Evidence for Effectiveness of Treatments for Autism Spectrum Disorders In Children and Adolescents

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David Pass, MD
Director, Health Resources Commission
Office for Oregon Health Policy & Research
1225 Ferry St. SE
Salem, Oregon 97301
Phone: 503-373-1629 (HRC Assistant)
Fax: 503-378-5511
Email: HRC.info@state.or.us
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Health Resources Commission and its Austism Spectrum Disorders Subcommittee – Background and membership

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

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Overview of the HRC Process and the Commission's Charge from House Bill 2918

The 2007 session of the Oregon Legislature passed House Bill 2918, relating to health care for children experiencing a pervasive developmental disorder, which it defined as "a neurological condition that includes Asperger's syndrome, autism, developmental delay, developmental disability or mental retardation". As a part of the legislation the Health Resources Commission was directed to develop a report on a medical evidence based standard of the effectiveness of treatments for autism spectrum disorders (ASDs) in children and adolescents working with the Public Employees Benefit Board, the Health Services Commission, the Department of Human Services and the Department of Education. The Commission is to report its findings and recommendations to the Seventy-fifth Legislative Assembly in the manner provided in ORS 192.245.
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In January of 2008 the Oregon Health Resources Commission (HRC) appointed a subcommittee to perform an evidence-based review of the effectiveness of treatments for Autism/ASDs in accordance with the usual methods and standards employed by the HRC. All meetings were held in public with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Medicaid Evidence-based Decision project (MED project) to develop the areas of interest for the MED project report "Behavioral and Other Interventions for the Treatment of Autism in Childhood and Adolescence." The MED project used a "Review of Reviews" approach. The process used for the MED project Review was to assess existing reviews which evaluate the quality of studies of interventions used with children and adolescents with ASD. The standard for this review is a medical scientific standard. Because of the complexity and nature of the subject involved, and methodological flaws in the existing studies due in part to these issues many of the studies do not meet the standard required to assert the highest level of evidence in relation to a specific intervention. New research projects are currently underway but time is needed for these efforts to be completed

The subcommittee accepted the MED project report as an accurate analysis of the current research based on methods that are generally accepted within the field of medical informatics for determining the efficacy of treatments and devices.

This report was prepared in response to the HRC's charge under HB 2918. The HRC report does not recite or characterize all the evidence that was discussed by the MED project report, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials.

Health Resources Commission Critical Policy:
1. "Clinical outcomes are the most important indicators of comparative effectiveness."
2. "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Clinical Overview

Brief description
Autism Spectrum Disorders (ASDs) are a group of neurodevelopmental disorders that affect a person throughout their lifespan. They include Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder, Not Otherwise Specified, as defined by the Diagnostic and Statistical Manual, IVth Ed., Text Revision (2000) [DSM IV-TR], published by the American Psychiatric Association. (Because the terms "ASD" and "autism" are often used interchangeably in discussions of these disorders, these terms are used interchangeably in this report, unless the context makes it clear that only Autistic Disorder is intended.) ASDs are viewed as a spectrum of disorders in that the core deficits common to all three diagnoses can range in severity. These core deficits are in the areas of communication and socialization, as well as patterns of restricted or repetitive behaviors. There are other symptoms and comorbidities commonly experienced by people with ASDs, which are discussed below. Thus, the clinical profile varies considerably between individuals depending on their language ability, cognitive ability and chronological age, among other things.

Functional impairments
The functional impairments associated with ASD fall within three broad domains. Owens et al. (2008) provide a comprehensive description of these which has been slightly modified for the purposes of this report.

Reciprocal social interaction - Early problems with joint attention are recognized as pivotal to the development of social problems for individuals with ASD (Charman, 2003). Joint attention involves the coordination of attention between people and objects in order to share an experience. It includes sharing emotions with another person, having empathy with others, following another's gaze or point and directing another's attention to objects or events in order to share an experience (Bakeman and Adamson, 1984). Impaired joint attention is thought to reflect a lack of basic awareness of other people's intentions (Tomasello, 1999) leading to a deficit in social reciprocity and the ability to understand other people's mental states (Baron-Cohen and Howlin, 1993) Individuals with ASD may show little interest in social interactions and often try to avoid them. The main deficit, present across all levels of functioning, is the infrequency with which individuals initiate social contact (Carter et al., 2005). Where individuals do participate in social exchanges, they are often characterized by inappropriate behavior and a lack of awareness of social rules. Interactions may also be difficult for the communication partner to sustain.

Verbal and nonverbal communication - Communication problems are usually the first symptoms to be recognized in children with ASD (Paul and Sutherland, 2005). Both verbal and non-verbal communication (such as pointing, making eye-contact, or smiling) is affected. Approximately 25% of individuals with a diagnosis of autism fail to develop any functional speech (Lord and Bailey, 2002) and these individuals have associated impairments in non-verbal communication such as gestures and facial expression. Where speech develops most children show slow or unusual development and some have a regression of spoken language skills. Those who speak fluently have problems with the

pragmatic use of language and may have unusual speech quality in terms of tone, pitch or volume. Similar to its role in social development, joint attention has also been identified as important for later language development (Charman, 2003).

Behavior - The third area of impairment lies in the presence of restricted repetitive and stereotyped patterns of behavior, interests, and activities. Repetitive behaviors include mannerisms such as hand flapping or spinning, playing with toys or objects in repetitive and sometimes inappropriate ways, or having very specific and inflexible ways of arranging items. It is also common for individuals with ASD to have very intense and unusual interests which they pursue to an obsessive degree. Individuals can become very rigid in their routines, and their obsessions can be very disruptive to the lives of the individuals and their families (Schulman, 2002).

Comorbid conditions

A number of specific physical, behavioral or psychiatric conditions are often comorbid with ASDs (Kerbeshian et al., 2001; Larkin, 1997). Individuals with ASDs may often have additional diagnoses of intellectual disability, disruptive behavior disorders, mood or anxiety disorders, and a range of medical conditions including neurological conditions (Rapin, 1997), GI difficulties, sensory disturbances and sleep disturbances.

Causes of autism

The biological causes of ASD are not known, nor are the pathways through which the underlying biology develops into the specific cluster of symptoms that must be present for a diagnosis. Given the diversity of symptoms shown by persons with ASDs, there appears to be a consensus within the scientific community that different biological causes can lead to the label ASD.

Prevalence

Currently, the exact number of people with an ASD in the US is unclear. Estimates usually depend on the method used to determine prevalence. Earlier studies estimated the prevalence of autism to be 4 to 5 in 10,000 persons (Lotter, 1966). More recently, estimates of prevalence have tended to rely on reviews of previously published studies.

Current figures show that autism occurs in all racial, ethnic and social groups equally. However, boys are three to four times more likely to be affected than girls (Ashley-Koch et al., 1999), the occurrence in siblings of those with ASDs is between 2 and 8 percent, and people with certain other developmental disorders are also more likely to have an ASD.

An increase in prevalence estimates has been observed over time, and in 2007 the CDC reported the prevalence of ASDs in the United States to be as high as 1 in 150. There are numerous reasons for this increase in prevalence, which may include: changes in study methodology; changes in diagnostic criteria; increased awareness among educational and clinical professionals leading to improved identification; diagnostic substitution; growing acceptance that autism can coexist with a range of other conditions; and a genuine rise in autism. Accurate estimates of the true prevalence are valuable in planning diagnostic and intervention services, and interest in explanations for the variability prompted a

systematic review by Williams and others to examine quantitatively the influence of study methodology and population characteristics on prevalence estimates of ASD (Williams et al., 2004). Forty studies met inclusion criteria, of which 37 estimated the prevalence of typical autism and 23 the prevalence of all ASD. The extent of variation among studies and overall prevalence were estimated using meta-analysis, and the influence of methodological factors and population characteristics on estimated prevalence was investigated using meta-regression and summarized as odds ratios (OR). This review found a wide variation in the prevalence estimates of typical autism and an increase in prevalence estimates over time. The overall estimate of prevalence across studies of typical autism using more rigorous and transparent methods was lower than estimated in previous reviews (IoM, 2004) at 7.1 per 10,000 (95% confidence interval for true prevalence 1.6 to 30.6), and estimates for all ASD were the same at 20.0 per 10,000 (95% confidence interval for true prevalence 4.9 to 82.1). These figures indicate that, on the basis of available prevalence data, the likely prevalence of ASD is 20 per 10,000 (1 in 500), but that there is a possibility that it could be as low as 4.9 per 10,000 (1 in 2041) and as high as 82.1 per 10,000 (1 in 121).

In Oregon, the only statewide measure of prevalence is the annually collected child count of students who are identified for special education under the eligibility of criteria for autism. The most recent data (December 2007 Special Education Child Count) shows that there were 7,078 students with a primary eligibility of autism out of a total statewide school enrollment of 566,067 (October 1 2007 Average Daily Membership), or 1 in 80 students. However, the regulations defining the special education eligibility of autism are different from (and somewhat broader than) the medical definition of the ASDs set forth in the DSM IV-TR (2000 American Psychiatric Association), possibly affecting Oregon's numbers compared to other states.

Available interventions
This report uses the term "intervention" and "treatment" to include services that (a) are called "treatments" and billed as health care services if performed by an appropriately licensed professional; (b) can be delivered by educators, speech language pathologists, or psychologists interchangeably (or by unlicensed individuals under their supervision) in either health care or educational settings; or (c) may be provided by people who are not licensed. Parents and providers have advocated that all three types of services be provided or reimbursed as health care or education.

The ambiguity of some services reflects a very real challenge posed by autism. The difficulty is that the biological impairments causing autism arise at or immediately after birth and impair the emotional engagement underlying all further developmental processes. The current neuroscience understanding of emotion is that it is the brain's way of assigning meaning and importance to a person's experience and is thus an inseparable part of all learning and thought, including "rational" thought. In addition, emotion also underlies all social interaction. However, health care and educational institutions have not been built on this understanding. Health care has mainly focused on gross physical aspects of the brain that can be cured by discrete, short-term interventions, because it has not until recently had a sufficiently detailed understanding of neurobiology to do anything else. Education has focused on the intellectual development of groups of

children, because it has been able to assume the social and emotional development that typically developing children have achieved before they enter school. By contrast, and of necessity, most autism interventions seek to guide individual children away from pathways of increasing dysfunction back toward the pathways followed by typically developing children across emotional, social, and intellectual development. These interventions are long-term and developmental in the same way that education is long-term and developmental, but they are also treatments in that they have almost all been devised by professionals in the health care disciplines to address a disease process. The challenges facing parents and institutions arise because for the most part health care is not structured or funded to deliver long-term developmental services and education is not structured or funded to deliver services that address the kinds of emotional and social deficits affecting children with autism.

No two people with ASDs are exactly alike and therefore there is no single treatment protocol for all individuals with ASD. Each person with an ASD needs intervention to meet his or her individual needs and the needs of the family. A wide range of psycho-educational, speech therapy, occupational therapy and physical therapy interventions are available, incorporating a mix of behavioral, developmental and education approaches. These services may be provided by professionals in a variety of settings and by or with the involvement of families. While educational, health care, and behavioral interventions continue to form the mainstay of treatment for ASD, increasing interest is being shown in the role of pharmacological treatments and complementary and alternative medicine as adjunctive therapies. Treatment of disabling symptoms such as aggression, agitation, hyperactivity, inattention, irritability, repetitive behaviors and self-injury may allow educational and behavioral interventions to proceed more effectively and may also assist individuals with ASD to function with greater independence (Posey and McDougle, 2001). Other types of treatment are also available, including sensory and auditory integration training, nutritional and hormonal interventions, and music therapy.

Treatment goals
When discussing both treatment goals and interventions, it is important to consider both (a) which symptom or symptoms an intervention is designed to address, and (b) whether the goal is to address underlying disease mechanisms.

The goals of treatment vary according to the type of intervention and the individual's strengths and weaknesses. Horner et al. (2002) propose that interventions for addressing behavioral problems in young children with autism should address prevention, functional assessment, comprehensive intervention, and systems change. Some interventions are intended to enhance cognitive, communication, and social skills while minimizing autistic symptomatology and other problem behaviors (e.g., psycho-educational programs). These approaches might be domain/impairment specific or more comprehensive. Other treatments may be intended to address the symptoms associated with ASD (e.g., pharmacological), to improve the process through which the brain organizes and interprets external stimuli (e.g., auditory integration training), or to improve general functioning (e.g., music therapy). A number of interventions are also intended to improve the experience and capacity of caregivers/parents and, indirectly, the child. The developmental approaches (floortime and RDI) seek to develop a child's

emotional engagement in order to help a child move through the social-emotional steps taken by typically developing children.

A variety of desirable short-, medium-, and long-term outcomes of treatment have been identified in the literature, including the following:

1. Those relating to the core features of ASD
    a. Communicative and social skills
    b. Repetitive and stereotyped behaviors
2. Non-core behaviors
    a. Sleep disturbance
    b. Self-injury
    c. Aggression
    d. Attention and concentration problems
    e. Sensory integration problems
    f. Cognitive ability
3. Associated medical problems
    a. Global health and function
    b. Quality of life in both school and home environments for individuals and caregivers
    c. Stress in the family
    d. Adverse events
4. Economic outcomes.

Role of Research in Evidence-Based Medicine

In order to fully appreciate the information presented in this report it is necessary to ensure that the reader understands some of the basic principles of evidence based medicine. The currently accepted definition of evidence based medicine is "The conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients." (Sackett et al. BMJ 1996; 312:71-72 [13 January]). The practice of evidence-based medicine requires integrating the following:

1. Individual clinical expertise of the practitioner
2. Best available external clinical evidence
3. Patient concerns, values, and goals.

The full integration of these three components into clinical decisions enhances the opportunity for optimal clinical outcomes and quality of life. **Evidence evaluation is only a part of the equation and must be evaluated in the context of the individual patient.** If the evidence does not apply to the patient (e.g., if the evidence applies to a different demographic group, or individuals with different manifestations of the condition or if the goals of treatment in the study group differ from the goals of the individual patient), then it will be of little value in determining a prescribed course of action. Understanding some of the unique issues related to these three key ingredients in this population will allow for a better understanding of the data presented.

In order for the reader to better understand the concept of "best evidence" it is important to know that there is a hierarchy of evidence. This refers to the amount of credibility that can be assigned to the study and the conclusions drawn by that study. While a full discussion of this is beyond the scope of this document a brief, basic discussion follows. To help with understanding the concept that some forms of evidence allow for stronger proof of conclusions reached by a study an illustrative device called an "Evidence Pyramid" is often used. An evidence pyramid is constructed with the types of studies that confer the strongest proof (stronger evidence) at the top and those that confer weaker levels of proof (weaker evidence) below. Figure 1 (page 13, courtesy of the Oregon Evidence-based Practice Center) is representative of evidence pyramids used to illustrate these points.
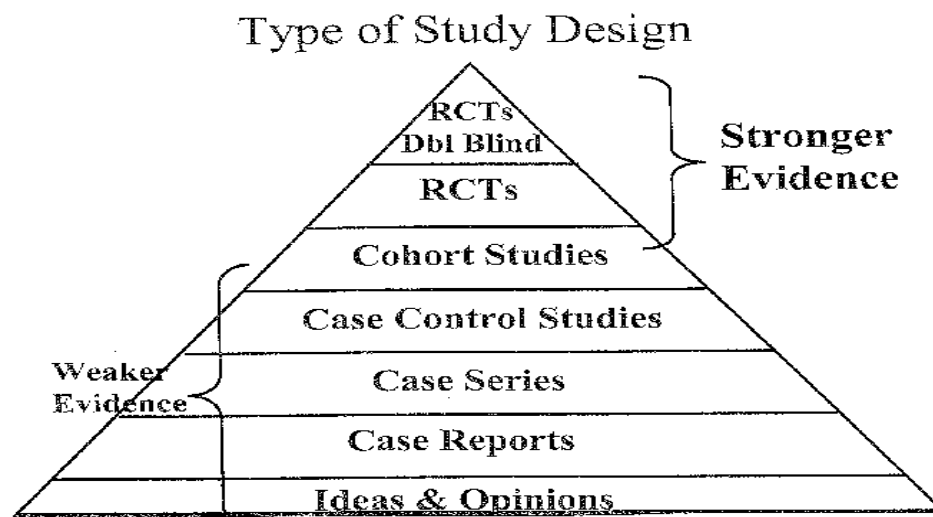
Figure 1 Evidence Pyramid

A brief explanation of each "level" follows below.

Ideas & Opinions consist of unscientific thoughts based on individual experience and observations. "Expert opinion" falls into this category. While these can form the basis for directing some scientific inquiry they have no statistical validity.

Case Series and **Case Reports** consist of collections (Case series) of reports on the treatment of individual patients or a report on a single patient (Case report). Because they are reports of cases and use no control groups with which to compare outcomes, they also have no statistical validity. It is in this category that what is referred to as "in subject" experimental design commonly used in ASD intervention research falls.

Case Control Studies are studies in which patients who already have a specific condition are compared with people who do not. They often rely on medical records and patient recall for data collection. These types of studies are often less reliable than randomized controlled trials and cohort studies because showing a statistical relationship does not mean than one factor necessarily caused the other. There can be many factors causing the result that are not apparent to the investigator.

Cohort Studies take a large population and follow patients who have a specific condition or receive a particular treatment over time and compare them with another group that has not been affected by the condition or treatment being studied. Cohort studies are observational and not as reliable as randomized controlled studies, since the two groups may differ in ways other than in the variable under study. These studies can be very useful in identifying rare adverse events.

Randomized Controlled Clinical Trials (RCTs) [Double Blind RCTs and RCTs] are carefully planned projects that study the effect of a therapy on real patients. They include methodologies that reduce the potential for bias (randomization and blinding) and that allow for comparison between intervention groups and control groups (no intervention). "Double Blind" refers to a procedure utilized in the study designed to eliminate biased results, in which the identity of those receiving a test treatment is concealed from both administrators and subjects until after the study is completed.

The "job" of a study is to show that the result of the intervention is due to the intervention itself and not to other factors that are not accounted for in the study. As one moves up the evidence pyramid, more of these unaccounted factors are removed leading to a more valid result. There are other factors that need to be taken into account when evaluating studies and one of the most important is how well the study was performed. As an example, in a randomized control study, was the group assignment truly random or how well did the study conceal the intervention from the subjects and the evaluators? If not adequately carried out, yielding a study with faulty design, the results of the study must be viewed as possibly invalid.

Historically, the concept associated with the evidence pyramid and increasing levels of validity of various study types has had an additional use. Ideas are tested using the simpler, but less valid methods as they are often less expensive and easier to perform. This "proof of concept" approach allows investigators to decide whether or not a particular intervention warrants being subjected to the more complex and often more expensive to perform studies that have higher validity to their results.

Limitations of Autism Research

Problems in the current body of research related to Autism Spectrum Disorders (ASDs) include the following:

1. Research subjects have not always been consistently or adequately described using generally accepted assessment tools.
2. There is a lack of standardization of outcomes and comparators.
3. There is uneven application of the intervention.

Since ASDs are developmental disorders, it may take years of treatment and follow-up to determine whether there is an ecologically relevant long-term improvement in outcomes. Inconsistency in the provision of services due to differences in the level of intensity, duration and expertise can also impact outcomes and uneven application of the intervention can cause difficulty in interpretation of the study results.

Consistent use of diagnostic and assessment tools is necessary to allow comparison and to promote collaboration across trial sites, which is necessary to increase sample sizes. Collection of more complete individual case data would enable individual patient data analyses and possible combination of patient's data from many studies in a meta-analysis

to help further assess these interventions. The lack of consistency makes meta-analyses of existing case studies extremely difficult and in many cases impossible to carry out. It also becomes difficult to generalize the results of a study to a broader population. With this lack of ability to generalize the results of these studies comes the inability to predict the situations in which individual methods might be more advantageous.

ASD represents a spectrum of conditions and there is much variation between individuals making larger group studies difficult and in some cases impossible to carry out. Further refinement of diagnostic criteria would allow for better definition of subgroups and would allow for better study design to determine what treatment modalities are effective for what groups of individuals. In our current state of understanding without these better defined diagnostic criteria, benefits to a subgroup might be masked by the lack of response by the overwhelming majority of treatment subjects even if larger better designed studies are done.

Much of the evidence in this field is of the "in subject" or single case study (case report) design which is regarded as one of the weakest forms of evidence. There is a need for more, and better designed research, including randomized control studies (RCTs), to assess the comparative effectiveness of a range of treatments for autism. A role exists for case-control/cohort studies because of the need to evaluate rare, multiple and/or long term outcomes. More experimental treatments need to be compared with a range of commonly used interventions that are already underpinned by some evidence.
Due to the variation in the types and severity of symptoms experienced by individuals with ASDs and the vast range of goals, there is little guidance in the research for developing treatment plans in individual cases. Defining and prioritizing goals in this population is of paramount importance. The needs of the caregiver also must be considered in this group.

Finally, it is critical to reinforce what is "critical policy" for the Health Resources Commission: **"If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."** In other words, lack of evidence of effectiveness does not equate to 'known ineffectiveness or effectiveness' of an intervention.

Conclusions

Prevalence
This review found a wide variation in the prevalence estimates of Autism Spectrum disorders (ASDs) and an increase in prevalence estimates over time.

Treatment
There is no single treatment protocol for all children with ASD. A wide range of psycho-educational programs are available, incorporating a mix of behavioral, developmental and education approaches. In addition, many individuals receive adjunctive therapies, such as pharmacological treatments and complementary and alternative medicine. Due in part to limitations in the evidence, there appears to be little consensus on how to prioritize and sequence treatments for children and adolescents with autism.

Research - effectiveness
A. Research in general in this field is limited by methodological concerns especially with regard to sample size, adequate description of subjects, and standardization of outcomes, comparators and diagnostic criteria; as well as the inherent heterogeneity of the study population.
B. There are no studies directly comparing the effectiveness of different therapies.
C. In practice, therapeutic methods are rarely used in isolation and studies to evaluate these complex interactions were not found.
D. Based on what research has shown about developmental processes in general, there is widespread acceptance that early intervention is vital to achieving early developmental benchmarks and reducing overall dysfunction. However, there are no studies seeking to determine whether effectiveness of a given treatment varies as a result of a child's stage of development at the time intervention begins, whether early intervention using that treatment confers significant *long-term* functional advantages; or the optimal duration of various interventions. In evaluating such issues, it is important to consider which stage of development a treatment targets. Treatments that target the earliest stages of emotional and social development may have a larger impact than treatments targeting later stages of development or may magnify the effectiveness of treatments that target later stages of development (such as cognition and language development). While it may be expected that recent research in the fields of developmental psychology, developmental linguistics, and neuroscience will lead to greater attention to these questions in the future, the present evidence base on these issues is lacking.
E. There is insufficient evidence to determine any comparative difference in therapeutic modalities based on subgroups.
F. Early Intensive Behavioral Interventions (EIBI) is the most widely studied intervention. Limited evidence suggests that this intervention is effective in some children but there is no method to determine which children are most likely to benefit.
G. Table 1 (page 17) summarizes the evidence of effectiveness for the included treatments.

Table 1. Evidence of Effectiveness by Intervention

Behavior analytic (applied behavior analysis)	
EIBI (Early Intensive Behavioral Interventions)	Limited evidence suggests that this intervention is effective in some children but there is no method to determine which children are most likely to benefit. EIBI includes DTT/DTL, PRT and other treatment modalities
Discrete Trial Training (DTT) Discrete Trial Learning (DTL)	Evidence suggests that DTT / DTL is less effective than other therapies for speech acquisition
Pivotal Response Training (PRT)	Very limited evidence exists for short term effectiveness in some children
Responsive Education and Prelinguistic milieu Therapy (RPMT)	Insufficient evidence to determine effectiveness
Developmental	
RDI (Relationship Developmental Intervention)	Insufficient evidence to determine effectiveness
DIR(floortime)	No Evidence found for the effectiveness of this intervention
More Than Words- The Hanen Centre	Insufficient evidence to determine effectiveness
Structured Teaching	
TEACCH	Insufficient evidence to determine effectiveness
Additional treatments	
1. Alternative and augmentative communication systems (AACs)	
General Statements	Insufficient evidence to determine effectiveness
A. Voice Output Communication Aids (VOCAs)	Insufficient evidence to determine effectiveness
B.Picture Exchange Communication System (PECS)	Insufficient evidence to determine effectiveness
2. Social skills training	
Cognitive Scripts	Insufficient evidence to determine effectiveness
Peer-Mediated interventions	Insufficient evidence to determine effectiveness
Social skills groups	Insufficient evidence to determine effectiveness
Assistive Technology for Social Skills (ATS*)*	Insufficient evidence to determine effectiveness
3. Sensory Integration Therapy (SIT)	Insufficient evidence to determine effectiveness
4. Behavior interventions for repetitive and stereotyped behaviors	
Behavior modification procedures	While some promising results have been achieved there is insufficient evidence to determine effectiveness
Teaching Alternative Activities	Insufficient evidence to determine effectiveness
Functional Communication Training	Insufficient evidence to determine effectiveness
5. Son Rise	No evidence was identified for effectiveness of this intervention
6. Minimal speech	Insufficient evidence for effectiveness of this intervention
Medication to target behavior	
Atypical antipsychotics	
General Statements	HRC class review concluded: 1. The comparative evidence in children and adolescents is poor. 2. No head-to-head trials have been reported. 3. No effectiveness trials exist.
Risperidone	Very limited evidence suggests that risperidone may be effective in improving some features of autism including irritability, repetition and

	hyperactivity and aggression
Other atypical agents (clozapine, olanzapine, quetiapine and amisulpride)	Insufficient evidence to determine effectiveness
Naltrexone	Insufficient evidence to determine effectiveness
Methylphenidate Immediate Release (MPH-IR) and Atomoxetine	Insufficient evidence to determine effectiveness
Complementary and Alternative Medicine	
1. Nutritional interventions	
Gluten and/or casein free diet	Insufficient evidence to determine effectiveness of this intervention. The Rochester study may further inform this discussion when results are available later this year
Combined B$_6$ Mg supplementation	Insufficient evidence to determine effectiveness
Folate and Vitamin B$_{12}$	No evidence found for effectiveness of this intervention
2. Secretin	Evidence suggests this therapy is ineffective
3. Sound therapies	
Auditory integration training	Insufficient evidence to determine effectiveness
Music Therapy	Insufficient evidence to determine effectiveness
4. N,N, Dimethylglycine (DMG)	Limited evidence suggests the intervention may be ineffective
5. Hyperbaric oxygen therapy (HBOT)	Insufficient evidence to determine effectiveness
6. Intravenous Immune Globulin (IVIG)	Insufficient evidence to determine effectiveness
7. Chelation Therapy	No evidence found for effectiveness of this intervention. Serious harms (death) have been reported in pediatric patients receiving edetate disodium

Recommendations

A. High quality research is needed to help determine what therapies are most effective and in what populations they are most effective.

B. In keeping with the principles of evidence-based medicine, the lack of strong evidence favoring one therapeutic modality over another and individual differences leading to a need for multiple therapies, it would appear prudent to create an ongoing, interdisciplinary panel of experts in the field to determine "Best Practices" with respect to diagnosis, assessment, and intervention. Given limited resources, defining and prioritizing goals in this population is of paramount importance. The recommendations of such a panel would be useful in assuring consistent, appropriate, cost-effective treatment of individuals identified as being at risk for or being diagnosed with an ASD.

Supporting Evidence

It is important to note that lack of evidence of effectiveness does not equate to 'known ineffectiveness' of an intervention.

In considering the reliability of the research findings addressed by this overview, it is essential to assess and take into account the methodological quality of the reviews, and to acknowledge the methodological weaknesses of many of the individual studies that they have reviewed. Despite the existence of a number of systematic reviews that performed well or reasonably well using a standardized tool for assessment of methodological quality (AMSTAR) it must be kept in mind that the primary studies upon which the reviews are based are, to a large extent, methodologically limited, particularly in relation to standardized outcomes and comparisons. More high quality studies, including randomized controlled trials, of interventions in autism are required to further evaluate effectiveness of these treatments and to elucidate which populations might benefit most from a specific intervention.

Howlin et al. have noted (2008 in press) that authors of recent reviews of interventions for children with autism have been critical of the standards of research in the field. Many interventions have attracted little evaluation and, where studies have been undertaken, methodological limitations and flaws in study design, as well as small sample sizes have often limited the conclusions that can be drawn or the reliability of their findings.

Psychoeducational interventions

A. *Behavior analytic (applied behavior analysis)*

ABA has become the most widely studied of all psychosocial interventions (Volkmar et al., 2004). However, the early work conducted by Lovaas and his colleagues has proved to be somewhat controversial and the validity of the findings has come under considerable scrutiny (Smith, 1999). Bassett et al. (2000) reviewed experimental studies of ABA, reporting that while many forms of intensive behavioral therapy (IBT) clearly benefit some children with autism, there is insufficient, scientifically valid effectiveness evidence to establish a causal relationship between a particular program and the achievement of "normal functioning" as defined by Lovass in 1987. They noted that the Lovaas study (Lovaas 1987, McEachin et al. 1992) included only 19 children in the treatment group and its finding could have been achieved by assembling a high-functioning group of autistic children. Horner (2002) concluded that interventions developed from functional assessment information appear more likely to result in significant behavior change. Campbell (2003) suggests that behavioral interventions are more effective when preceded by a functional assessment. In reaction to the widespread criticism of the early ABA studies, attempts have been made to study the effectiveness of IBT more systematically.

1. EIBI (Early Intensive Behavioral Interventions)

EIBI are the most studied interventions based on ABA and have been shown to be highly effective *for some children*, while other children make modest or little/no progress, even after lengthy periods of treatment (Howlin, 2005 *personal communication*). The only outcome variable consistently reported across studies of EIBI is IQ, derived from different tests (between and within studies). Smith, Groen and Wynn (2000) carried out a randomized control trial (RCT) of IBT and found children made greater gains than controls on educational placement, tests of IQ, visual-spatial skills and language but not on adaptive behavior. This program was effective despite being less intensive (though arguably more feasible) than other ABA interventions. Eikeseth, Smith and colleagues (2002) studied 13 children (aged 4 to 7 years) who received school-based IBT (Intensive Behavioral Therapy) for 29 hours per week plus consultation for 1 year compared to 12 children who received eclectic 1:1 therapy in school at the same level of intensity. Children were assigned to the two groups according to the availability of personnel at the time that each child was referred to the specialist school service. The IBT group demonstrated greater improvement than the control group on several measures such as IQ, language and adaptive behavior. In this study, children were not randomly assigned to groups. The children were also relatively able (all were selected to have IQ over 50), so findings may not generalize to children with lower functioning. In a recent comprehensive and systematic review, Howlin et al. (2008 in press) confirms that current evidence demonstrates the effectiveness of EIBI for some children but that gains are not universal and that it is not possible to determine which children are most likely to benefit, or what factors are likely to moderate or mediate outcomes. Furthermore, studies indicate that the largest increases tend to occur in the first 12 months of intervention; thereafter, the rate of progress appears to slow down.

Finding: Limited evidence suggests that this intervention is effective in some children but there is no method to determine which children are most likely to benefit.

2. Discrete Trial Training (DTT) / Discrete Trial Learning (DTL)

Note: Discrete Trial Learning is actually a form of ABA that can be used with several treatment outcomes in mind and is typically part of most EIBI; however for our report the only evidence that met inclusion criteria for our source document were regarding its use for speech acquisition.

In a narrative review of studies of language training, Delprato (2001) found that naturalistic approaches were more effective than Discrete Trial Training for successful speech acquisition and also that outcomes were better in terms of generalization.

Finding: Evidence suggests that DTL is less effective than other therapies for speech acquisition.

3. Pivotal Response Training (PRT)

PRT Studies have shown that, in the short term at least, children have made gains in language use and social skills following PRT and were able to use these with some flexibility, spontaneity and generalization (Koegel and Koegel, 1996). Taylor et al. (2005b) report another example of a naturalistic behavioral approach to teaching spontaneous use of language by 'systematic manipulation of establishing operations'. Its effectiveness for eliciting spontaneous initiations towards peers was studied in three children with ASD. After training, all three children were able to make spontaneous requests for desired snack items or toys from a peer, where none had readily displayed this behavior prior to training. Evidence of true generalization was limited however, and as the items of interest were always visibly present, it is difficult to qualify exactly how spontaneous the communication was. Additionally, one child experienced difficulty when he found himself in a situation where a peer refused a request. This example illustrates questionable validity of training children to use speech in the absence of the pragmatic knowledge gained through prior development of communicative intent and function (Wetherby and Prizant, 2005).

Finding: Very limited evidence exists for short term effectiveness in some children.

4. Responsive Education and Prelinguistic Milieu Therapy (RPMT)

This intervention was developed for use with children with developmental disabilities, though a recent RCT showed RPMT was successful at increasing the frequency of initiated joint attention amongst young children with ASD who had some joint attention initiation behavior to start with (Yoder and Stone, 2006).

Finding: There is insufficient evidence to determine effectiveness.

B. *Developmental*

1. RDI (Relationship Developmental Intervention)

In the preliminary evaluation study of RDI (Gutstein et al., 2007), it was demonstrated that after 18 months, children participating in the RDI program made significantly greater improvement on measures of communication and social interaction compared to a group of children whose parents had chosen not to pursue RDI training. The RDI children also had better outcomes in terms of school placement. Whilst these results suggest that RDI might be an effective intervention program for children with ASD, this study is limited by the lack of random assignment.

Finding: There is insufficient evidence to determine effectiveness.

2. DIR (floortime)

No evidence regarding effectiveness of this intervention was identified using our search criteria.
Finding: No evidence was found for the effectiveness of this intervention.

3. More Than Words - The Hanen Centre

"More than words" is one of the four mediator programs offered/developed by the Hanen Centre for caregivers of young children. It is designed for parents of children with autism spectrum disorders and is a parent focused model of language intervention.

McConachie, Randle, Hammal and Le Couter (2005) recently completed a controlled trial of this training course for parents of children with suspected ASD in the UK. According to parental report, by follow-up, children in the intervention group had significantly more words than the children in the control group. There was also a significant effect of treatment on facilitative communication behavior during parent-child interactions but this was only seen amongst the parents whose children had confirmed diagnoses of ASD from the outset. Limitations of the evidence base mean that conclusions cannot be drawn with confidence.

Finding: There is insufficient evidence to determine effectiveness.

C. *Structured teaching*

1. TEACCH
   (**T**reatment and **E**ducation of **A**utistic and related **C**ommunication-Handicapped **CH**ildren)

   Ozonoff and Cathcart (1998) conducted a non-randomized controlled study (n=22) of the effectiveness of TEACCH for young children with ASD. The program was implemented in the home over a period of 4 months. By the end of the training, children were performing significantly better on tests of non-verbal skills and cognitive abilities compared to the control group, though outcome in terms of social communication skills was not measured.

   TEACCH provides a system for organizing work tasks and is widely used in conjunction with other methods such as alternative communication. Some evaluative studies have been undertaken however these are extremely limited.

   Finding: There is insufficient evidence to determine effectiveness.

Additional treatments targeting specific areas that don't fall into the above areas

A. *Alternative and augmentative communication systems (AACs)*

1. General statements

AACs and facilitated communication interventions include Signing, Functional Communication Training, Voice Output Communication Aids (VOCAs), Pictures/symbols systems, and Verbal Behavior Interventions (VBI). As well as enabling functional communication, AAC has also been associated with a decrease in unwanted behavior and has been used successfully to replace challenging behavior in individuals with ASD (Mirenda, 1997; Charlop-Christy et al., 2002). there is little evidence that AACs can stimulate or accelerate the development of speech itself (Paul and Sutherland, 2005; Rogers, 2006). Nevertheless, AACs are widely used with children with ASD. A review of studies of facilitated communication found very little to no support for the effectiveness of these interventions from controlled studies (Mostert, 2001).

Finding: There is insufficient evidence to determine effectiveness.

2. Voice Output Communication Aids (VOCAs)

Despite their sophistication, VOCAs have been criticized for their failure to tackle the central issue of the deficit in motivation to communicate (Paul and Sutherland, 2005). Children have been successfully taught to use VOCAs to repair communicative breakdowns and to make spontaneous requests (Sigafoos et al., 2004a; Sigafoos et al., 2004b). Currently, little is known about which children might respond to VOCA training.

Finding: There is insufficient evidence to determine effectiveness.

3. Picture Exchange Communication System (PECS)

We found one RCT which examined Response Education and Prelinguistic Milieu Therapy (RPMT) compared to the Picture Exchange Communication System (PECS). The study included 36 individuals who received 1hr/wk of the intervention for a period of 6 months. The study concluded that RPMT increased the frequency of turn-taking and initiation of joint attention more than PECS, only for children who started treatment with some initiating of joint attention. PECS facilitated generalized requests more than RPMT in children with very little initiation of joint attention prior to intervention. Yoder and Stone (2005) in a systematic review concluded there was insufficient evidence to determine effectiveness of this intervention.

Finding: There is insufficient evidence to determine effectiveness.

B. *Social skills training*

1. Cognitive scripts

Results from small scale, multiple-baseline and reversal studies suggest that the use of cognitive scripts has a positive impact on children's pro-social behavior (Sasso et al., 1990), interaction skills (Goldstein and Cisar, 1992) and the frequency and duration of social interactions (Kamps et al., 1992b; Gonzalez-Lopez and Kamps, 1997). One commonly used variation of cognitive scripts is Gray's social stories (Gray and Garand, 1993; Gray, 1994, 1998). These are individually written stories that describe social cues, address the feelings and reactions of others and provide appropriate responses to specific social situations. Social stories are widely used for children with ASD, yet there is limited research evaluating their effectiveness. Case studies that have been published demonstrate variable outcomes in terms of social behavior (Swaggart et al., 1995; Lorimer et al., 2002; Bledsoe et al., 2003; Delano and Snell, 2006; Reynhout and Carter, 2006) suggesting that the technique may be more effective with some children than others. Cognitive scripts are low-cost and easy to implement and can be taught by teachers, parents, and other professionals without complex training. They can also be used in multiple settings, increasing the likelihood of skill generalization. However, the research supporting their effectiveness is limited and their comparative effectiveness to other approaches is not known.

Finding: There is insufficient evidence to determine effectiveness.

2. Peer-mediated interventions

The cumulative results from small scale multiple-baseline and reversal studies indicate that peer-mediated strategies are helpful to increase the social behavior of young children with ASD (Strain et al., 1979; Goldstein et al., 1992; McGee et al., 1992; Kamps et al., 1994; Kamps et al., 1997; Odom et al., 1999; Whitaker, 2004). In a review of studies of interventions aimed at improving social interaction, McConnell et al. concluded that studies have indicated that, under at least some circumstances, children with autism can benefit reliably from social interaction skills interventions (McConnell et al., 2002). However, the review authors note the limitations of evaluations, which raise questions about different treatment strategies and tactics, about the effects of different treatment components, and about the short- and long-term generalization effects of interventions. Limitations of the evidence base mean that conclusions cannot be drawn with confidence.

Finding: There is insufficient evidence to determine effectiveness.

3. Social skills groups

   As yet there is little empirical evidence to guide how often, with whom, in which contexts and with which curricula the groups are most successfully implemented.

   Finding: There is insufficient evidence to determine effectiveness.

4. Assistive Technology for Social Skills (ATS)

   One example of ATS, Mind Reading (Baron-Cohen et al., 2004), a DVD; has been recently evaluated. It is an interactive DVD suitable for 4 years to adulthood that is designed to teach emotions and mental state understanding (Baron-Cohen et al., 2004).
   Its effectiveness was evaluated for 8-11 year olds with high functioning ASD and Asperger Syndrome (Golan and Baron-Cohen, in preparation). Children used Mind Reading for 20 hours over a 10 week period. In comparison to matched controls who received no intervention, children significantly improved in their ability to recognize emotions. However, the skills did not generalize beyond the material included in the software or stimuli closely related to those which appeared in the program. One reason for this could be due to the unnatural nature of computerized interventions (Parsons and Mitchell, 2002). Limitations of the evidence base mean that conclusions cannot be drawn with confidence.

   Finding: There is insufficient evidence to determine effectiveness.

C. *Sensory Integration Therapy (SIT)*

In a 2003 review Tochel et. al. evaluated children with ASDs receiving Sensory Integration Therapy vs. multiple comparators. Insufficient evidence was found about the clinical effects of SIT in children with ASD.

Finding: There is insufficient evidence to determine effectiveness.

D. *Behavior interventions for repetitive and stereotyped behaviors*

To date no randomized controlled trials of these approaches have been carried out, rather, research mostly consists of case studies with varied results. These are summarized below.

1. Behavior modification procedures

   Although some case studies have shown response blocking to lead to a decrease in repetitive behavior, blocking has also been associated with lowered adaptive behavior, increases in different stereotyped behavior, and sometimes aggression (Lerman et al., 2003). Children have also successfully been taught an effective self-management procedure (see social skills section) to reinforce the absence of

their own repetitive behavior (Koegel and Koegel, 1990). Other approaches have used visual cues to prompt times when it is or is not appropriate to engage in repetitive behavior (Conroy et al., 2005).Though results from these procedures seem fairly promising, recent studies have shown that while being successful in decreasing the rate of repetitive behaviors, they can also increase the persistence of the behavior (Mace, 2000; Nevin and Grace, 2000; Ahearn et al., 2003). A meta-analysis looking at several studies of behavior modification procedures found overcorrection and punishments to be most effective, followed by rewarding alternative adaptive behaviors (Didden et al., 1997). This is a complex area, and factors controlling the effectiveness of behavior modification procedures require further systematic investigation.

Finding: While some promising results have been achieved there is insufficient evidence to determine effectiveness.

2. Teaching alternative activities

Early studies found that teaching appropriate play behaviors did lead to a reduction in the number of stereotyped movements in children with ASD (Eason et al., 1982). Later studies demonstrated that prompting interaction with the alternative activity was necessary to decrease rates of stereotyped behavior (Britton et al., 2002), and that prompting correct responses for task completion through verbal cues or visual schedules reduced stereotyped behavior and increased functional behavior (MacDuff et al., 1993; Pierce and Schreibman, 1994; Symons and Davis, 1994). In some cases these gains generalized to other tasks and settings. Piazza et al. (2000) found that the provision of alternative behaviors is most effective when the alternative item produces the same type of sensory stimulation as would be produced by the repetitive behavior. The repetitive vocalizations of children and adolescents with ASD have been significantly reduced when more appropriate forms of auditory stimulation (i.e. music) were provided (Falcomata et al., 2004). However, the constant playing of music may also interfere with necessary auditory input (e.g., instructions) and may inhibit appropriate verbalizations. Combining this approach with a reinforcement procedure as in Taylor et al. (2005a) where a four year old with ASD showed a reduction in vocal stereotypes when given access to toys that made noises. Because it was not appropriate to provide these toys all the time, they were used as reinforcement for the absence of vocalizations. This method showed significant reductions in vocalizations in a multiple base-line design and was maintained for 1 year in a classroom setting although results from this study cannot be generalized to the wider population, its findings suggest that important gains can be made by combining different approaches for the treatment of stereotyped behavior. This suggestion is somewhat supported by the results of a case study showing the success of a combination of reinforcing other behaviors, self monitoring and discrimination training in reducing repetitive body rocking in a 12 year old boy with ASD (Shabani et al., 2001).

Finding: There is insufficient evidence to determine effectiveness.

3. Functional Communication Training (FCT)

This is a technique that was initially developed to reduce problem behavior. Keen et al., (2001) studied the implementation of FCT in a classroom environment, reporting how behaviors in four young children with ASD were successfully replaced with alternative forms of communication. The success of this approach appears to depend on careful and thorough training of implementers. The authors emphasized the need for further study of the generalization and maintenance of communication skills taught in this way.

Finding: There is insufficient evidence to determine effectiveness.

E. *Son Rise*

Although this program makes strong claims about improving social communication, and even 'curing' ASD, this is based on anecdotal reports rather than controlled research. There are no controlled studies of Son-Rise.

Finding: There is insufficient evidence to determine effectiveness.

F. *Minimal speech*

Minimal speech (Potter and Whittaker, 2001) can also be considered as a naturalistic approach to speech training. Unlike discrete trials or incidental teaching, it focuses primarily on changing the communication behavior of the teacher or parent (rather than the child) in order to encourage the child to initiate communication. Adults are encouraged to speak less, introduce pauses and remove prompts to induce children to communicate spontaneously. Where necessary, nonverbal prompts are used and single words are modeled. This approach is similar to the communicative style used by many people who work with individuals with ASD and Potter and Whittaker (2001) describe anecdotal evidence of the efficacy of this intuitive approach. As yet, no empirical evidence of its effectiveness exists (Paul and Sutherland, 2005).

Finding: There is insufficient evidence to determine effectiveness.

Medication to target behavior

Pharmaceutical agents are frequently used in this population to address specific symptoms and comorbid conditions. Commonly used medications include stimulants, atomoxetine, alpha 2 agonists, SSRI's, SNRI's, buproprion, buspirone, lithium, antiepileptics, lamotrigine, atypical antipsychotics and typical antipsychotics. Available evidence for treatment of individuals diagnosed with ASDs is discussed below.

A. *Pharmacological treatments in general*

Broadstock et al. (2007) undertook a systematic review of the effectiveness of pharmacological treatments in general in managing ASD in adolescents and adults. Only five double-blind, randomized controlled trials were eligible for appraisal. All had small sample sizes (mean = 30) and brief treatment duration of no more than 12 weeks. The paucity of trials and their methodological limitations means that there is only preliminary evidence about the short-term efficacy of a few drug treatments for this age group. There was also a lack of reliable data reported on drug safety profiles.

B. *Atypical antipsychotics*

1. HRC class review

The HRC conducted an in-depth review of Atypical antipsychotics (Health Resources Commission August 2008) in collaboration with the Drug Effectiveness Review Project (DERP, a multi-state consortium funding comparative effectiveness reviews of pharmaceutical agents) in 2008. The information from that review is presented below.

The HRC review found that there are no head-to-head trials of atypical antipsychotics in children and adolescents with autism or disruptive behavior disorders that met inclusion criteria. Indirect evidence for efficacy in these populations is available from 10 trials comparing risperidone with placebo, 1 trial comparing olanzapine with placebo, and 1 trial comparing olanzapine with haloperidol. Five studies were conducted in children with disruptive behavior disorders and 7 in children with autism or other pervasive developmental disorders. No trial was considered an effectiveness trial. Quetiapine for children with autism or disruptive behavior disorders has been studied only in short-term observational studies, or in studies that are not fully published. These studies did not meet inclusion criteria for this HRC review.

Three recent systematic reviews on atypical antipsychotic use in children and adolescents have been conducted. These reviews included trials of olanzapine and risperidone in children with autism or disruptive behavior disorders. A Cochrane Review included risperidone in autism spectrum disorder only. Only the Cochrane Review performed a quantitative synthesis. Compared with placebo, risperidone showed improvements on several subscales of the Aberrant Behavior Checklist: Irritability (mean difference compared with placebo -8.09, 95% CI -12.99 to -3.19), Social withdrawal/lethargy (-3.00, 95% CI -5.03 to -0.97), Hyperactivity (-8.98, 95% CI -12.01 to -5.94), Stereotypy (-1.71, 95% CI -2.97 to -0.45), and Inappropriate speech (-1.93, 95% CI -3.79 to -0.07). Compared with placebo, the relative risk of improvement on the CGI was 4.83 with risperidone (95% CI 2.21-10.59), but there was significant heterogeneity in the 3 trials reporting this outcome.

The other systematic reviews analyzed the data qualitatively only. Both concluded that risperidone and olanzapine were effective for behavioral symptoms in autism and disruptive behavior disorders, but neither review found evidence that 1 drug was superior to the other. The conclusions that could be drawn from these reviews were limited by the small number of available trials, small sample sizes within trials, and lack of long-term follow-up data.

a. *Effectiveness*

The evidence for the effectiveness of atypical antipsychotics in children with autism is limited, with only 5 placebo-controlled trials of risperidone, 1 trial comparing olanzapine with placebo, and 1 small pilot study (N=12) comparing olanzapine with haloperidol. One study was unusual in that it measured relapse after discontinuation of risperidone. All of the studies demonstrated improvement with risperidone or olanzapine on at least some outcome measures. No conclusions about comparative efficacy of olanzapine and risperidone can be drawn from this body of evidence because the trials differed in their populations (age, diagnosis), durations (6 weeks to 6 months), and outcome measures.

b. *Short-term safety*

Withdrawals overall and withdrawals due to adverse events were low. The most common adverse event reported in studies in children was weight gain. Increases ranged from 2.7 kg to 5.7 kg. Weight increase was significantly greater with olanzapine and risperidone than placebo and, in 1 trial, greater with olanzapine than haloperidol. In a Cochrane meta-analysis of 2 trials of risperidone in children with autism, the mean difference between placebo and risperidone in weight gain 1.78 kg (95% CI 1.15-2.41).

Other adverse events, including extrapyramidal symptoms, were infrequent in short-term trials. Prolactin levels were measured in 3 risperidone trials. Significant increases from baseline were found in all the risperidone groups. No clinical signs of hyperprolactinemia were reported during these short-term trials. There were no clinically significant changes in electrocardiograms or QTc abnormalities. In 1 6-week trial, the risperidone group showed a temporary increase in heart rate (11 beats per minute) compared with the placebo group during the first 2 weeks of treatment. Thereafter, heart rates returned to normal.

c. *Longer-term safety*

Evidence about the longer-term safety of risperidone in children with autism and other pervasive developmental disorders is available from three 6-month placebo-controlled trials and from uncontrolled, open-label extension studies of short-term efficacy trials . There is no information about longer-term safety of olanzapine or other atypical antipsychotics in children and adolescents.

Few serious adverse events were reported in these studies. Weight gain ranged from 2.1 kg to 5.6 kg in studies up to 1 year. In a 2-year open-label extension study of 14 children, mean weight gain was 8.09 kg.

An observational study examined the safety of atypical antipsychotics in children using prescription event monitoring data from New Zealand. The study included 420 children aged 2 to 15 years who were prescribed an atypical antipsychotic between April and July 2003. Forty-three percent were diagnosed with disruptive behavior disorders and 34% with pervasive developmental disorders. During the treatment period, 93% of the children were prescribed risperidone, 8% quetiapine, 2% olanzapine, and 1% clozapine. Adverse events were identified in 131 children (31% of the cohort). Of 352 clinical adverse events, 331 occurred in children taking risperidone and 15 in children taking quetiapine. In patients taking risperidone, the incidence of weight increase was 7.4%. Two reports of diabetes mellitus were identified, 1 new onset case and 1 worsening of pre-existing diabetes. Of 275 patients who returned a questionnaire, 8% reported discontinuing medication for an adverse reaction and 11% discontinued because the medication was no longer needed. Overall, 73 of 275 patients discontinued medication (26.5%).

d. *HRC conclusions for antipsychotic use in Autism Spectrum Disorders*

The HRC report concludes:
1. The comparative evidence in children and adolescents is poor.
2. No head-to-head trials have been reported.
3. No effectiveness trials exist.

2. Risperidone

   The most commonly used drug in this class is risperidone, with over two-thirds of the published cases concerning this agent. Barnard et al. (2002) found only one study involving risperidone that used a randomized, double-blind and placebo-controlled cross-over design. The findings of this study, in combination with the case studies and uncontrolled prospective trials, produce preliminary evidence that risperidone may be effective in treating overall autistic behaviors. Specifically, risperidone's most pronounced effects appear to be in the realms of hyperactivity, aggression and repetitive behavior. To a lesser extent, risperidone was found to be beneficial at improving mood states such as depression, irritability and nervousness. There was little evidence for improvement in social functioning, language or cognition. Adverse events included extrapyramidal side-effects (which generally did not lead to withdrawal from the study), as well as weight gain, transient sedation, possible chemical hepatitis, possible seizures, galactorrhea, amenorrhea and gynecomastia. Patients discontinued risperidone (and olanzapine) due to weight gain after as little as 14 weeks, although it was noted that weight increases on risperidone stabilized between 2 and 6 months (Perry et al., 1997). It is not clear whether the disproportionate number of side-effects associated with risperidone reflect a true difference or is an artifact of the greater number of reports, particularly case studies.

A subsequent well-conducted Cochrane review of risperidone, undertaken by Jesner et al. (2007), identified three randomized controlled trials, and undertook a meta-analysis of these. This review found some evidence of the benefits of risperidone in irritability, repetition and social withdrawal, but the authors pointed out that these need to be considered against the adverse effects, the most prominent being weight gain. Extra-pyramidal effects were experienced in 27.5 percent of the risperidone group compared to 12.8 percent of placebo in one trial (Shea 2004). In RUPP (Research Units on Pediatric Psychopharmacology) 2002 parents did report extra-pyramidal side effects, of which tremor was most common. Jesner et al. conclude that risperidone can be beneficial in some features of autism irritability, repetition and hyperactivity, but again acknowledge that there are still only limited data available from studies with small sample sizes. Risperidone is now FDA approved for the treatment of behavior problems in individuals with ASDs. The FDA approval is for "Treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years."

Finding: Very limited evidence suggests that risperidone may be effective in improving some features of autism including irritability, repetition, hyperactivity, and aggression.

3. Other atypical agents (clozapine, olanzapine, quetiapine, and amisulpride)

The majority of these reports are based on case series and, currently, there is inadequate evidence to inform practice reliably. Well designed randomized trials are needed. Barnard et al. identified one study that used amisulpride in a randomized, double-blind cross-over (with bromocriptine) manner. Amisulpride was reported to have a 'moderately positive' effect; however, it is not clear in which behavioral domains this applies. This agent was less well tolerated than the others, although all adverse reactions were reported to be of 'mild' intensity. Barnard et al. found that, with the exception of quetiapine, the drugs were all relatively well tolerated, with the most common adverse reactions being sedation and weight gain. Sedation tended to be transient and was alleviated over time or with a reduction in dose. Weight gain was a cause for withdrawal from studies in patients taking olanzapine as noted above in the section on risperidone.

The literature reviewed here does not allow a comparison of the efficacy of atypical and typical antipsychotics in the autistic population.

Finding: There is insufficient evidence to determine effectiveness.

4. Naltrexone

Three case reports, 8 case series, and 14 clinical studies were identified by ElChaar et al., (2006). They found that Naltrexone has been used most commonly at doses ranging from 0.5 to 2 mg/kg/day and was found to be predominantly effective in decreasing self-injurious behavior. Naltrexone may also attenuate

hyperactivity, agitation, irritability, temper tantrums, social withdrawal, and stereotyped behaviors. Patients may also exhibit improved attention and eye contact. Transient sedation was the most commonly reported adverse event. Small sample size, short duration, and inconsistent evaluative methods characterize the available research.

Finding: There is insufficient evidence to determine effectiveness.

5. Methylphenidate Immediate Release (MPH-IR) and Atomoxetine

The Health Resources Commission (June 2008) in cooperation with the Drug Effectiveness Review Project (DERP) recently completed a comprehensive look at medications used for ADHD and in that review looked at medications used in patients diagnosed with PDD/ASD. The information from that report is reproduced below.

Few, short-term placebo-controlled trials of either MPH IR [Research Units on Pediatric Psychopharmacology Autism (2005)] or atomoxetine (Arnold L 2006) have explored treatment of ADHD symptoms in children with PDD/ASD. Collectively, findings from these trials suggest that atomoxetine and MPH IR are both feasible options for ADHD symptom control in children with PDD/ASD. Compared to placebo, atomoxetine and MPH IR significantly improved scores on the Hyperactivity subscale of the Aberrant Behavior Checklist (ABC-H), which was the primary efficacy measure in the most recent trials. Although encouraging, compared to effects in typically developing children, atomoxetine and MPH IR may be less efficacious in reducing ADHD symptoms and associated with more frequent adverse effects in children with PDD/ASD.

Due to heterogeneity in methods and patient populations, these trials provided inconclusive evidence regarding the indirect comparative efficacy and adverse effects of atomoxetine and MPH IR.

Finding: There is insufficient evidence to determine effectiveness.

Complementary and alternative medicine

A. *Nutritional interventions*

1. Gluten- and/or casein-free diet

The committee is aware of the Rochester trial, a 5-year study to evaluate the effectiveness of the Gluten-Free/Casein-Free diet in patients with ASD, which has not as of yet reported results. Results are due in 2008 and will be included in the report if available at the time it is released.

Trials of gluten- and casein-free diets were reviewed by Millward et al. (2004). Extensive literature searches identified only one randomized control trial of gluten and/or casein free diet as an intervention to improve behavior, cognitive and social functioning in individuals with autism. The trial was small scale, with only 10 participants in the treatment group and 10 participants in the control group. Results indicate that a combined gluten and casein free diet may reduce some autistic traits. Though the results of one small trial adds weight to the existing anecdotal evidence for a gluten and/or casein free diet for autism, there is not yet sufficient evidence for clinicians to advise the use of such diets in cases of autistic spectrum disorder.

Finding: There is insufficient evidence to determine effectiveness of this intervention. The Rochester study may further inform this discussion when results are available later this year.

2. Combined B_6 Mg supplementation

Trials of combined B_6-magnesium were reviewed by Nye and Brice (2005). A total of three included studies were identified (total n=33) and, of these, only one study reported adequate data for analysis. Results were inconclusive and sample sizes were small. Therefore the use of vitamin B_6 for improving the behavior of individuals with autism cannot currently be supported.

Finding: There is insufficient evidence to determine effectiveness.

3. Folate or Vitamin B_{12} supplementation

No evidence was found for the effectiveness of Vitamin B_{12} or Folate supplementation in the treatment of ASD that met inclusion criteria.

Finding: No evidence was found for effectiveness of this intervention.

B. *Secretin*

A review by Williams et al. (2005) of thirteen randomized studies found no evidence that single or multiple dose intravenous secretin is effective across a range of outcomes, and concludes that as such it should not currently be recommended or administered as a treatment for autism.

Finding: Evidence suggests this therapy is ineffective.

C. *Sound therapies*

1. Auditory integration training

A review by Sinha et al. (2004, 2006) identified a total of nine small studies that met the reviews inclusion criteria, but failed to provide clear evidence for the

effect of auditory integration therapies on autism. A review by Tochel (2003) concluded that weak evidence exists from limited research suggesting that auditory integration training is unlikely to be more effective than unprocessed music in children with ASD. Further research is required to determine the effectiveness of sound therapies. In the absence of evidence, the treatment must be considered experimental and care must be taken not to risk hearing loss.

Finding: There is insufficient evidence to determine effectiveness.

2. Music therapy

Gold et al. (2003) identified three small studies which examined the short-term effect of brief music therapy interventions for autistic children. Music therapy was superior to "placebo" therapy with respect to verbal and gestural communicative skills, but it was uncertain whether there was an effect on behavioral outcomes. The included studies were encouraging, but of limited applicability to clinical practice. Ball (2004) also concluded that insufficient existed to determine the effects of music therapy. A review by Whipple (2004) was assessed as lower quality using AMSTAR criteria and will therefore not be considered.

Finding: There is insufficient evidence to determine effectiveness.

D. *N,N, Dimethylglycine (DMG)*

We identified two studies of DMG in the literature. The first was a placebo controlled trial (PCT) of 37 age and gender matched children between 3 and 11 years of age with a diagnosis of "autism or pervasive developmental disorder." Children were assessed before and after treatment with the Autism Research Institute's recommended dosing schedule (treatment duration was for 4 weeks) on the Vineland Maladaptive Behavior Domain and the Aberrant Behavior Checklist (Kern et al. 2000). The second study was a smaller study (n=8) of low dose DMG using a double blind, placebo controlled, crossover study. All participants were male ranging from 4 years of age to 30 years of age and evaluation was by multiple scales including the Campbell-NIMH rating scale (Bolman and Richmond 1999). Both studies showed no statistical difference between groups.

Finding: Limited evidence suggests the intervention may be ineffective.

E. *Hyperbaric Oxygen Therapy (HBOT)*

Two studies were identified which addressed HBOT in autism. The first study (Rossignol 2006) is a retrospective case study of 6 individuals. Individuals were allowed to continue all previous therapies and to add new therapies during the study, there was no blinding of the parents who were the evaluators so the results could be due to a variety of factors and the study is severely underpowered. The second study by the same authors (Rossignol 2007) is an open label pilot study of 18 children ranging from 3 years of age to 16 years of age who received HBOT treatment. There were two intervention groups 1.3atm at 24% oxygen and 1.5atm at 100% oxygen. Parents rated change by using the Aberrant

Behavior Checklist-Community (ABC-C), Social Responsiveness Scale (SRS) and the Autism Treatment Evaluation Checklist (ATEC). While both treatment groups showed statistically significant improvement in SRS and ATEC scales (but not the ABC-C) the results must be viewed very cautiously as the study has significant methodological flaws. Specifically, lack of blinding of the evaluators (parents), lack of random assignment to treatment group, no control groups or placebo control, lack of adequate sample size and multiple other possible confounding variables (such as increased interactions due to the study protocol).

Finding: There is insufficient evidence to determine effectiveness.

F. *Intravenous Immune Globulin (IVIG)*

Five studies were identified that addressed the use of IVIG in individuals diagnosed with ASDs. In a study (Gupta 1996) of 25 individuals (ages 3-12 years, 17 male, 8 female) a subset of 10 individuals (ages 4-6 years 9 male, 1 female) were treated with IVIG (400mg/kg) and rated on an arbitrary 4 level system of minimal, modest, marked and striking improvement. Five individuals showed minimal improvement, four showed marked improvement and one showed striking improvement. There is no data given for the other subjects and it is unclear if any control group was utilized. Method of selection for IVIG administration is not defined and although it is stated that "in a few" individuals discontinuation of therapy resulted in regression, then improvement with reinstitution of therapy. However, details are not given. Two individuals were reported to be attending regular school but no baseline data are reported with respect to functionality so it is not possible to determine whether this is due to the IVIG treatment.

In a review Gupta (2000) discusses the results of the 1996 study as well as the results of the Plioplys study (below) and mentions that he had undertaken a prospective trial of IVIG in 24 children ages 3-7 years; however this study was not found using our search criteria.

In a study of 10 children (ages 4-17 years) Plioplys (1998) administered IVIG in varying doses (200-400mg/kg) over a six week period. In five children there was no detectable change in behavior during the treatment program, in four children there was mild improvement in attention span and hyperactivity. None of the parents of those four individuals felt the results warranted continuation, and in one individual there was almost total amelioration of symptoms over the treatment period. After the treatment period this individual returned to his previous state over a five month time period. There was a baseline physical and neurological examination done but there is no mention of formal evaluation of the individuals on any standardized measure related to ASDs.

An open pilot study (DelGiudice-Asch 1999) evaluated seven children (ages 3 ½-6 years 6 male, 1 female) with the diagnosis of autism established using the Autism Diagnostic Interview (ADI) and DSM IV criteria (APA, 1994) who were enrolled in full day educational programs for autistic children whose parents requested IVIG therapy based on anecdotal reports. The children were evaluated on the Ritvo-Freeman Scales (1-5), CYBOCS, NIMH autism, NIMH OCD, and CGI Scales after 6 months of IVIG therapy

(400mg/kg monthly). There were no statistically significant changes on any of the scales utilized.

The final study reported in a letter to the editor (Niederhofer 2003) was of ten male children (ages 4.2-14.9 years) in a double blind placebo controlled crossover study. The children were treated with IVIG (400mg/kg) in a single dose design. The children were evaluated by parents and teachers on the Aberrant behavior Checklist (ABC) and were also evaluated by clinicians. There was a statistically significant improvement for the treatment group on the ABC for irritability, hyperactivity, inadequate eye contact, and inappropriate speech when compared to the placebo group. There were no significant differences found between groups in the clinician evaluations. There was a statistically significant increase in drowsiness and decreased activity in the treatment group compared to the placebo group.

The studies in this intervention utilize differing doses (time and mg/kg) and evaluation criteria making comparison difficult. This may help partially explain the conflicting results. Methodological concerns in some of the studies and small sample sizes limit the usefulness of the data.

Finding: There is insufficient evidence to determine effectiveness.

 G. Chelation therapy

There was no evidence found that met inclusion criteria for the effectiveness of this intervention. However, there have been reports of deaths when children were given edentate disodium due to hypocalcemia (Brown et al. 2006, Sinha et al. 2006).

Finding: No evidence was found for effectiveness of this intervention. Serious harms (death) have been reported in pediatric patients receiving edentate disodium.

Comprehensive Intervention Programs

Comprehensive treatment approaches as defined by Rogers and Vismara (2008), are those that address the core deficits in autism, including language, social cognition and play. A broad review of studies of comprehensive treatment approaches conducted by Rogers and Vismara, supports the conclusions drawn by others that young children with autism, as a group, benefit from comprehensive treatment approaches (Rogers and Vismara, 2008 in press). Rogers and Vismara note results suggesting accelerated developmental gain and significant increases in language and communication skills, increases in IQ, and reduction in severity of autism symptoms in groups receiving these treatment programs. However, the authors acknowledge that lack of comparative studies make it impossible at this time to determine which comprehensive approach is best or to determine whether findings from studies are likely to generalize to different ethnic groups than those studied.

Comparative Effectiveness/Efficacy

In practice, there is often a degree of overlap between many of these interventions and, indeed, some treatments, such as Applied Behavior Analysis (ABA), form the basis of other more comprehensive packages. It is therefore not necessarily appropriate for comparisons to be made between these interventions as they are not intended to be used in isolation in children with Autism Spectrum Disorders (ASD). For example, both ABA and Discrete Trial Training/Learning (DTT/DTL) are likely to make up part of any special education or practical intervention program for children with ASD and will be found, for example in programs such as TEACCH (**T**reatment and **E**ducation of **A**utistic and related **C**ommunication-Handicapped **CH**ildren), and many other early intervention programs.

Psycho-educational and behavioral treatments
Howlin et al. (2008 in press) described the comparisons made by individual studies of Early Intensive Behavioral Interventions (EIBI). Studies employed various comparisons, including: less intensive or minimum therapy; standard, eclectic and special schooling; parent-directed EIBI; and 'mix of therapies'. However, Howlin concluded that studies have not established the comparative effectiveness of EIBI and alternative, high quality autism-specific interventions such as specialist pre-school provision.

The review by White (2004) of Cognitive Behavioral Therapy (CBT) reported studies that compared CBT to no treatment, sensory integration therapy, play therapy, speech and language therapy, medication, and 'other therapies'. The lack of reliable controlled studies made it impossible to compare effects of CBT with other interventions.
In the case of the reviews of parent related treatments, one review (Diggle et al., 2002) identified one study that demonstrated that intensive intervention (involving parents, but primarily delivered by professionals) was associated with better child outcomes on direct measurement than were found for parent-mediated early intervention. A second review (McConachie, 2007) found very few research studies of adequate design and concluded that none of the studies of early parent-mediated intervention provide evidence of effectiveness.

There were no comparative studies identified for pharmacological treatments, nutritional treatments, intravenous secretin, and sensory and auditory integration treatments.
The review by Ball (2004) of music therapy was designed to include studies that used a range of comparisons, including no treatment, functional training, sensory integration, cognitive behavioral therapy and other psychological therapies, play therapy, medication, speech and language therapy, alternative therapies. However, the authors concluded that insufficient evidence exists on the effect of music therapy and that it is not possible to assess comparative effectiveness from existing research.

Subgroups

In this section, we have looked for literature that discusses subpopulations that may respond uniquely to a particular intervention. Our findings are discussed below:

IQ and language acquisition
All of the evidence in this section is from the literature evaluating EIBI (Early Intensive Behavioral Interventions).

Smith et al. (2002) found that children with autism actually made less progress in EIBI than those with Pervasive Developmental Disorders-Not Otherwise Specified (PDD-NOS). Several studies indicate that IQ and language levels are also important predictive variables (Harris and Handleman, 2000). However, although some studies conclude that the more cognitively impaired children made least progress; this is not invariably the case (Koegel, 2000). It is also important to note that the original EIBI studies specifically excluded children with an IQ below 30. Magiati (2005) examined the relationship of factors such as age at intervention, mental age, language and severity of autism to outcome. Sixteen early intervention studies using ABA (9 of these were from EIBI replication sites) were reviewed, together with the data from Magiati's own study. It was not possible to identify any factors that were consistently related to outcome. There is an indication from *some* studies that children who are younger, more able and show fewer autistic features at the start of treatment may have a better outcome but these findings were not consistent across studies.

Atypical antipsychotics
Having found risperidone more effective than placebo, McDougle et al. (1998) analyzed treatment responsiveness in adults and found no relation to diagnostic sub-types (autistic/PDD), sex, treatment setting, age, full-scale IQ, dose or baseline measures of repetitive behavior. There was also no correlation with olanzapine response and age, IQ, dose, repetitive or self-injurious behaviors, or overall severity of autism (Potenza et al., 1999). However, these sub-group analyses are based on very small numbers.

Age at treatment initiation
It is widely accepted that early intervention is beneficial in helping children with Autism Spectrum Disorders (ASDs) to develop essential skills in the earliest years, and in preventing the escalation of later behavioral difficulties. However, evidence that early pre-school intervention does confer significant long-term advantages compared with later therapy is limited. Several studies report positive outcomes for children enrolled in intervention programs (of a variety of different kinds) prior to 4 years of age (Anderson et al., 1987; Birnbrauer and Leach, 1993; Sheinkopf and Siegel, 1998) but there are few systematic comparisons between children of different ages.

Lovaas (1993) noted that the younger children in his intervention studies did much better than those who were older, but again there was no direct comparison between children who began therapy at the recommended age (i.e. around 2) and those who started later, at around 4 or 5 years of age. Fenske, et al. (1985) conducted a small scale comparative study of 9 children under 5 years old, and 9 children over 5 years old when therapy

began. Six children in the early treatment group went on to main stream school, compared with only one child in the later intervention group. This was despite the fact that the younger children were actually in therapy for a shorter period of time. However, school placement was the only outcome measure utilized and the children were not matched prior to the onset of treatment. Thus, there is no way of assessing the impact of other variables (e.g., pre-existing differences, IQ or language ability) on outcome. Harrison and Handleman (2000) found that children admitted to a specialist pre-school program before the age of 3½ were more likely to be placed in a regular educational classroom than those who were aged on average 4½ years of age when pre-school intervention began. However, outcome, in terms of later educational placement was also significantly related to pre-intervention IQ. The relative importance of IQ vs. age was not explored.

Other studies have failed conclusively to demonstrate that age at start of therapy is a crucial mediating variable. For example, Eikeseth et al. (2002) reported positive effects of the UCLA YAP (UCLA Young Autism Project) model with children up to 7 years of age. Gabriels et al. (2001) found that differences in outcome were not related to age at which treatment began, and there was only a marginal relationship with time in therapy. Luiselli et al. (2000) did find a difference in outcome between children commencing treatment before and after the age of 3 years (n=8 in each group) but statistical analysis indicated that it was total time in intervention, (12 months for the <3 age group, compared with 7 months in the 3+ group) not age per se that was the main predictor of change. Stone and Yoder (2001) also found that the amount of time in language therapy from the age of 2 tended to predict outcome at 4.

In summary, while early intervention is used widely and accepted by many experts in the field, there is no good experimental evidence that therapy beginning at 2 years of age leads to greater progress *in the longer term* than intervention beginning at 3 or 4 or 5 years of age.

Comorbidities

In addition to the triad of impairments, children with Autism Spectrum Disorders (ASDs) may also show associated problems such as co-morbid anxiety (Muris et al., 1998; Gilliott et al., 2001), hyperactivity (Frazier et al., 2001; Goldstein and Schwebach, 2004) and sensory problems (Keintz and Dunn, 1997), to name a few. A randomized controlled trial has been done to show that cognitive behavior therapy can be effectively used to treat anxiety in children with Asperger's syndrome (Sofronoff et al., 2005). However, in general, from the sources identified for this overview it was not possible to locate any information that addressed this question.

Summary

Autism is a lifelong disorder that can be devastating for an individual and their family. The majority of the research studies looking at treatment interventions have significant limitations and most show insufficient evidence; however, the lack of evidence of effectiveness does not equate to 'known ineffectiveness' of an intervention. For this reason, experts in autism have relied on "Best Practices" and guidelines. Consensus in the autism community agrees that early intervention with active engagement of the child at least 25 hours per week is important. (AAP clinical report, Management of Children with Autism Spectrum Disorders, Nov. 2007) This requires trained individuals to conduct the therapeutic intervention. Availability of trained individuals may be lacking in any one geographic area which could affect the provision of services there. It is also important to remember that this is an evolving field and new research is being done every day, but obviously takes time to complete. Likely many of the therapies reviewed here have effectiveness in certain children with ASDs. More research with randomized controls needs to be done to be certain that these therapies are effective.

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Glossary of Treatment Modalities

Alternative and augmentative communication systems (AAC) - AAC are tools that allow children with little or no functional speech to communicate, such as sign language, picture exchange systems, and voice output communication aids. They also have the potential to increase an individual's capacity to spontaneously initiate functional communication (Romski and Sevcik, 2005). Duchan (1987) emphasized the importance of teaching the pragmatic aspects of communication, irrespective of the form used: by enabling independent communication (e.g., by using an AAC system), the 'power' of one's own behavior to direct the behavior of another in order to reach a goal is explicitly demonstrated.

Applied Behavioral Analysis (ABA) - Applied Behavior Analysis (ABA) means the systematic application, at any time during the child's day, of behavioral principles to modify behavior. The primary technique employed by ABA is operant conditioning. ABA is a general approach to intervention which is readily adaptable to many different circumstances and settings and can therefore be used in ASD, either as a technique for teaching specific skills, or to form the basis of a comprehensive treatment program in combination with a range of other psycho-educational and behavioral strategies.

Assistive Technology for Social Skills - Assistive technology (AT) can be used for a wide range of skills, including social interaction, communication, daily living skills, and independence (see Golan et al., 2006 for a comprehensive review). AT can be as simple as a visual schedule or as complex as a virtual reality system and can vary from low to high tech levels. It can be used to teach social rules, emotion understanding and pro-social behaviors. AT may be particularly useful for children with ASD due to the systematic nature of the technology. Individuals with ASD show good and sometimes superior skills in 'systemizing' compared to people without ASD (Baron-Cohen, 2006). Systemizing is the drive to analyze and build systems in the world in order to predict events. AT might be able to harness this affinity to help children cope with areas of difficulty such as social functioning. Low-tech AT includes social scripts, social stories and visual schedules that have been discussed earlier. Mid-tech AT includes battery operated or electricity-based products. One example of teaching social skills using mid-tech AT is using video-tapes of TV programs (e.g., 'Saved by the Bell' and 'Third Rock from the Sun') to model appropriate and inappropriate social interactions (Myles and Southwick, 2005). High-tech AT usually involves specifically designed computer software. This has several advantages for children with ASD. Computer environments are predictable and free from social demands, children can work at their own pace and level and lessons can be repeated until they are understood. Computerized rewards can also be used to maintain motivation. Software is commercially available to teach various social skills.

Atypical Antipsychotics - The atypical antipsychotics (licensed medication for the treatment of acute and chronic psychoses) address both 5-HT and DA function and may have less frequent extrapyramidal symptoms (EPS), such as the antipsychotic-related dyskinesias, than typical antipsychotics (the 5-HT2 antagonism has been hypothesized to underlie the lower incidence of EPS). Atypical antipsychotics are termed 'atypical'

because of their tendency to cause fewer unwanted motor side effects than the typical antipsychotics. Antipsychotic drugs generally tranquilize without impairing consciousness and relieve psychotic symptoms (BNF 2003). Examples of this class of drug include amisulpride, clozapine, olanzapine, quetiapine and risperidone. They are a mainstay treatment for schizophrenia and other psychoses. They act by blocking dopamine receptors (D2) in the brain, and may also affect cholinergic, alpha-adrenergic, histaminergic and serotonergic receptors.

Auditory Integration Training - AIT involves listening to electronically modified music for varying periods of time and is intended to ameliorate auditory processing defects and improve concentration. For example, Berard's method of AIT involves 10 hours of listening to electronically modified music delivered byheadphones during 2 half-hour daily sessions over 10 days. The AIT device uses filtering to dampen peak frequencies to which the individual is "hypersensitive" and delivers sounds modulated by random dampening of high and low frequencies and intensities (Berard 1993).

Behavior modification procedures – Some repetitive behaviors might be learned and maintained because of the perceptual, tactual or auditory stimulation they provide (Lovaas et al., 1987). They can be thought of as having 'self-reinforcing' properties, i.e. the performance of the behavior itself provides sensory stimulation which is inherently rewarding (e.g., repetitive vocalizations provide auditory stimulation). Behavior such as this is very resistant to change, and interventions have tried punishments such as time out (Harris and Wolchik, 1979), overcorrection (Azrin et al., 1973; Wells et al., 1977; Maag et al., 1986) or even a slap (Koegel and Covert, 1972; Koegel et al., 1974) and electric shock (Risley, 1968) to try and reduce the frequency of these behaviors. More recent case studies have looked at the effects of response blocking (e.g., by physical restraint) in the extinction of repetitive behavior, however, results are not simple.

Chelation therapy - Chelation therapy uses organic compounds (such as dimercaptosuccinic acid, DMSA or edetate disodium) to remove heavy metals from the body. Medically, chelation therapy is used in treating patients with heavy metal poisoning (especially lead, arsenic or mercury intoxication). Some individuals believe that autism is caused by high levels of toxic heavy metals that cause damage to the brain.

Cognitive Behavioral Approaches - Cognitive behavioral interventions can be used to teach children with ASD to monitor and manage their own behavior through changing their perceptions, self-understanding and beliefs, based on the assumption that change is most likely to occur when a child is actively involved in their own behavior management. For this reason, cognitive behavioral methods are most appropriate for children with some degree of self-understanding and self- awareness and are therefore mostly used with school-age children and adolescents with high- functioning ASDs or Asperger's Syndrome. Self monitoring and self-management techniques are two cognitive behavioral approaches used. Children are taught to be aware of certain target behaviors and their impact on learning. They are then trained to monitor their behavior with the goal of reducing maladaptive behavior or increasing the frequency of appropriate behavior and alternative strategies. The need for external reinforcement from adults or peers is reduced as the child becomes more independent in their behavior management (Quinn et al.,

1994). For example, children can be trained to use a wrist counter to tally the frequency of their appropriate verbal responses to other people's social initiation. Frequencies are converted to points and exchanged for rewards though in general, these rewards should be quickly faded (Koegel et al., 1992).

Use of cognitive scripts is another method used to teach appropriate interaction in a wide variety of contexts to verbal school-age children. These might be more appropriate for children with lower levels of self-understanding and self awareness. A cognitive script is a repeated script of a familiar event that children with ASD can use in a particular set of circumstances, for example, to initiate a social interaction. Scripts are first written by an adult and their correct use is modeled by adults or through videotapes. The child rehearses the script before using it in appropriate contexts. The child's reliance on the script is gradually faded until it is not used at all (Odom et al., 1992). One commonly used variation of cognitive scripts is Gray's social stories (Gray and Garand, 1993; Gray, 1994, 1998). These social stories are individually written stories that describe social cues, address the feelings and reactions of others and provide appropriate responses to specific social situations.

Developmental Individual Relationship-based (DIR) - See "Floortime

Discrete Trial Training (DTT) / Discrete Trial Learning (DTL) - Discrete Trial Training/ Learning refers to a behaviorally-based instruction routine in which a particular trial may be repeated several times in succession, several times a day, over several days (or even longer) until the skill is mastered. It is used where a stimulus is presented to the child and the child is rewarded for correct responses. Therapists give short and clear instructions with carefully planned prompts and reinforce closer and closer approximations to correct responses.

Early Intensive Behavioral Intervention Program (EIBI) - EIBI (the program described by Lovaas and his colleagues; Lovaas, 1987; McEachin et al., 1993) is a prescriptive, manualized program in which children are required to spend at least 40 hours a week in therapy, which is supervised (but not conducted) by experienced behavioral consultants. Lovaas strongly recommends that intervention should start at around two years of age and last for two years or more. When the program is followed consistently major improvements in cognitive ability (30 IQ points or more) have been reported. Lovaas and his group also claim that around 47% of participants become "indistinguishable" from their normally developing peers. However, despite the impressive claims, it is important to recognize that the number of children involved in the original Lovaas study was very small, only 19 cases. Moreover, in a recent re-analysis of the data published by Lovaas and his colleagues, Shea (2004) suggests that the reports of children reaching normal developmental status (defined as having an IQ in the normal range and attending mainstream school without assistance) are not substantiated. Thus, among the "best-outcome" individuals described by Lovaas, abnormality scores on the Clinical Rating Scale (McEachin, 1987) were well above those of normal controls. Shea (2004) notes that Lovaas himself (Lovaas, 2000) has recently indicated that the rate of "normal functioning" amongst children involved in the UCLA-YAP is probably closer to 20%; the rate amongst children attending less closely monitored EIBI programs is around 10%. Shea (2004) also examined outcome in 8 additional research investigations of children

receiving EIBI Although most reported positive gains these were consistently much less in magnitude than those reported in the initial studies (Lovaas, 1987; McEachin et al., 1993), even though some of the authors, such as Smith and McEachin, had been involved in the original research. Shea calculated that the average proportion of participants in those studies who were reported as achieving "normal functioning" was closer to 6% (range 0-27%). Moreover, in all these studies there is generally a dearth of information on wider aspects of children's social functioning or the severity of autistic features etc. Scores on formal cognitive and achievement measures and school placement tend to be the principal outcome measures used. EIBI uses DTT/DTL , PRT and other treatment modalities. The program is also sometimes known as the UCLA Young Autism Project or YAP.

Floortime - Developed by child psychiatrist Stanley Greenspan, Floortime is a treatment method and a philosophy for interacting with autistic children. It is based on the premise that the child can increase and build a larger circle of interaction with an adult who meets the child at his current developmental level and who builds on the child's particular strengths.
The goal in Floortime is to move the child through the six basic developmental milestones that must be mastered for emotional and intellectual growth. Greenspan describes the six rungs on the developmental ladder as: self regulation and interest in the world; intimacy or a special love for the world of human relations; two-way communication; complex communication; emotional ideas; and emotional thinking. The autistic child is challenged in moving naturally through these milestones as a result of sensory over- or under-reactions, processing difficulties, and/or poor control of physical responses. In Floortime, the parent engages the child at a level the child currently enjoys, enters the child's activities, and follows the child's lead. From a mutually shared engagement, the parent is instructed how to move the child toward more increasingly complex interactions, a process known as "opening and closing circles of communication." Floortime does not separate and focus on speech, motor, or cognitive skills but rather addresses these areas through a synthesized emphasis on emotional development. The intervention is called Floortime because the parent gets down on the floor with the child to engage him at his level.

Functional Communication Training – FCT identifies behaviors that are potentially communicative and seeks to replace them with functional, socially acceptable forms of communication (Durand and Merges, 2001). Acts that might be identified as having communicative potential include challenging behavior, aggression and self-injury as well as idiosyncratic behaviors such as hand flapping. FCT begins with the assessment of these behaviors in order to understand their function and seeks to replace them with forms that are more adaptive and easier to interpret, thus enabling children to become more effective communicators.

Gluten or casein free diets - It has been suggested that peptides from gluten and casein may have a role in the origins of autism and that the physiology and psychology of autism might be explained by excessive opioid activity linked to these peptides. Research has reported abnormal levels of peptides in the urine and cerebrospinal fluid of persons with autism. If this is the case, diets free of gluten or casein, or both, should reduce the

symptoms associated with autism, and appropriate diets would facilitate learning, social behavior, cognitive functioning and communicative skills in individuals with autism.

'More Than Words' - The 'More Than Words' program (Sussman, 1999) focuses on enhancing parents' ability to observe their child, to engage in structured routines of joint attention, and to make use of everyday opportunities to teach communication and social skills.

Music Therapy - Music therapy has been defined as "a systematic process of intervention wherein the therapist helps the client to promote health, using musical experiences and the relationships that develop through them as dynamic forces of change" (Bruscia 1998, p. 20). Central techniques in music therapy include free and structured improvisation, songs, and listening to music. The processes that occur within musical improvisation may help people with autism spectrum disorder to develop communicative skills and their capacity for social interaction. Musical interaction in music therapy, in particular musical improvisation, is sometimes understood and described as a kind of non-verbal and pre-verbal language which enables verbal people to access pre-verbal experiences, enables non-verbal people to interact communicatively without words, and enables all to engage on a more emotional, relationship-oriented level than may be accessible through verbal language (Alvin 1991). Listening to music within music therapy also involves an interactive process that often includes selecting music that is meaningful for the person (e.g., relating to an issue that the person is occupied with) and where possible reflecting on personal issues related to the music or associations brought up by the music. For those with verbal abilities, verbal reflection on the musical processes is often an important part of music therapy (Wigram 2002).

Naltrexone - An increased production of b-endorphin (b-EP) or alterations in the system's normal activity may exist in autism, flooding the immature brain with β-endorphins may delay the maturational manufacturing of encephalins, causing the brain of autistic children to remain in the infantile stage of development, preventing it from becoming responsive to sensory and social environment. As a result, there has been growing interest in the use of opiate antagonists for the treatment of behavioral symptoms in children with ASDs. Naltrexone is primarily an opiate antagonist with minimal agonist activity. As with the other medications mentioned previously, naltrexone is not currently approved by the Food and Drug Administration for the management of AD-associated symptoms and behaviors.

Occupational therapy - Occupational therapy can be used to help people with autism find ways to adjust tasks and conditions that match their needs and abilities. The aim is to maintain, improve, or introduce skills that allow an individual to participate as independently as possible in meaningful life activities.
Through occupational therapy methods, a person with autism can be aided. both at home and within the school setting by teaching activities including dressing, feeding, toilet training, grooming, social skills, fine motor and visual skills that assist in writing and scissor use, gross motor coordination to help the individual ride a bike or walk properly, and visual perceptual skills needed for reading and writing. Such help may include finding a specially designed computer mouse and keyboard to ease communication, or

identifying skills that build on a person's interests and individual capabilities. Occupational therapists may also do many of the same types of activities as physical therapists. Occupational therapy is usually part of a collaborative effort of medical and educational professionals, as well as parents and other family members. Through such collaboration a person with autism can move towards the appropriate social, play and learning skills needed to function successfully in everyday life.

Peer-Mediated Interventions - In peer-mediated interventions typically-developing peers are trained by an adult to initiate, elicit, prompt and reinforce social behaviors for children with ASD. The adult then prompts the peers to interact with the child during specific activities or play sessions.

Pharmacological treatments - Most biological research has emphasized serotonin (5-hydroxytryptamine [5-HT]) and dopamine (DA) neuronal dysfunction in the pathophysiology of autism. Consequently, medications that target these systems, such as the atypical antipsychotics and the selective serotonin reuptake inhibitors (SSRIs), have been particularly investigated as potential treatments.

Physical therapy - Physical therapists design activities and exercises to build motor control and improve posture and balance. For example, they can help a child who avoids body contact to participate in activities and games with other children.

Pictures/symbols systems – Pictures and photographs are widely used with individuals with ASD to communicate needs or to introduce new activities.

Picture Exchange Communication System (PECS) – This is a type of augmentative and alternative communication technique where individuals with little or no verbal ability learn to communicate using picture cards. Children use these pictures to "vocalize" a desire, observation, or feeling. These pictures can be purchased in a manualized book, or they can be made at home using images from newspapers, magazines or other books. Since some people with autism tend to learn visually, this type of communication technique has been shown to be effective at improving independent communication skills, leading in some cases to gains in spoken language.

Pivotal Response Training (PRT) - Incidental language teaching takes place during normal activities and focuses on children's own initiated behavior. PRT is one example of this approach and teaches cue responsiveness during everyday activities capitalizing on children's preferred items or activities and motivation to communicate (Koegel, 1995).

Relationship Development Intervention Program (RDI) - Based on the work of psychologist Steven Gutstein, RDI focuses on improving the long term quality of life for all individuals on the spectrum. The RDI program is a parent- based treatment that focuses on the core problems of gaining friendships, feeling empathy, expressing love and being able to share experiences with others. Gutstein reported that individuals on the autism spectrum seemed to lack certain abilities necessary for success in managing the real life environments that are dynamic and changing. He calls these abilities dynamic

intelligence and describes six aspects (Emotional Referencing: The ability to use an emotional feedback system to learn from the subjective experiences of others; Social Coordination: The ability to observe and continually regulate one's behavior in order to participate in spontaneous relationships involving collaboration and exchange of emotions; Declarative Language: Using language and non-verbal communication to express curiosity, invite others to interact, share perceptions and feelings and coordinate your actions with others; Flexible thinking: The ability to rapidly adapt, change strategies and alter plans based upon changing circumstances; Relational Information Processing: The ability to obtain meaning based upon the larger context. Solving problems that have no "right-and-wrong" solutions; Foresight and Hindsight: The ability to reflect on past experiences and anticipate potential future scenarios in a productive manner).

Repetitive and Stereotyped Behaviors - The term repetitive behavior refers to a large variety of behaviors, interests and activities, all of which could be the result of different underlying brain functions (Militerni et al., 2002). These occur in many conditions, but are particularly common in ASD (Schreibman, 1988; Carcani- Rathwell et al., 2006). All are characterized by a high degree of repetition, rigidity, invariance and inappropriateness (Turner, 1999). Some researchers have loosely classified repetitive behaviors into lower level and higher level categories. Lower level repetitive behaviors include repetitive motor behaviors (e.g., hand flapping or body rocking), whereas higher level repetitive behaviors include circumscribed interests (such as fans or serial numbers), resistance to change and rigid routines and rituals (Turner, 1999). Though both types of repetitive behavior are present in individuals with ASD, stereotyped movements and vocalizations have been the focus of most intervention as these tend to cause the most significant problems with daily life, learning and adaptive functioning (Risley, 1968; Koegel and Covert, 1972).

Responsive Education and Prelinguistic Milieu Therapy (RPMT) – Responsive Education and Prelinguistic Milieu Therapy (RPMT; Yoder and Warren, 2002) incorporates a parent training component with an incidental teaching approach in one-to-one sessions between a child and trainer. The therapy sessions teach children to initiate joint attention and increase their prelinguistic intentional communication behaviors. Prompts, gradually faded, are used to elicit behaviors such as pointing to request (i.e. imperative communication). Modeling is used to teach children to initiate shared attention with another person such as directing another's attention to a different item using gaze switching or pointing (i.e. joint attention).

Secretin - Secretin is a hormone produced by the small intestine that helps in digestion. Its role in gastrointestinal function is well described. There is a postulated role in decreasing immune responses in the gut lumen. Secretin receptors have also been demonstrated in the brains of rats and pigs (Freier 1981), but the exact role of secretin and of its mechanism of action in the central nervous system has not been determined. The behavior of rats after secretin infusion has been studied (Charlton 1983). When injected intracerebrally, secretin decreased the locomotor activity of rats. However, there is uncertainty about the role of secretin in the human brain. Currently, the FDA approves a single dose of secretin only for use in diagnosing digestive problems.

Selective Serotonin Reuptake Inhibitors (SSRIs) - SSRIs (e.g., fluoxetine, fluvoxamine, sertraline and paroxetine) are currently recommended for the treatment of obsessive obsessive-compulsive disorder, depression and anxiety disorders. Because of their efficacy in treating obsessive-compulsive symptoms, their better side effect profile compared with tricyclic antidepressants (fewer antimuscarinic and cardiotoxic effects), and the fact that they address the serotonin function, SSRIs have been receiving increasing attention as a potential treatment for the highly prevalent repetitive thoughts and behaviour associated with PDDs.

Sensory Integration Therapy - Sensory Integration is the process through which the brain organizes and interprets external stimuli such as movement, touch, smell, sight and sound. Autistic children often exhibit symptoms of Sensory Integration Dysfunction (SID) making it difficult for them to process information brought in through the senses. Children can have mild, moderate or severe SID deficits manifesting in either increased (hypersensitivity) or decreased (hyposensitivity) to touch, sound, movement, etc. For example, a hypersensitive child may avoid being touched whereas a hyposensitive child will seek the stimulation of feeling objects and may enjoy being in tight places. The goal of Sensory Integration Therapy is to facilitate the development of the nervous system's ability to process sensory input in a more typical way. Through integration the brain pulls together sensory messages and forms coherent information upon which to act. SIT uses neurosensory and neuromotor exercises to improve the brain's ability to repair itself. When successful, it can improve attention, concentration, listening, comprehension, balance, coordination and impulsivity control in some children.

Social skills groups – Social skills groups are suitable for children and adolescents with high functioning ASD and Asperger Syndrome, and allow members to practice skills in reasonably naturalistic environments. They have been used as part of the TEACCH program since its conception and may be used in clinic-based or school-based settings. Several authors have outlined suggestions about how to run social skills groups, and for whom they are most suitable (Mesibov, 1986; Krasny et al., 2003). However, as yet there is little empirical evidence to guide how often, with whom, in which contexts and with which curricula the groups are most successfully implemented. School-based social skills interventions have focused on increasing a broad range of skills in short and frequent classroom sessions (Matson et al., 1991; Kamps et al., 1992a), or have focused on teaching specific skills such as eye-contact and play with preferred toys (Koegel and Frea, 1993; Baker et al., 1998). Both approaches have shown improvements in skills taught in small-scale, multiple baseline studies. Some group studies have focused on teaching theory of mind skills to children with ASD. Theory of mind is the ability to understand other people's mental states, and is thought to be a core deficit in ASD (Baron-Cohen, 1995). Teaching individuals this skill has resulted in improvement on experimental tasks compared to controls, but not in natural settings (Hadwin et al., 1997) or on ratings of social behaviors (Ozonoff and Miller, 1995). Social skills groups carried out in clinic settings are generally delivered less frequently, for a longer amount of time (usually 1hr) and usually without the presence of typically developing peers.

Son Rise - The 'Son Rise' program (Kaufman, 1994) is a home-based program where parents are regarded as the key 'therapists'. Families attend workshops mostly run in the

USA, often lasting many weeks, where they are trained to engage with their children through energetic and exciting interactive play sessions and to get involved with their child's repetitive behaviors. The program undoubtedly provides an optimistic and empowering approach for parents, however there are considerable financial and emotional commitments required. Whilst the program makes strong claims about improving social communication, and even 'curing' ASD, this is based on anecdotal reports rather than controlled research.

Speech/language therapy - This can help people with autism improve theirgeneral ability to communicate and interact with others effectively, as well as develop their speech and language skills. Speech and language therapists may teach non-verbal ways of communicating and may improve social skills that involve communicating with others. They may also help people to better use words and sentences, and to improve rate and rhythm of speech and conversation. The communications problems of autistic children vary to some degree and may depend on the intellectual and social development of the individual. Some may be completely unable to speak whereas others have well developed vocabularies and can speak at length on topics that interest them. Any attempt at therapy must begin with an individual assessment of the child's language abilities by a trained speech and language pathologist. Though some autistic children have little or no problem with the pronunciation of words, most have difficulty effectively using language. Even those children who have no articulation problems exhibit difficulties in the pragmatic use of language such as knowing what to say, how to say it, and when to say it as well as how to interact socially with people. Many who speak often say things that have no content or information. Others repeat verbatim what they have heard (echolalia) or repeat irrelevant scripts they have memorized. Some autistic children speak in a high pitched voice or use robotic sounding speech.

*TEACCH (**T**reatment and **E**ducation of **A**utistic and related **C**ommunication-Handicapped **CH**ildren)* - TEACCH is a special education program that is tailored to the autistic child's individual needs based on general guidelines. It dates back to the 1960's when doctors Eric Schopler, R.J. Reichler and Ms Margaret Lansing were working with children with autism and constructed a means to gain control of the teaching setup so that independence could be fostered in the children. What makes the TEACCH approach unique is that the focus is on the design of the physical, social and communicating environment. The environment is structured to accommodate the difficulties a child with autism has while training them to perform in acceptable and appropriate ways. Building on the fact that autistic children are often visual learners, TEACCH brings visual clarity to the learning process in order to build receptiveness, understanding, organization and independence. The children work in a highly structured environment which may include physical organization of furniture, clearly delineated activity areas, picture-based schedules and work systems, and instructional clarity. The child is guided through a clear sequence of activities and thus aided to become more organized. It is believed that structure for autistic children provides a strong base and framework for learning. Though TEACCH does not specifically focus on social and communication skills as fully as other therapies it can be used along with such therapies to make them more effective.

Teaching Alternative Activities – Rather than seeking to reduce unwanted behaviors it is also possible to teach and prompt other appropriate activities as alternatives to undesirable behavior, and so expand the behavioral repertoire of the individual.

Verbal Behavior Intervention (VBI) – VBI is often seen as an adjunct to Applied Behavior Analysis (ABA). Though both are based on theories developed by Skinner there are differences in concept. Skinner postulated that language could be grouped into a set of units, with each operant serving a different function. The primary verbal operants are what Skinner termed echoics, mands, tacts, and intraverbals. The function of a mand is to request or obtain what is wanted. For example, the child learns to say the word "cookie" when he is interested in obtaining a cookie. When given the cookie, the word is reinforced and will be used again in the same context. In a VB program the child is taught to ask for the cookie anyway he can (vocally, sign language, etc). If the child can echo the word he will be motivated to do so to obtain the desired object. There is an emphasis on "function" of language. Another operant, "intraverbals" describes verbal behavior that is under the control of other verbal behavior and is strengthened by social reinforcement. Intraverbals are the way people engage in conversational language. They are responses to the language of another person, usually answers to "wh-" questions. If you say to the child "I'm baking..." and the child finishes the sentence with "Cookies," that's an intraverbal fill-in. Also, if you say, "What's something you bake?" (with no cookie present) and the child says, "Cookies," that's an intraverbal (wh- question). Intraverbals allow children to discuss stimuli that aren't present, which describes most conversation and is a goal of Verbal Behavior Intervention.

Vitamin B_6-Magnesium (Mg) - The use of mega-vitamin intervention began in the 1950s with the treatment of schizophrenic patients. Pyroxidine (vitamin B_6) was first used with children diagnosed with "autism syndrome" when speech and language improvement was observed in some children as a result of large doses of B_6. A number of studies attempted to assess the effects of vitamin B_6-Magnesium (Mg) was found to reduce undesirable side effects from B_6) on characteristics such as verbal communication, non-verbal communication, interpersonal skills, and physiological function, in individuals with autism.

Vitamin B12 and Folate – The use of these Vitamins in treatment of ASDs is based on research showing that in some "psychiatric" (depressive and psychotic symptoms as well as epileptic individuals) patients there was a reduced level of serum Folate and B_{12} (Edwin et al.,1965; Pauling, 1974; Carney, 1967). Studies showed some improvement with folate supplementation but not with B12 supplementation (Carney and Sheffield, 1970; 1978).

Voice output communication aids (VOCAs) – Voice output communication aids (VOCAs) are portable communication devices that can produce synthesized or recorded speech output. Such devices vary in complexity: they can be simple single-switch units or may hold thousands of communication messages.