



**Evidence for Effectiveness of Treatments
for Autism Spectrum Disorders
In Children and Adolescents
Executive Summary
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Introduction and Method

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 as directed by HB 2918. The review was conducted 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. There were five additional areas of interest in the local community, not covered in the MED report, that were identified by the subcommittee as commonly used enough to warrant investigation by the subcommittee. A formal search for information on these areas was conducted with assistance from the Oregon Health Sciences University medical library staff. Articles identified that met inclusion criteria were evaluated by the subcommittee. The subcommittee report was reviewed and approved by the full Commission in Nov, 2008.

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. 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.

Evidence Discussion

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. 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. The most recent data from Oregon reveals an incidence of 1 in 80 students. However, the method used by Oregon to identify individuals with ASDs differs from other States; possibly affecting Oregon’s prevalence estimates compared those other States.

Interventions

No two people with ASDs are exactly alike and therefore there is no single treatment protocol for all individuals with ASD. For a large number of these interventions the

evidence was insufficient to allow us to draw any conclusion about their effectiveness or ineffectiveness. Full discussion of these interventions can be found in the body of the full report. For the purposes of this document we will limit discussion to the entities where we could make some determination. A summary of all interventions is included in Table 1 on page 6 of this summary and is also included in the full report.

Psychoeducational Interventions

A. Behavior Analytic (Applied Behavior Analysis/ ABA)

1. EIBI (Early Intensive Behavior Interventions)

EIBI are the intensive application of various interventions. These include Discrete Trial Training (DTT), Pivotal Response Training (PRT) and other modalities. 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. There is a large body of case study/series literature supporting this approach. Randomized control trials (RCTs) have been attempted, but most have been methodologically flawed to some extent. There is no method to determine which children will benefit, and the majority of the benefit appears to occur in the first twelve months of treatment.

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/ Discrete Trial Learning (DTT/DTL)

The only study that met inclusion criteria for this section was for speech acquisition which is not a common use of this intervention. This study found that for speech acquisition there were other methods that were more successful.

Finding: Evidence suggests that DTT 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 .

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

B. Medications to Target Behavior

1. Atypical Antipsychotics

A report by the Health Resources Commission (August 2008) concluded:

- The comparative evidence in children and adolescents is poor.
- No head-to-head trials have been reported.
- No effectiveness trials exist.

2. Most Common Atypical Antipsychotic, Risperdone

The most commonly used drug in this class is the atypical antipsychotic risperidone. 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.

C. Complementary and Alternative Medicine

1. Secretin

A review of 13 studies found no evidence that single or multiple dose intravenous secretin is effective across a range of outcomes.

Finding: Evidence suggests this therapy is ineffective.

2. N,N, Dimethylglycine (DMG)

We identified two studies of DMG in the literature. Both studies showed no statistical difference between groups.

Finding: Limited evidence suggests the intervention may be ineffective.

3. 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.

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

4. Age at Treatment Initiation

While it is widely accepted that early intervention is beneficial, evidence that early pre-school intervention confers significant long-term advantages compared with later therapy is limited.

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. Many individuals receive adjunctive therapies, such as pharmacological treatments and complementary and alternative medicine interventions. 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 differences between individuals in 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 important in 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.

Table 1 summarizes the evidence of effectiveness for the report’s included treatments:

Table 1 Evidence of Effectiveness by Intervention

<i>Behavior analytic (applied behavior analysis)</i>	
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
<i>Developmental</i>	
RDI (Relationship Developmental Intervention)	Insufficient evidence to determine effectiveness
DIR(floor time)	No Evidence found for the effectiveness of this intervention
More Than Words- The Hanen Centre	Insufficient evidence to determine effectiveness
<i>Structured Teaching</i>	
TEACCH	Insufficient evidence to determine effectiveness
<i>Additional treatments</i>	
<i>1. Alternative and augmentative communication systems (AACs)</i>	
General Statements	Insufficient evidence to determine effectiveness
A. Voice Output Communication Aids (VOCAs)	Insufficient evidence to determine effectiveness
B. Picture Exchange	Insufficient evidence to determine effectiveness

Communication System (PECS)	
<i>2. Social skills training</i>	
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
<i>3. Sensory Integration Therapy (SIT)</i>	
	Insufficient evidence to determine effectiveness
<i>4. Behavior interventions for repetitive and stereotyped behaviors</i>	
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
<i>5. Son Rise</i>	
	No evidence was identified for effectiveness of this intervention
<i>6. Minimal speech</i>	
	Insufficient evidence for effectiveness of this intervention
Medication to target behavior	
<i>Atypical antipsychotics</i>	
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
<i>Naltrexone</i>	
	Insufficient evidence to determine effectiveness
<i>Methylphenidate Immediate Release (MPH-IR) and Atomoxetine</i>	
	Insufficient evidence to determine effectiveness
Complementary and Alternative Medicine	
<i>1. Nutritional interventions</i>	
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
<i>2. Secretin</i>	
	Evidence suggests this therapy is ineffective
<i>3. Sound therapies</i>	
Auditory integration training	Insufficient evidence to determine effectiveness
Music Therapy	Insufficient evidence to determine effectiveness
<i>4. N,N, Dimethylglycine (DMG)</i>	
	Limited evidence suggests the intervention may be ineffective
<i>5. Hyperbaric oxygen therapy (HBOT)</i>	
	Insufficient evidence to determine effectiveness
<i>6. Intravenous Immune Globulin (IVIg)</i>	
	Insufficient evidence to determine effectiveness
<i>7. Chelation Therapy</i>	
	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.

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.