE et al., 2006).

Citalopram was the most tried antidepressant. The participants' perspective was that it was helpful to manage anxiety, agitation and anger. This is in contrast to what was reported in other studies (King BH et al, 2009 and Ipser JC, Stein DJ et al, 2009) where no benefit was demonstrated. Clonidine was another medication that was tried by the children in our sample: parents thought that it was beneficial for sleeping, agitation and to help children settle down before bedtime; other studies have supported its use (Fankhauser MP et al., 1992; Jaselskis CA et al., 1992).

Melatonin was the most commonly used OTC product in our study subjects and more than half of the parents/caregivers found it effective for their children's sleeping difficulties, which is in line with the evidence provided by other studies (Appleton RE et al., 2013; Appleton RE et al., 2012; Andersen IM et al., 2008).

Natural products and supplements were commonly used by children in our sample. Some parents/caregivers found modest benefits on the general well-being of their children as a result of using such products.

It was observed that children were subjected to polypharmacy and many therapy trials, (e.g., multiple psychotropic medications, natural products, over the counter drugs, complementary therapies). This may be the consequence of the need to cope with multiple problems; however, the combination of various agents might be conducive of additional issues. It would be important that all therapies used (both prescribed and non-prescribed/alternative) be documented both in the medical charts and at the pharmacy level.

Among the non-pharmacological interventions, the most tried therapy in our sample subjects was occupational therapy (OT), followed by speech therapy, and ABA. More than half of the parents/caregivers found all these interventions very helpful for their children. Although one of the most recommended non-drug therapies for ASD is behavioral treatment (LeBlanc LA et al., 2012; Myers SM et al., 2007, 2009; Rogers SJ et al., 2008), ABA did not seem to be one of the most commonly utilized therapies by the children in our sample. Reasons for this can be attributed to a number of factors: (i) ABA appeared to be covered only until age 3 in Manitoba; in fact, from our results it appeared that if a child was diagnosed after the age of 3, access to ABA was problematic; however, this may change in the future as in the DSM-V the age restriction for ASD diagnosis was lifted (Halfon, N et al., 2013); (ii) waiting time to get access for ABA services was at least 2 years; (iii) there was no funding available for highly functioning children; (iv) the number of ABA-certified staff was limited.

As per our study participants' perspective, the success of non-pharmacological therapies was affected by a number of factors which included the number of sessions attended, the introduction of the therapy at an early age, parents' compliance, parents' level of stress, coverage, access to centers providing therapies. These factors were also discussed in several previous studies (Howlin P et al, 2009; Maglione MA et al, 2012; Myers SM et al, 2007; Orinstein AJ et al, 2014).

An important issue that became apparent in our study was the need for parents/caregivers to receive more coverage and services for ASD children of older age (teenagers and adolescents) and concerns were expressed about the future of the children into adulthood. Concerns were also voiced about changes that occurred in the DSM-V, as with the inclusion of all ASD subtypes in one diagnostic category, high functioning ASD children would be at disadvantage in obtaining eligibility for services and coverage. Parents/caregivers reported a significant positive effect of

non-pharmacological therapies and their opinion was clearly that coverage and eligibility should be extended to older children regardless of their family's financial status. Some participants also wished to see more professionals trained in behavioural therapies in schools and specialized centers.

Parents/caregivers also identified the necessity to have health care professionals (physicians, pharmacists, nurses, laboratory technicians, teachers) receive training in psychological disorders for them to be better prepared to meet the needs of ASD children and their families. It was suggested that having more visual aids and signs in public places (e.g., walk-in clinics, shopping centers, community pharmacies, hospital and labs) for special need children would help them understand and be prepared about the standard procedures of the site.

It was also suggested to have specific areas or lines in public places for parents/caregivers of children with ASD, as they get irritated and anxious because of noise and crowd, (e.g., quiet, noise- and scent-free areas, special fast-line for families with children with special needs).

Strengths of our study are seen in the naturalistic approach and on the combination of collecting accurate histories of pharmacological and non-pharmacological treatments received by children with ASD diagnosis both by chart-review and by collecting a direct parent/caregiver's perspective on their effectiveness. Another strength is that OTC therapies, natural products and non-pharmacological therapies, which are usually not captured in medical charts, were documented as reported by our participants.

In addition, parent/caregiver's perspective on their childrens' general well-being were captured. Sleeping difficulties appeared to be one of the major issues in children with ASD; our study highlighted the fact that stimulants such as methylphenidate and amphetamines, worsened children symptoms while other medications such as risperidone, melatonin, and clonidine had positive

effects. Eating and GI disturbances attributed to ASD could also be the result of medication side effects; in fact, stimulants decreased appetite while antipsychotics increased appetite and caused weight gain in some children in our sample; other medications seemed to have caused diarrhea or constipation. All these observations are in line with what has been reported in the literature (Appleton RE et al., 2013; Cortese S et al., 2012; Doyle CA et al., 2012; Fankhauser MP et al., 1992; Myers SM et al., 2007; Politte, L. C et al., 2014) but our study results reported also some of the strategies adopted by parents/caregivers to overcome such problems such as a change in diet (e.g., gluten free diet), use of products to help with lactose intolerance, use of probiotics or OTC products for diarrhea or constipation.

Our study is not without limitations. This is a pilot study, which provides a snapshot of a limited number of participants. It focused on school age children and teenagers (5-17 years old) with a significant proportion (approximately 40%) of high functioning children. In addition, the survey/interview study design relies on parents/caregivers' perspective; therefore, parents' emotion/stress could influence the accuracy of the results. Parents/caregivers reported their perception and own experience with their children, which cannot be generalized to all children with ASD. The duration of the study (two interviews/questionnaires administered at a four-month interval) was too short to evaluate effectiveness of therapies and document significant changes in children's outcomes and situations. The fact that some interviews were conducted during school time and other during summer time must have affected perceptions as more stress is often associated with school commitments or, conversely, the lack of routine during the summer months can negatively affect the well-being of children with ASD.

Our sample is affected by selection bias since all our participants (except one) were clients of the same health clinic (MATC). Furthermore, it is common for individuals who agree to participate in

a research study to be more educated, to be of high socioeconomic status, to be working and having private insurance, to have access to technology, not to have language barriers; in fact, certain populations (e.g., low income families, children in care, ethnic minorities, rural residents) may have been underrepresented in our sample.

Conclusion

Our study testifies to the high comorbidity of ASD and ADHD. As the DSM-V now does not preclude the co-occurrence of the two conditions in the same child, it is expected that its prevalence will increase. It also reports how parents/caregivers perceive the effectiveness of therapies used in their children and what the most important needs for children and their families are, in particular the need to receive continued support in terms of services and therapies was recognized as paramount. A recent announcement by the government of Manitoba (News Release, 2016) will hopefully address some of the concerns. In fact, on Jan 7, 2016, the Minister of Education and Advanced Learning confirmed an increase of $75.5 million in funding for students with special needs and easier access to support for these students through the elimination of applications as recommended by the Task Force on Special Needs Education.

More collaboration between healthcare professionals, researchers, decision makers and parents/caregivers would be important in order to optimize health outcomes (including quality of life) in children with ASD. This can be accomplished by initiating more therapy intervention trials, which aim at improving autism symptoms, updating therapy recommendations, assessing combination therapy outcomes, enhancing support for older children with ASD, and for high functioning children, and introducing more services/support for ASD families. Better education and awareness is crucial for health care professionals, school staff and the public to be able to help children and their families overcome their challenges.

It was noted that in the current literature, the pharmacist is usually not included in the ASD management team; we think the pharmacist (e.g., psychiatric pharmacist) should definitely be included in the team as the expert in evaluating medication choice, effectiveness and safety.

This was a pilot study, future studies should be conducted in a larger population with enrollment from several location and sites. A longer observation time would also be beneficial in order to document the changing needs of children with ASD. Further studies should also focus more on the general well-being of ASD children, and on the assessment of the needs of older ASD populations (adolescents and young adults).

Reflection

From this research I gained a better understanding of the needs of children with ASD and I have learned many strategies that positively influenced my professionality as a pharmacist. I realized that as the experts in evaluating medication effectiveness and safety, pharmacists should be active members of the team of health professionals responsible for the care of children with ASD. Furthermore, pharmacists can contribute in so many ways and help parents/caregivers of children with ASD. Pharmacists can find in their community pharmacies easy solutions to facilitate parents/caregivers in obtaining medications for their children and in reducing stress; understanding that children with ASD have difficulties waiting and may easily get agitated in public places, pharmacists can prioritize prescriptions for ASD children and/or offer delivery service; they can offer a noise/scent free waiting area. In addition, pharmacists should discuss with parents the option of enrolling their child in a maintenance medication system with an auto-reminder, which means that the pharmacist will fill the child's prescription when due and will take care of contacting the doctor to get refills when needed. Pharmacists should document OTC/natural product therapies in the child's file, check for their safety and effectiveness, and counsel parents.

They can also offer convenient blister pack options for multiple medications. Pharmacists need to be responsive to the challenges posed by any medication change that can be relevant for children with ASD such as changes in taste, texture, or color due to a change in product brand, or changes that are important to parents/caregivers such as costs and coverage issues. Pharmacists should become more aware of the needs of children with ASD and become an integral part of the team that cares for them.

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The author(s) declare no conflict of interest.

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APPENDICES

Appendix I: Copy of Autism Society Canada's Statement on Latest Estimated Prevalence Rates of ASD June 2014

Appendix II: Copy of DSM-V Autism Spectrum Disorder Diagnostic criteria, American Psychiatric Association

Appendix III: Diagnostic Measures Of the main Clinical and Behavioral Scales

Appendix IV: University of Manitoba HREB Approval

Appendix V: Permission to contact consent form

Participant information and consent form

Appendix VI: Questionnaire 1

Appendix VII: Questionnaire 2

Appendix VIII: HREB amendments approval and Advertising Flyer copy

Appendix IX: Complete Participants' Comments

(i) Symptoms Comments

(ii) Therapies Comments

(iii)Services/Support Comments

(iv) School Comments

Autism Society Canada's Statement on Latest Estimated Prevalence Rates of ASD
June 2014

According to the latest estimates (March 2014) of the Centre for Disease Control (CDC) 1 in every 68 children is born with an Autism Spectrum Disorder (ASD). This results in approximately 515,000 Canadians living with an ASD. This figure does not account for the numerous family members and caregivers whose lives are impacted by autism.

"New data from CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network show that the estimated number of children identified with autism spectrum disorder (ASD) continues to rise, and the picture of ASD in communities has changed. This new data can be used to promote early identification, plan for training and service needs, guide research, and inform policy so that children with ASD and their families get the help they need. CDC will continue tracking the changing number and characteristics of children with ASD, researching what puts children at risk for ASD, and promoting early identification, the most powerful tool we have now for making a difference in the lives of children."

In May 2013 the American Psychiatric Association (APA) completed the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5). The DSM is the standard reference for diagnosing mental illness and disabilities in North America, and was last fully revised in 1994. The latest version introduces a new diagnostic category called Autism Spectrum Disorder that replaces the previous diagnoses of Autistic Disorder, Asperger's Disorder, and PDD-NOS (Pervasive Developmental Disorder Not Otherwise Specified).

A diagnosis of Autism Spectrum Disorder recognizes individuals with a wide range of needs, strengths and challenges. People on the autism spectrum depend on lifelong supports and services. It is the hope of ASC that the updated prevalence rates and changes to the Diagnostic and Statistical Manual of Mental Disorders (DSM 5) will provide a better basis for expanded access to supports and services that will result in better outcomes for those on the ASD Spectrum.

Autism Spectrum Disorder (ASD), also referred to as autism, is a neurological disorder which affects the way the brain functions, resulting in difficulties with communication and social interaction, and unusual patterns of behavior, activities and interests. Autism Society Canada actively advocates for services and support for individuals living with Autism Spectrum Disorders (ASD), their families and their communities. Autism Society Canada's mission is to work with our many partners to address the national priorities facing the Autism Community. Autism Society Canada is the largest collective voice for autism in Canada.

Autism Society Canada / Société canadienne de l'autisme

Diagnostic Criteria

299.00 (F84.0)

A . Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive; see text in DSM-5 for details):

1 Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

2 Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

3 Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

B . Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text in DSM-5 for details):

1 Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

2 Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).

3 Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

4 Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

C . Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D . Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E . These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Diagnostic Measures Of the main Clinical and Behavioral Scales (a cited brief description)

Autism Diagnostic Observation Schedule (ADOS)

Is an instrument for diagnosing and assessing Autism. The protocol consists of a series of structured and semi-structured tasks that involve social interaction between the examiner and the subject. Categorized observations are subsequently combined to produce quantitative scores for analysis. Research-determined cut-offs identify the potential diagnosis of autism or related autism spectrum disorders, providing a standardized assessment of autistic symptoms. The Autism Diagnostic Interview-Revised (ADI-R), a companion instrument, is a structured interview conducted with the parents of the subject, which covers the patient's full developmental history. The ADOS generally takes from 30 to 60 min to administer. Each subject is administered activities from just one of the four modules. The selection of an appropriate module is based on the developmental and language level of the patient. The only developmental level not served by the ADOS is that of nonverbal adolescents and adults (Lord et al., 1989).

Childhood Autism Behavior Scales (CARS)

Is a behavioral rating scale used for assessing the presence and severity of the symptoms of autism spectrum disorders. The child's behavior is rated on 15 dimensions or symptoms. The scale yields a total score, which provides a continuous measure of the severity of autism, as difficulties (Schopler et al., 1980).well as a categorical diagnosis of not autism (b30), mild/moderate autism, or severe autism. CARS include items related to social and emotional responses, verbal and nonverbal communication, and various

repetitive behaviors, yet it does not explicitly include peer relationships, joint attention, or symbolic play. In addition, CARS includes a number of symptoms, which are frequently present and clinically relevant in autism, such as sensory abnormalities, anxiety and activity levels, and imitation

Aberrant Behavior Checklist (ABC)

Is a 58-item caregiver report checklist that assesses maladaptive behaviors in individuals with developmental disabilities using a simple four-point rating scale (0–3) with higher scores reflecting more problems. ABC items are grouped into five subscales: (1) Irritability, Agitation, Crying (15 items); (2) Lethargy, social withdrawal (16 items); (3) Stereotypic behavior (seven items); (4) Hyperactivity, non-compliance (16 items); and (5) Inappropriate speech (four items). ABC-Community Subscale scores are constructed by totaling the scores of the subscale items. The ABC was originally developed to measure problem behaviors in developmentally disabled populations and it has been demonstrated as a good measure of the non-diagnostic or associated features of autism. Irritability, as defined by the ABC, includes aggression, self-injurious behavior, and tantrums in Children and adolescents diagnosed with autism and related pervasive developmental disorders (PDDs). A significant number of pharmacological trials in autism have relied on the ABC as one of the main end points for treatment evaluation (Aman et al., 1985).

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Research Ethics Board

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES

Full Board Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Noor Breik	U of M/Faculty of Pharmacy	H2014:392
HREB MEETING DATE:	**APPROVAL DATE:**	**EXPIRY DATE:**
November 24, 2014	December 16, 2014	November 24, 2015
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):		
Dr. Silvia Alessi-Severini		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
N/A	Therapies used in Children with ASD: a pilot study of caregivers' perspective linked to H2014:052
SPONSORING AGENCIES AND/OR COORDINATING GROUPS:	
N/A	

Submission Date(s) of Investigator Documents:	REB Receipt Date(s) of Documents:
November 3, December 3 and 12, 2014	November 3, December 3 and 12, 2014

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol:		
Protocol (with changes outlined in sub form of December 3, 2014)		November 3, 2014
Consent and Assent Form(s):		
Research Participant Information and Consent Form		03/12/2014 submited November 3, 3014
Permission to Contact Consent Form(Appendix 1)		
Other:		
Appendix 3(Questionnaires)		submited December 3, 2014

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the research study/project named on this ***Certificate of Final Approval*** at the ***full board meeting*** date noted above and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in

Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

John Arnett, PhD., C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

UNIVERSITY OF MANITOBA | Research Ethics - Bannatyne
Office of the Vice-President (Research and International)

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HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Ms. Noor Breik	U of M/Pharmacy	HS17901 (H2014:392)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** November 12, 2015	**EXPIRY DATE:** **November 24, 2016**
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. S. Alessi-Severini		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	Therapies used in Children with ASD: a pilot study of caregiver's perspective (Linked to H2014:052)
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: NA	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
October 28, 2015	October 28, 2015

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name(if applicable)	Version(if applicable)	Date

Annual approval

*Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.*

Consent and Assent Form(s):

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this ***Certificate of Annual Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of annual approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

John Arnett, PhD., C. Pysch.
Chair, Health Research Ethics Board
Bannatyne Campus

UNIVERSITY OF MANITOBA

Permission to Contact Consent Form

Dear Parent/Caregiver,

You are being asked to give your permission to be contacted by a health researcher who is conducting a study on Autism Spectrum Disorders (ASD) therapies (title: "Effectiveness of therapies used in children with ASD"). The purpose of the study is to collect information about therapies, health progress and general comments on health services provided to children with ASD.

The principal investigator is a licensed pharmacist with the College of Pharmacists of Manitoba and a graduate student in the College of Pharmacy, Faculty of Health Sciences, University of Manitoba.

You will be asked to complete two questionnaires during two interviews with the researcher, which will be scheduled at your convenience. The questionnaires will include general questions on your child's symptoms and medications used, access to non-pharmacological interventions, support services and specialist's visits. Information on school attendance and performance, sleeping and eating patterns, social activities will also be collected. There will be also the opportunity for you to provide specific comments on what is working and what is missing in terms of support to children with ASD and their families.
Each interview will take approximately 30 minutes of your time. A modest honorarium will be provided for your time. More information regarding the study will be provided by the researcher at the time of first contact.

Please note that all data collected will be completely anonymized and that your personal information will be kept confidential. Your decision to decline participation in this study will not affect in any way your child's services at MATC.

I give permission to be contacted by the researcher conducting the study.

Name _____Signature _____ Date _____

Phone Number:_____ E-mail: _____

College of Pharmacy
Faculty of Health Sciences
University of Manitoba

Apotex Centre 750 McDermot Avenue
Winnipeg, Manitoba
Canada R3E 0T5
Telephone (204) 474-9306

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

Tiltle of Study: "Therapies used in children with ASD: a pilot study of caregivers' perspective"

Principal Investigator
Noor Breik, Licensed Pharmacist with the College of Pharmacists of Manitoba, Member of the Manitoba Society of Pharmacists, Graduate student in the College of Pharmacy, Faculty of Health Sciences, University of Manitoba, Ph. 204 [redacted] e-mail: breikn@myumanitoba.ca

Supervisor
Dr. Silvia Alessi-Severini, College of Pharmacy, University of Manitoba, Ph. 204 –[redacted] email:[redacted]

Dear Parent/Guardian;

You are being asked to participate in a research study. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your friends, family or (your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Purpose of the Study

This research study is being conducted to study

1) what medications are prescribed to a pediatric population diagnosed with

Autism Spectrum Disorder and how effective these medications are in controlling ASD symptoms, and symptoms that can be associated with Attention Deficit Hyperactivity Disorder,

2) the use of non-prescription medications such as over-the-counter agents, supplements and herbal products,

3) and identify unmet needs and gap in services provided to children with ASD and their families.

Study Procedure

You will be asked to provide answers to two questionnaires that will be given to you at 4-month interval during private interviews with the principal investigator or a designated person. The questionnaire will include general questions on patients' symptoms and medications, access to non-pharmacological interventions, support services and specialist's visits. Information on quality of life parameters such as school attendance and performance, sleeping and eating patterns, social activities will also be collected.

Please note that all data will be collected in a completely de-identified database. No personal information that could in any way identify the patient will be stored.

Risks and Discomforts

There will be no risks associated with your participation in the study. No interventions will be applied to your child's treatment.

Benefits

While there will be no direct benefit to you and/or your child, this pilot study will contribute important clinical information on the effectiveness of prescription and non-prescription medications in children with ASD. It will also provide the basis for a larger study that will determine patients/caregivers' perspective and preferences on the use of medications and therapeutic interventions. Please note that the study will not interfere with the optimal care your child will receive.

Costs

Participation in the study will be at no cost to you.

Payment for participation

You will be offered $50 as compensation for your time at completion of the study.

Confidentiality

Information gathered in this research study may be published or presented in public forums; however, your child's name and other identifying information will NOT be used or revealed in any way. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

As part of the study, access to the patient's medical chart will also be granted; however, medical records that contain identifying information will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. All records will be kept in a locked secure area and only the study staff (researchers identified on this consent) will have access to these records. If any of your medical/research records need to be copied, your name and all identifying information will be removed. No information revealing any personal information such as your name, address or telephone number will leave MATC (Manitoba Adolescent Treatment Centre) clinic.

The University of Manitoba Health Research Ethics Board may review records related to the study for quality assurance purposes.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. Your decision not to participate or to withdraw from the study will not affect your care at the clinic. If the study staff feel that it is in your best interest to withdraw you from the study, they will remove you without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

Questions

You are free to ask any questions that you may have about the study and your rights as a research participant. If any questions come up during or after the study contact the study researchers: *Noor Breik* at [redacted] *or Silvia Alessi-Severini at* [redacted].

For questions about your rights as a research participant, you may contact The University of Manitoba, Bannatyne Campus Research Ethics Board Office at (204) 789-3389

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Statement of Consent

I have read the consent form and I give permission to the principal investigator, NOOR BREIK, to set up interview times at my convenience and to access my child's chart for the purpose of collecting data required for this study. I have had my questions answered in language I understand. The risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statements or implied statements. Any relationship (such as employer, supervisor or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my child's identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of any of my records that relate to this study by the University of Manitoba Research Ethics Board and MATC for quality assurance purposes.

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

I agree to be contacted for future follow-up in relation to this study,

Yes _ No _

Participant signature_____Date _____
(day/month/year)

Participant printed name: _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Printed Name: _____Date _____

(day/month/year)

Signature: _____

Role in the study: _____*[This must be done by an authorized/qualified member of the research team i.e. investigator, study nurse, etc.]*

Questionnaire 1 (DATE: dd/mm/yyyy)

Patient ID number:

(1) Demographic characteristics

Question	Answer
1-Sex	Male ( ) Female ( )
2- Age	
3-Age at ASD diagnosis	
4-Any comorbid medical conditions	Yes ( ) specify…….. No ( )
5-School	No ( ) Yes ( ) School grade …….
6-School Support	No ( ) Yes ( )
7- Area of residence	Urban ( ) Rural ( )
8- Number of siblings and child order in the family	Yes ( ) …….. Not Applicable ( )
9-Primary caregiver	( ) Parents ( )Other guardian …….

Comments:

(2) Symptoms

Questions	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Don't Know
1-My child faces difficulties in giving close attention to details						
2-My child faces difficulties in sustaining attention in play activities						
3-My child looses his/her things (toys, books…etc.) and is forgetful in daily activities						
4-My child fidgets with hands or feet						
5-My child runs or jumps excessively / has difficulty to await his/her turn						
6-My child has difficulties in playing quietly						
7-My child avoids direct eye contact or seems to not listen when spoken directly						
8-My child gets annoyed by others' requests; he/she argues and dislikes to obey orders						
9-My child deliberately does things that annoy other people						
10-My child is often angry or vindictive						

Comments:

(3) General well being

Questions	Yes	No	Sometimes	Comments
1-My child has difficulties sleeping				
2-My child has difficulties with eating				
3-My child attends school regularly				
4-My child is involved in extracurricular activities				
5-My child often has gastro--intestinal issues (diarrhea /constipation)				

(4) Therapies

1. Medications prescribed

No.	Name	Date prescribed	Dose	Changes in dose	Date discontinued	Comments
1.						
2.						
3.						
4.						
5.						
6.						
7.						
8.						
9.						
10.						

2-Over The Counter (OTC) medications used

No.	Name	Dose	Reason of using	Date started	Date discontinued	Comments
1.						
2.						
3.						
4.						
5.						

3-Supplements/herbal products used

No.	Name	Dose	Reason of using	Date started	Date discontinued	Comments
1.						
2.						
3.						
4.						
5.						

4-Behavioral therapy received/prescribed

No.	Name/Type	Location	Covered Yes No	Date started	Number of sessions since	Date stopped	Comments
1.							
2.							
3.							
4.							
5.							

Comments:

5-Number of physician's (GP) visits per month

(0) (1---4) > 5 .....

6-Number of specialist's visits per month

(0) (1---4) > 5 .....

Comments:

(5) Support

1. Support at school

My child's school meets his/her needs	Yes	No
My child's school helps the development of his/her skills (reading, communication, speaking..etc)	Yes	No
My child's school staff creates a supportive environment for my child	Yes	No

2.Family/Friends support

Our Family/Friends understand my child's needs	Yes	No
Our Family/Friends offer the help and support	Yes	No

3.Financial Support

Our child's medications are covered by prescription insurance	Yes	No
All services for our child are covered (e.g., supported by the government)	Yes	No

(6) Comments:

*Do you have any comments you would like to add?

*Do you think there are more services needed or needing improvement?

Questionnaire 2 (DATE: dd/mm/yyyy)

Patient ID number:

(1) Symptom improvement

Questions	Improved	Worsened	Same	Comments
1-My child faces difficulties in giving close attention to details				
2-My child faces difficulties in sustaining attention in play activities				
3-My child looses his/her things (toys, books…etc.) and is forgetful in daily activities				
4-My child fidgets with hands or feet				
5- My child runs or jumps excessively / has difficulty to await his/her turn				
6-My child has difficulties in playing quietly				
7-My child avoids direct eye contact or seems to not listen when spoken directly				
8- My child gets annoyed by others' requests; he/she argues and dislikes to obey orders				
9-My child deliberately does things that annoy other people				
10-My child is often angry or vindictive				

(2) General well-being

Questions	Yes	No	Sometimes	Improved Y/N
1- My child has difficulties sleeping				
2-My child has difficulties with eating				
3-My child attends school regularly				
4-My child is involved in extracurricular activities				
5- My child often has gastro-intestinal issues (diarrhea /constipation)				

(3) Therapies

1. Medications prescribed

No.	Name	Changes in dose	Changes in symptoms Improved Y/N	Comments
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				

Comments:

2-Over The Counter (OTC) medications used

No.	Name	Dose	Reason of using	Date discontinued	Changes Improved Y/N	Comments
1.						
2.						
3.						
4.						
5.						

3-Supplements/herbal products used

No.	Name	Dose	Reason of using	Date discontinued	Changes Improved Y/N	Comments
1.						
2.						
3.						
4.						
5.						

4- Behavioral therapy received/prescribed

No.	Name/Type	Location	Covered Yes No	Date started	Number of sessions since initiations	Changes Improved Y/N	Comments
1.							
2.							
3.							
4.							
5.							

5- Number of physician' (GP) visits since last interview (Please specify):

( ) Same as before ( ) More visits ….. ( ) Fewer visits……

6- Number of specialist's visits:

(3) Support

1. Support at school –changes?

---

2. Financial support – changes?

---

(4) Comments:

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Board

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF FINAL APPROVAL FOR AMENDMENTS AND ADDENDUMS

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Ms. Noor Breik	U of M/Faculty of Pharmacy	HS17901(H2014:392)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** April 14, 2015	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE: "Therapies used in Children with ASD: a pilot study of caregivers' perspective "(linked to H2014:052)
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: N/A	

REMINDER: THE CURRENT HREB APPROVAL FOR THIS STUDY EXPIRES: November 25, 2015

REVIEW CATEGORY OF AMENDMENT:	Full Board Review ☐	Delegated Review ☒
Submission Date of Investigator Documents: March 31, 2015	**HREB receipt date of Documents:** April 10, 2015	

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol: Extend recruitment to St. Amant Autism Program, The Autism Society of Manitoba and WRHA Psychology Services as outlined in the Research Ethics Board Amendment submission form subject to **INSTITUTIONAL APPROVAL AT THESE LOCATIONS**		March 31, 2015
Consent and Assent Form(s):		
Other:		

CERTIFICATION
The University of Manitoba (UM) Health Research Board (HREB) has reviewed the amendment to the research study/project named on this ***Certificate of Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. The amendment and documents listed above were granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulation of Manitoba.

In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE

The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. This amendment is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Board

P126-770 Bannatyne Avenue
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HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF FINAL APPROVAL FOR AMENDMENTS AND ADDENDUMS

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Ms. Noor Breik	U of M/Faculty of Pharmacy	HS17901(H2014:392)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** May 1, 2015	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE: "Therapies used in Children with ASD: a pilot study of caregivers' perspective "(linked to H2014:052)
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: N/A	

REMINDER: THE CURRENT HREB APPROVAL FOR THIS STUDY EXPIRES: November 25, 2015

REVIEW CATEGORY OF AMENDMENT:	Full Board Review ☐	Delegated Review ☒
Submission Date of Investigator Documents: April 27, 2015	**HREB receipt date of Documents:** April 27, 2015	

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date

Protocol:

Consent and Assent Form(s):

Other:
Advertising Flyer

submitted April 27, 2015

CERTIFICATION
The University of Manitoba (UM) Health Research Board (HREB) has reviewed the amendment to the research study/project named on this ***Certificate of Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. The amendment and documents listed above were granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulation of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in

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7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

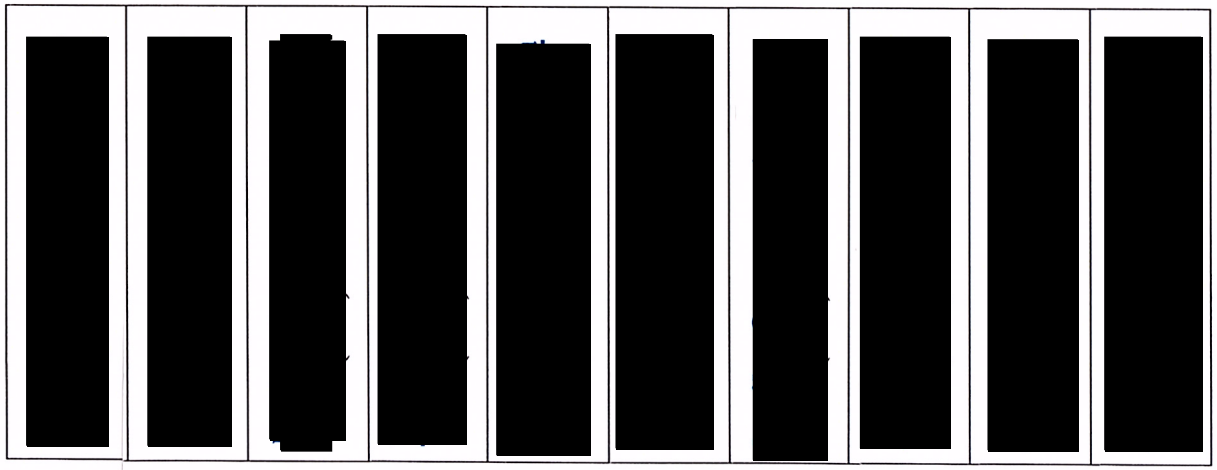
Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255/ **Fax:** (204) 789-3414

UNIVERSITY OF MANITOBA

Autism Spectrum Disorder Research

If your child is diagnosed with Autism and his/her age is between 5 and 17 years of age, you can participate in our research project.

Please contact Noor Breik at [redacted] ([redacted]) to find out how to be part of the study.



Appendix IX: Complete repertoire of interview response and caregivers' comments

(i) Symptoms comments

Detailed comments were reported as follows:

ASD01: "*impulsive aggression due to sensory overload and emotion disregulation", "ADHD symptoms started at age 2, started stimulants in Grade 4", "Still has inattention symptoms", "not feeling full, not controlled appetite, has to lock the fridge/ has diarrhea".*

ASD02: *"my son can usually get angry if agitated. He typically is happy, but gets angry if doesn't get what he wants, or feels things are unfair.* About his appetite, " *not feeling full, may wake up at night to ask for snack, could eat anything left out. Has diarrhea often, because of overeating*". For attending school, "*creates excuses everyday to leave the school early, e.g., feeling sick*" and for having friends: "*has few friends, likes his grandfather, likes to go with him*". Regarding activities" *likes archery, doesn't like group games or activities*"

ASD03: "*he had sleeping difficulties before meds, meds has improved his sleeping, but he has eating difficulties from meds, also he is triggered from noise, smell for example when janitor using cleaning agents (hypersensitive)*". For activities, "*he takes swimming lessons and violin lessons, does not like team games*".

ASD04: both parent's comments were collected: mother: " *my son is talking non-stop/unpredictable/rigidity and seems not listening"* and "*does not like any changes in routine*".

Difficulties with eating were described in detail (as per his father): "*Healthy eater as a baby. Became a fussier eater around 3-4 years of age (when autistic tendencies became more noticeable). With medication for ADHD the fussiness has become more pronounced. Fussiness has definitely increased with age" (Not eating well).* Also father added "*not very good in sports" (lack muscle strength).* Additional comments: "*I think it is great that you are doing work into ASD. It is hard as a parent to watch other children grow up and mature, while your child does not hit those same milestones. Our son has classmates but no true friends. He does not get invited to anybody's house to play or any parties. We have placed our son in community center sport teams and have been quite fortunate that coaches have accepted him (despite his limitations in gross and fine motor skills,*

social interactions with his teammates, and attention). I would also like to add that it is extremely difficult to follow the thought patterns of an ASD child. It is often very hard to predict and deal with the next crisis".

ASD05: mother said that her daughter was annoyed by loud noises, which trigger misbehaviour, and that she had trouble focusing when many people around, she got distracted. She had ADHD comorbidity (recently diagnosed with ADHD). Regarding sleeping issues (restlessness), the mother noticed this issue before medications and it seemed that after using medication her child became more restless.

In addition, "*my daughter is extremely picky eater (not overeating) and it is very hard to convince her to try food. Any changes in food brand are not accepted (sensitive to texture). In addition to that she is not so good at physical activity, but she is highly functioning and so far "ahead" academically*". "*My daughter has gross motor skills delay, sensitivity to noise and focus issues, which makes physical activities a challenge. Gym classes typically have many students, as two classes are in the gym at the same time, so it makes it even harder for her to grasp the rules of the game or the physical skills being taught"*.

ASD06: the mother reported that her son *"does not like to be around a lot of people, such as shopping places", "he gets agitated when it gets cloudy "and "he likes tight feeling, and deep pressure,* so she thought that massage therapy would be helpful. He was practicing swimming (private lessons), but no group activities.

ASD07: mother reported: *"although he is the twin brother of ASD01, ASD07's autism symptoms are less severe than those of his twin bother ASD01", " ASD07 has less ADHD-like symptoms compared to his twin bother ASD01", "but ASD07 has attention problem, and he is a picky eater regarding to texture"*. In the second interview, ASD07 mother reported improvement in his ASD/ADHD symptoms and general well being was overall improved.

ASD08: mother's comments regarding her child's symptoms were "*he does not seem to feel full", "he only does swimming (private lessons) and he dislikes group activities"*. Four month later, in the second interview, ASD08 mother noticed that her son had less anxiety during summer because he was out of school and felt no peer-pressure related to school environment (he exhibited more aggression symptoms when in school).

ASD09: the mother reported: "*my son wants to sit, play and follow me all the time*", "*he wants to play by himself, and he makes noises while playing"*. She added: "*he had sleeping problems before taking medications and got worse with medications (specially from Ritalin) so he was prescribed risperidone to help him sleep"*. Regarding activities questions, the mother informed us that her son was taking cooking classes and music classes and that he liked horse riding, but he did not like group activities (did not know how to join a group).

ASD10: parents mentioned that their child did not like loud noises or crowded places or surprises, but they noticed he was getting better since he had a newborn brother, and he was paying attention to details (he had ADHD comorbidity, but symptoms were improving). They added that he had sleeping issues before, but now his sleeping problems seem related to side effects from ADHD medications (Dexedrine). In addition, parents started noticing eating problems.

ASD11: the mother noticed that he was uncomfortable in crowded places, and did not like noise; his ADHD-associated symptoms were getting better with medications but he had sleeping problems, and was getting worse with ADHD medications. Regarding eating issues, she noticed that it was getting worse with ADHD medications (tried several ADHD medications: Ritalin, Concerta, Biphentin and Vyvanse). Regarding activities, he liked swimming and curling (but not group activities). ASD11 also had G.I issues (especially diarrhea) and the mother thought this was because he had allergies for many things (milk, peanut and others).

ASD12: mother reported that her son was afraid to sleep by himself in the beginning; he was a very picky eater regarding food texture and had G.I irregularities (often constipation).

ASD13: the foster mother thought that his ADHD-associated symptoms were getting better with medications and with new family support. She added: " *he doesn't like noises, crowded places and noisy people, these thing make him agitated, overwhelmed and crying", "he eats a lot, but not showing, he is skinny "and "he has sleeping issues, but it is controlled by risperidone"*.

ASD14: mother has four children, two boys with autism, ASD14 and ASD15 (non-verbal) and two daughters with Asperger's disorder. The mother thought that her daughters were doing fine, they were independent, had

high IQs, their communication skills were fine, therefore she felt that it was unfair to have functional and nonfunctional ASD children in the same category as per the new DSM-5; this did not make sense to her! She added that ASD14 had sleeping, eating and G.I irregularities (diarrhea), and not going to school regularly (special needs class-non verbal ASD). For ASD15, the mother reported overeating and G.I irregularities (diarrhea).

ASD16: the mother provided no comment for her daughter symptoms.

(ii) Therapies comments

Detailed parents/caregivers' perspective and comments for tried and currently used therapies (pharmacologic and non pharmacologic) in their children were reported.

ASD01: the mother's comments about therapies were the following: "*he refused capsule form even when I used capsule ingredients and added it to his jam sandwich, still he could recognize it", "my child feels that the capsule is a strange object and wondering why he should put this in his mouth?"* This was explained as*" high sensory awareness, he could not mentally accept such thing. It is not a swallowing problem"*. The mother noticed when he was getting older; he started to understand the rationale behind taking the capsule " medication concept" and started to accept it. Although she noticed that risperidone had increased his appetite, his nipple size and weight, she thought that the advantages of risperidone outweighed the disadvantages as it was very helpful for sleeping and agitation, also she found that melatonin was effective for his sleeping difficulties.

ASD02: the mother thought that methylphenidate made her son violent, so the drug was stopped, risperidone increased his cholesterol level and it was not found helpful, therefore it was stopped; she thought that amphetamine salt (Adderall®) made her son unhappy, therefore it was stopped. Melatonin was used to help her son sleep and milk thistle (natural product NP) was used to assist with liver function. Coverage for medications was through private insurance (both parents were working). Four month later, ASD02 parents were trying dietary natural medicine (follow up with a naturopath/ specialist): the mother was giving her son olive leaf and HMF forte® "probiotic", both NP products were used for yeast overgrowth, as per the mother

her son was showing improvement and seemed less irritable.

ASD03: the mother stated that they had tried many psychotropic medications for their son, but because of side effects and poor response many were eventually stopped; citalopram, prescribed for anxiety and anger, had lead to an emergency visit and it was stopped; risperidone increased appetite and caused weight gain, it was stopped as well; fluvoxamine increased his anger and violent behavior; fluoxetine increased self-harm talk and anger; olanzapine increased his weight and cholesterol level, aripiprazole (Abilify®) upset his stomach, they were all stopped. Methylphenidate CR (Biphentin®) capsule / Methylphenidate (Ritalin®), could not be administered because they child refused to take them. Clonidine was used just a few times when the child was on Biphentin to help him sleep and settle down. At the time of the interview, the child was on quetiapine, which helped him settle down and sleep, and on paroxetine, which "*has [made a] huge difference in reducing his anxiety at home"*. Parents found that OT therapy helped his sensory sensitivity (reduced his irritation caused by smells) but it was stopped because it was hard to continue with school schedule (also the service was not covered by insurance). Acupuncture therapy was tried but found not helpful.

Four months later his psychiatrist added guanfacine (Intuniv®) to help him sleep and to control aggression. As per the mother, medications are noticeably helping but there is too much fluctuation. Most information about their son's medications was provided by the doctors at MATC. The child was back to receiving OT service through the school (covered service), but the mother found it "neutral/not so helpful". Apparently when the child was younger and had OT private sessions, those were helpful!

ASD04: the mother's comments regarding her son's therapies included mention of refusal to take either Biphentin or Concerta®, "*Hard time in taking medications*". The mother noticed that her older son with primary diagnosis of ADHD only (no ASD symptoms) was responding much better to ADHD medications compared to ASD04 (second son who has ASD and ADHD), she thought that ASD04 was not really getting so much benefits from ADHD therapy compared to his brother. Currently he was using Ritalin for ADHD symptoms (not helping so much) and citalopram for anxiety. Melatonin was tried but stopped because ASD04

refused to take it. He never received any ABA (diagnosed after the age that would have qualified him for ABA); he only received OT and support groups through MATC. Four months later he was switched to Vyvanse® (for ADHD), stopped Ritalin® and was still on citalopram. Significant improvement was noticed. The child was back to using melatonin and additional Theanine supplement added for sleeping, and improvement was noticed.

ASD05: the mother's report on her daughter medications was that fluoxetine was prescribed for excessive anxiety, worrying and obsessiveness. Biphentin was tried, but discontinued because of irritability and inability to sleep well. Then Vyvanse® (lisdexamfetamine) was tried, but the mother thought that Biphentin was more effective than Vyvanse® but because of Biphentin side effects experienced, the psychiatrist switched her daughter to Vyvanse®. There were plans to switch it again. Medications were covered through private insurance (father's work's insurance). No ABA therapy/coverage was provided. The mother found helpful to use melatonin for sleeping. Also general physiotherapy through school's physiotherapist was found helpful. Four month later ASD05 was switched to atomoxetine (Strattera®) (non stimulant ADHD medication), which was not covered by insurance (parents had to pay out-of-pocket).

ASD06: the mother found prescribed medications helpful (risperidone, paroxetine, and aripiprazole), but OTC melatonin for sleeping (not regularly used) was not so helpful.

ASD07: the mother informed us that her son did not use any psychotropic medications, only melatonin was occasionally used and helpful with sleeping issues. The child was taking regularly asthma medications. ASD07 had completed ABA program and received huge benefit, more than his twin brother ASD01. As per the mother, parents' compliance, parent's level of stress, financial situation, and follow up play role in ABA good results for ASD children. She added "*my son is independent in taking his asthma medications, he is starting recognizing when he needs it*".

ASD08: the mother's comments regarding her son's therapies were that dextroamphetamine (Dexedrine®) was tried and stopped the same day because it worsened his insomnia and increased hyperactivity. Citalopram

helped to stabilize his mood (less anxiety), so he was performing better in school. Methylphenidate (Concerta®) was used initially at 27 mg and it seemed to increase his aggression, but with the combination of citalopram and Concerta® he seemed to be in a better mood and experienced fewer incidents at school. The mother noticed that his appetite was reduced because of Concerta®. Melatonin, helpful for sleeping, was used when needed. Parents were giving ASD08 hemp seed oil (for brain regulation and clarity); they believed that the Omega fatty acids 3,6,9 in it would help with brain regulations. Mother found non-pharmacological therapies (such as OT, ABA, support group at MATC and school support) helpful. In the second interview, Abilify® was added as a trial for ASD08 to stabilize his mood and reduce his aggression, but as per the parents it did not appear to be useful, in fact they observed the opposite effect. Because of summer time, parents stopped all OTC, supplements and natural products for their son. The mother was thinking of discussing with his doctor the idea of tapering down or stopping citalopram (she noticed an increase in her child's size and she was worried about long term effect of an increased appetite). Concerta® might have been kept at an increased dose to help him focus. Decisions about therapies would depend on his behavior in the new school.

ASD09: the mother's comments regarding her son's medications were that risperidone helped him sleep, while paroxetine, that was tried for a while, was not useful (it made him more agitated), therefore it was stopped. Aripiprazole was tried then stopped because it was not helping (not sleeping, not eating, and increased anxiety). Ritalin was tried and stopped because it made him hyperactive, agitated, and not sleeping. The mother administered melatonin when the child was using aripiprazole, but when it was discontinued there was no longer need for melatonin. B-complex and magnesium were used when he was on a gluten-free diet, but no real benefits were seen with dietary restriction. The mother tried several non-pharmacological therapies for her son such as physiotherapy (mixed coverage and benefits " *helpful and not helpful*"), both chiropractic approaches and homeopathy were tried but they were neither covered nor helpful. While ABA, speech, music, OT therapies were helpful. Prescriptions were not covered by government, but through private insurance. Four month later, during a time when the mother was away, he was more agitated and aggressive, therefore

risperidone dose was increased and a new antipsychotic, quetiapine was added to the regimen because of trouble sleeping and the behavioural changes at summer time. Also he was back to ABA, which unfortunately was no longer covered because of his age. The mother was having difficulties to send him to his ABA sessions because of her marital situation (recent divorce), a full time job and going back to college without any support. The child went back to OT and speech therapy through school (services were covered).

ASD10: parent's comments for their son's therapies were that he had tried Biphentin®, but it was discontinued because very bad side effects on sleeping, eating, and causing agitation. Currently he was using Dexedrine®, but only on school days. Parents noticed a big change in concentration and school performance, but still he had sleeping and eating side effects. Melatonin was administered to ADS10 only on school days (evening) and was found helpful. Several non-pharmacological therapies had been tried such as biofeedback, which is a technique that could help the patient gain more control over involuntary functions (not covered); it was used in the attempt to avoid using meds, but it was found not helpful. When switched to Dexedrine®, parents noticed a huge difference (*definitely better than biofeedback*); tried OT and speech therapy were also found helpful (the child was still on speech therapy). In addition, massage therapy had been administered to him by his mother who has experience with the technique and it was very helpful. Coverage for medications was available through private insurance (work insurance).

ASD11: the mother's comments regarding her son's therapies were that Concerta®, Ritalin®, and Biphentin® had been tried at different time, but they had caused sleeping issues and were all discontinued. Also ASD11 didn't like the texture for Concerta® and Ritalin®. He didn't like to take Biphentin® (has difficulties with capsule form). Mother found risperidone helpful for sleeping and Vyvanse® improved the child's performance at school. Melatonin was helping him with sleeping problem. He was taking immune echinacea, probiotics, omega-3 products, fish oil for general well-being. Prescription medications were covered through father's work private insurance. The mother found ABA, OT, speech and massage therapies to be helpful. Her son was no longer receiving any of the non-pharmacological therapies, but the mother thought that continuing

ABA and/or OT in older ASD children would have been very helpful. Four month later, it was discovered that ASD11 had lactose intolerance, and adding lactase enzyme before eating dairy products was helpful and improved his G.I symptoms.

ASD12: the mother had only one comment regarding her son's medication *"Biphentin® was tried and discontinued due to lack of sleep and side effects affecting his appetite"*.

ASD13: the foster mother did not know about previously used therapies, but current medications were risperidone, clonidine (for sleeping and agitation) and Concerta® (for ADHD symptoms), which were all helping as she had noticed improvement.

ASD14: the mother's comments on her son's therapies were that paroxetine caused bruising in the skin and was not helpful, therefore it was discontinued. Ritalin® caused hyperactivity and aggression, the mother thought that this medication could have been responsible for speech delay (" *stop talking*"). It was discontinued. Abilify® was prescribed to calm the child down but it was not helping, so it was discontinued. Probiotics were tried for G.I irritabilities, but were not helpful, and they were discontinued. Currently the child was on quatiapine and clonidine, which were helpful; it seemed that without them the child would not sleep, however, citalopram did not seem to help much with anxiety. The mother's opinion regarding OT, ABA, speech, and child developmental playing support group therapies was that they were not so helpful for her son. Medications' coverage was available through work insurance. Four month later, the mother said that her child was overeating because of the medications; both citalopram and clonidine doses were increased.

ASD15: the mother's commented that her son had tried risperidone (for sleeping), but it had caused weight gain and did not help; valproic acid, as mood stabilizer, made him violent and did not help; both were stopped. Abilify® (for daytime behavior) and both quatiapine and clonidine at bedtime for sleeping were used. Melatonin for sleeping had been tried but discontinued when clonidine was started (melatonin was no longer needed). OT, speech, and equestrianism therapies were tried but none was really helpful, while music therapy (which is not covered) appeared to have helped him to calm down.

ASD16: the mother comments regarding her daughter's therapies were that she had tried Biphentin but stopped because of taste problem (the child would refused to take it), Concerta® was tried, but the child refused to take it because the tablet was too big. Also OTC Gravol® was tried for sleeping, but the mother was advised to use melatonin for her daughter, rather than using Gravol® for sleeping issue.

(ii) Services/support comments

Detailed services/ support comments as follow:

ASD01: the mother felt lucky to have had access to ABA for her children at an early stage. Treatment was quite intensive with 32 hour per week per child, but the number of hours had decreased as her children got older: at school age it was 10 hors per week, and currently they were not receiving any ABA. She went on to say that St. Amant's ABA program was funded and covered by the government, but that recently the program had been overloaded, with so many cases put on the waiting list which meant at least 2 years of wait time. Since ABA and EIBI are most effective in the first 2-3 years of life, this delay in accessing the program would create a huge gap in service to help ASD children. Regarding services/support, she stated that "*Support is needed when attending a diagnostic lab to get blood work done* (her son cannot wait in turn, cannot stay in crowded places, he refuses needles), there are *no special lab services for ASD children", "visual aids should be available in the doctors' offices to inform children of what to expect during their visit*", "*Respite – it is dreadfully challenging to find trained workers who know anything about ASD"*. She added: *"Medications are often not taken in pills form (refusal to swallow med. Need help) may be a challenge for many parents"*." *Lab techs/pharmacists/secretarial staff need to know more about ASD to support needs during visits". "Need a center for ASD which provide special services and a trained team (lab tech, pharmacist, ..etc.) to understand their needs"; "medications are covered through private insurance, but not everything is covered, coverage will run out, what will happen when children get older?"*

ASD02: the mother comments and suggestions were the following: "*we don't have a lot of support, no ABA because he was diagnosed after the age which qualifies him for ABA services, and behavioural therapies if*

started earlier would be more helpful". They have access to a support group through MATC only and to a school psychologist who is only available half a day per week (the service is offered in a public school where there are many other students, which means the service in inadequate). Because ASD02 is highly functioning, he is not eligible for many services. However, the mother appreciated Children Special Services and she wished if she had contacted them earlier. She would advise ASD parents and caregivers to contact Children Special Services early because they have very good resources for special needs children.

ASD03: the mother said that *"not everything is covered", "it is difficult to manage all behaviours in an inclusive setting"*. She thinks that *"programs like the Interdivisional Program for Students with Autism (IPSA) are needed for high functioning, verbal students"*. She also added that *"parents of ASD children need guidance on how to navigate the network of different services, it would be helpful if school staff would know what MATC is offering, – family services etc. More communication is required between different services and departments (schools/MATC/children special services …etc.)"*.

ASD04: the father's specific message: *"I truly believe that our society is failing ASD children and I only see this getting worse. I do not believe our education, health and social systems are capable of meeting the increasing needs of all ASD children. It appears there is more support for the more severe cases but it is limited for children that have a more likely chance of being able to contribute to society if given the resources"*.

ASD05: the mother's specific message was *"I had asked about a part time Education Assistant (EA) during grade 2 when anxiety issues were going on and I was told that I could apply, but that we would never get one because my child was basically too functional and she was not a threat to herself or others. I asked about having a visit with a physiotherapist; she was evaluated in grade 2, but didn't see her at all in grade 3. And I watched her in physical class in grade 4 after we had asked to have her fully evaluated again!!"*

ASD06: the mother would like to see a massage service for ASD children (supported, available and covered), she thinks this would be helpful. She felt lucky because when her son was diagnosed with ASD in preschool age, parents had received right away "*good support*" from full time EA, OT and help from a service worker.

Unfortunately speech therapy was not covered but it is helpful. Expenses can be claimed on her tax return.

ASD07: the mother's specific message, which fits in both services/support and school support comments, was the following: "*children with ASD who are high functioning tend to fall through the cracks in the educational system. Schools do not see these children as having behavioural issues, therefore they do not implement necessary programming to support the social skill development required for future well-being. These children are at higher risk of depression and suicide later in life because they acknowledge their own limitations of "not fitting in". There is a lack of trained individuals available to provide respite to families".*

ASD08: the mother found ABA, OT and MATC services and school support helpful (overall satisfied from services and support).

ASD09: the mother was not satisfied, because she thought they are not enough services, not enough support and no coverage for ABA after age 3.

ASD10: parents suggested the need to have easy accessible services, easy to obtain funding for ASD children and their families and a simplified process for parents to get services and school support (e.g., pamphlets, booklets…etc.). This family was without any family support, because they did not disclose their son's condition to their extended family members.

ASD11: only comment: *"not all services are covered".*

ASD12: parents' message: "we *would like to find a behavioural specialist to deal with anxiety issues. We need to have more help with kids with autism when they become 11 or 12 years old. We don't get assistance from family services in terms of transportation issues, soon enough the child will be old for daycare. I don't feel good leaving him alone at home".*

ASD13: the foster mother informed us that all services were covered by Non-Insured Health Benefits (NIHB) and she added that a new agency which provides services for children's families was very supportive (foster mother is satisfied). The foster mother had concerns for when the child was going to be older than 18 years (e.g., continued support, safe place and work). She wished to see more appreciation and support for foster

families.

ASD14: the mother's comments and suggestions were as follows: services are not enough and need improvement. She would prefer if specialists were required to prescribe and refill ASD prescription; currently, it happens that medications are originally prescribed by a specialist (psychiatrist) but then parents have to go to family physicians/general practitioners (GP) to refill prescriptions and for follow up; sometimes these doctors know nothing about mental health medications. Furthermore, the mother added that: "*GP refills my son prescription without checking the child's health*". *In addition*, she has to go by herself (without her son) to the GP's office to renew her son prescriptions, because her son does not behave well at the doctor's office; same problem for blood work, lab and pharmacy.

ASD15: the mother informed us that they were living in a rural area and because funding for a psychologist in their area was cut, there were no more services; she was sent to MATC as an emergency case to see a specialist who gave her son a prescription. Her opinion about ASD services/support at rural area was that there were no services or poor services in rural areas (funding issue), not enough specialists, very long waiting lists, overall it was "*very hard for families there*". They moved to Winnipeg, but no more MATC services were available because of her son's school age (she is unsatisfied about ASD children services and support).

ASD16: although parents were living in rural area, they did not specify any comments about ASD services/support.

(iv) School support comments

ASD01: the mother's comments were: "*The school has had to make many accommodation to support my son's daily functioning. They provide a quiet space for him and made adjustments to his routine to reduce sensory overload*".

ASD02: the mother's comments: "*my son has a high IQ, but he is not good in terms of school performance*". She had requested to keep him in grade 8 and not to move him to grade 9 because he was not ready; the school refused. Mother felt very frustrated from the lack of school support, "*school has to be more focus on what*

these special kids need". *"The school system is not helpful for him*" and "*the school staff is bound to school protocol, they are patient with my son and they are understanding but they are restricted in what they can do by the school regulations"*.

ASD03: the mother thought, "*having* a *specialized school to support high functioning children with ASD is essential"*. Four month later, they succeeded in obtaining level 3 funding (full time) for an education assistant; it was only part time before. Parents were feeling better because of this.

ASD04: the father sent the following comment: "*Support in the form of teaching assistants is hard to come by especially for family support from social services (we have been waiting over 2 years to get support from disability services/respite). More education is needed for teachers, daycare workers, etc. on working with ASD children. Outsiders have no clue on what it is like to live with autism 24/7. It would be nice if there were social activities, i.e. sports for ASD children"*. Four month later parents finally succeeded in getting a social worker (and approval for FT EA), parents were happy about that.

ASD05: the mother commented that the school does not understand her daughter's needs and that the staff needs more training. "*More services needing improvement include*:

- *more EA support available in the school system,*
- *more access to physiotherapists/occupational therapists,*
- *more training for teachers about autism and teaching kids with ASD,*
- *classroom programs for kids to teach about peers with ASD.*

ASD06: the mother was satisfied with the school support received. In the second interview, parents were glad that the child was now attending St. Amant center (moved to new school). As per the mother: "*His symptoms are improving; he does very well with staff and students. He is now involved with current school activities"*.

ASD07: the mother said about school support that "*he has a good friends-network*", and that was the reason why she was keeping him in this specific school although she was not fully satisfied with the school support

in general. She thought that the school had a poor safety monitoring and poor programming outside the academic box.

ASD08: parents were happy about his public school's support; however, they were looking into private schools for more academic support. The mother thought that a "*version of ABA could be introduced in public schools as a regular part of the curriculum (this would be helpful to continue ABA in older children. It would be helpful to have trained ABA staff at schools) and to have programs like the one offered at his school and available at other sites, this program is a support group for your child on the spectrum, the siblings and the parents."*

The mother said that during the summer months there were no school psychologist or social worker services. In the second interview (which occurred during the school new year), ASD08's parents registered him in a new private school, because they thought he "*needed more one-to-one attention to improve his academic performance"*.

ASD09: the mother had no comments regarding school support.

ASD10: parents' suggestions were that there was a need for more one-to-one support in the school system, and for clear, specific guidelines for school services (e.g., accessible transportations for special needs children). "*It would be useful to have a website to explain the school system in details to parents of children with ASD*".

ASD11: the mother wished to see more EA and more school staff with training in ABA in order to continue ABA in older ASD children. As per the mother's own words " *He is not funded for any support, but has an EA with him for music class, it has been always been challenge (before that he had part time EA)"*.

ASD12: the mother's comments were *"Needs to have more support for families when it comes to kids anxiety. Dealing with kids 12 years and older who are old for daycare?"*

ASD13: the foster mother had no comments regarding school support.

ASD14: the mother talked about the difficulties when they were living in rural areas, she described that "*it was horrible*", "the *school was not helping at all*". They moved to Winnipeg, but she was still noticing that the school was not very helpful for her ASD child. She wished to see special-need schools back. She added: "*not all public schools are accepting special-need children (not equipped, no trained staff).* She mentioned transportation problems for ASD children (from and to school). Four month later, she moved her son to a new school, which has an autism program.

ASD15: same comments as for ASD14 regarding school support.

ASD16: the mother had no comments regarding school support.