November 5th, 2013

Dear Dr Coffman,

I am sorry I cannot attend the November 7th session of the committee, due to previous professional commitments that could not be changed.

First, I want to make a few comments following the first committee session that I attended.

I. ABA: definition and terminology

In reviewing this issue, the committee should really appreciate that 'ABA' is an umbrella term used with different meanings in the literature and by professionals as well as advocates. ABA refers to a well-established theory laid out by the psychologist Skinner decades ago. It is a well accepted theory that has shown applications in different experimental methods to investigate human behavior and in different treatment approaches used in various populations. To give an example, ABA principles are used in various cognitive-behavioral therapies (CBT) employed to treat anxiety and depressive syndromes in both children and adults. They play a core role in some therapeutic techniques comprised in these interventions (but not necessarily for all aspects of these treatments) and are widely regarded to be effective guiding principles to engineer efficacious therapies in psychiatry. Having said that, ABA refers to the underlying theoretical framework, and not to a specific technique or a particular treatment. In CBT used to treat depression, behavioral activation is one technique that is inspired by the ABA theoretical framework, but it is not referred to as 'ABA'. Ditto for many validated behavioral techniques (exposure, exposure-response prevention, etc..) used to treat anxiety or other similar conditions.

Thus, the term 'ABA' in itself does not define a specific treatment technique nor even a treatment package that can be reviewed directly for its efficacy unless the treatment technique (derived from the ABA theory) is fully specified or the treatment package entirely defined for its technical components, the sequence in which they are applied and the procedures that are used to modify their implementation and measure their effect.

To give a simple (and probably simplistic) analogy, evaluating the efficacy of ABA in autism would be like evaluating the efficacy of 'Chemotherapy in cancer' or of 'Antibiotherapy in infections'. As for ABA, there is evidence that chemotherapy and antibiotics can work in principle but evaluating their efficacy requires detailed knowledge about which cancer/infection to treat, which compound to use, which dose to employ, and procedures for adjusting dose to response etc…

II. 'ABA': An approach to recommend?

All professionals in the field have witnessed with much satisfaction the changes in the approach to the treatment and education of children with ASD that occurred when the first ABA studies emerged in the 1980-90s. In fact, a first pivotal change occurred in the field in the 1970s when Schopler and his TEACCH approach developed in the early 1970s, showing in empirical studies that children with autism could

learn and improve, provided that they were educated in classrooms and with approaches that would take into account their specific difficulties as well as maximize their strengths, and that a close collaboration would occur between parents and professionals. TEACCH became the point of reference for families and professional associations worldwide for 30 years. The claims by Lovaas that a (quasi-) cure could result from his approach shifted the attention on ABA that now plays the role that TEACCH once had. The initial study by Lovaas was ingenious, creative and audacious, but the claims went beyond what the design of the study should have allowed (lack of randomization, lack of blindness of assessment, very crude outcome measures (eg attends a 'normal classroom'..)), as has been documented in the professional literature. The replication by his follower Smith in 2000 provided much more scientific grounding to the approach (with welcome modifications to the treatment approach), and tempered the assessment of its efficacy (see below). Meanwhile, other investigators had developed techniques that were also grounded, partially at least, in ABA theory although the packaging of the treatment had different names: Denver model (Rogers), pivotal response training (Koegel and Koegel) and others. Empirical studies supporting the efficacy of these approaches were also produced between 1980 and 2000 (although not at an RCT level). In 2001, an influential review of all available evidence about early intervention was performed by the National Research Council (Lord et al. 2001; see slide 4). Overwhelmingly, experts from different disciplines, sensitivities and backgrounds concluded that enough evidence had accumulated to recommend, as a standard of care, at least 25 hours of early intervention services for preschool-age children diagnosed with ASD. This was a pivotal document that had a wide-ranging influence. Since then, more RCTs have added evidence for the efficacy of various early interventions, administered in preschool class settings, family homes or centers, either one-on-one or in naturalistic settings. The evidence for efficacy of these approaches has accumulated, but, again, the need remains, in assessing this body of studies, to qualify which treatment is administered by whom to which children in each specific investigation. ESDM (Dawson and Rogers, 2009; see slide 8) is one treatment approach (using ABA-informed techniques that are embedded into a more relationship, play-based, child-centred mode of delivery) is a recent important development for which a RCT has shown efficacy persuasively (see slide 8; and my Commentary in Pediatrics 2010). Although it is not usually referred to as 'ABA', it belongs to this family of comprehensive early intensive behavioral interventions (EIBI) reviewed by your Committee. It has not been available in Oregon until fairly recently.

Altogether, the review of existing studies by various professional organizations has led to the recommendation of early intensive behavioral intervention for young children diagnosed with ASD. This is not to say that all children will respond to it, but this is the best intervention we can recommend that we know will bring about positive changes in some children. As a practitioner, and as most of my colleagues in academic centers that operate autism services, we make this recommendation to families. We are aware that not all children will respond to it but we are, at present, unable to identify characteristics of an individual child that will predict response to 'ABA'-like treatments. We are also aware that this recommendation might mean different things depending on the level of expertise in the community centers or professionals who deliver the treatment in a given area and at a given time. However, using another analogy with pediatric oncology, pediatric oncologists that diagnose some forms of cancer in children for which an efficacious treatment will bring remissions (or cure) in (only) 40% of patients will universally recommend the treatment in the absence of alternatives. Nobody would

want to impose restraints on these doctors' prescriptions or deny treatment to these children because the likelihood of response is considered to be too low, or uncertain in that particular child, or because we anticipate lesser success when the treatment will be disseminated at large in non-academic medical centers.

As a practitioner who has seen, diagnosed and treated hundreds of individuals young children with ASD, I endorse fully the initial recommendation to engage a child and his parents in a comprehensive intensive treatment approach that is often loosely referred to as 'ABA', but actually means a variety of treatment packages inspired by ABA theory but containing different ingredients administered in varying sequences from one provider to another.

III. Unanswered questions in 'ABA'-type treatments

I, and most of my academic colleagues, are fully aware of the number of questions that are left unanswered by the current state of knowledge. Of these, the most critical ones are:

a. The optimal intensity is unknown. Lovaas made claims of '40 hours/week of treatment' but there was actually no direct measurement of actual treatment time in his original study. The 40 hours were assumed, but not measured. In the study by Smith (his follower), the treatment was meant to be 30 hours by study design, but turned out to be only 24.5 hours/week when actually measured. Yet, a treatment effect was obtained. Other treatment packages usually rely on 20 or 25 hours/week as a goal. Some children respond well with fewer hours, others do not respond with more hours. There is no strong evidence today as to what is the optimal intensity. The rule of 20 or 25 hours/week seems a good starting point in most clinical settings. How to adjust treatment intensity as a function of response is unknown.

b. The age at which treatment should be started is also uncertain. Most professionals agree that early detection and diagnosis is needed. Presumably, brain plasticity is higher in younger children but we have little, if any, insight on what brain mechanisms support treatment effects or gains. We do not have strong evidence that starting a treatment at 24 months, as opposed to 36 months, will produce more gains, and if yes which ones. It is a logical and appealing principle, but empirical evidence in support of this expected difference is lacking. Interestingly, the relationship between early treatment and treatment response is much more complex insofar as children who are diagnosed at an earlier age also tend to have more severe clinical presentations, precisely showing deficits (eg cognitive) that tend to be less responsive to treatment. Disentangling the effects of age at early intervention from severity of the phenotype require more research that has not been conducted yet, and will be extremely difficult to perform.

c. Response to treatment is difficult to predict and most practitioners would not make such predictions. However, it has been a consistent clinical observation that those children who

respond well to 'ABA-type' treatments tend to have a less severe phenotype at baseline. Evidence of this can be found in the most robust RCT favouring ABA-Lovaas treatment (Smith 2000; see slide 7, Table 2). There, considering IQ as a key outcome measure, it is clear that most of the gains are accounted for by the PDDNOS group and not the autism group. Considering that PDDNOS is an ill-defined group of children who, on average, have less severe deficits, this difference within the RCT should be given full attention.

d. Similarly, precise attention should be paid to exclusion/inclusion criteria in treatment studies. To continue on Smith et al (2000), it appears that children who failed to progress were not retained in the study (see slide 6). The ABA-Lovaas therapists have actually devised an instrument that examines response of a child to the early phases of a treatment. This instrument has been used in some studies, but I am unaware of the extent it continues to be used in clinical settings to guide treatment decisions (as far as my clinical experience goes, it is not). Intent-to-treat analyses have not typically been carried out in this behavioral literature. Equally, some children with known genetic syndromes or co-occurring medical conditions (eg epilepsy) have been excluded from studies.

e. The combination of remarks made in c. and d. point towards a persisting issue in the ABA debate with respect to defining the underlying population to which the available positive study results can confidently be extrapolated.

f. In the same vein, it is crucial to recognize that RCTs and less controlled studies have been carried out in academic centres with well-funded and trained teams. This has guaranteed high internal validity of the studies, but leaves open issues of external validity and transition from efficacy to effectiveness studies. Fidelity in treatment implementation is measured in RCTs but real world application of these treatment will likely be associated with decreased efficacy. This, however, is not specific to the ABA interventions and it applies equally to diagnostic practices and management of other aspects of the condition.

g. One specific issue concerning treatment delivery, particularly relevant for a vast state like Oregon, is that of access to ABA interventions for families living in remote rural areas. Attempts have been made to deliver treatment through parents with more minimal engagement of professional therapists, but results have been somewhat disappointing (see for example the ESDM study published in late 2012 in J Amer Acad Ch Psych; see slide 9 showing no significant gains in a sample approaching N=100). Investigators in the US and other vast countries like Canada and Australia are tackling these problems currently. There are 2 factors involved at least. First, treatment delivery in remote areas usually relies more heavily on parent-mediated interventions; on average, parent-based interventions have shown less efficacy (not necessarily because it is parent-administered but because , due to lack of fidelity measurement, we do not know what parents actually do in their homes and whether or not the intervention is actually delivered). Second, there is a general trend for

lesser intensity of treatment when administered remotely and through non-professional interventionists. These 2 factors probably add up to explain decreased effects. Again, this issue is not specific to ABA-treatments of ASD, they apply to an array of other child health conditions.

h. There are major issues in treatment studies of ASD, both behavioral and otherwise. There is no biomarker available to monitor progress or response to treatment. In the absence of such biomarkers, change is evaluated by observational methods such as paper and pencil questionnaires (behavioral inventories, adaptive behavior evaluations,…), or structured testing (language and cognitive testing, for example). Many of them are actually parent-based. For example, the Vineland scales are scored after an interview of the main caregiver, or even more recently as a simple parent-rated questionnaire. Similarly, many behavioral measures (Child Behavior Checklist, Aberrant Behavior Checklist; the ABC has 58 items and one factor with 15 items has been used repeatedly as a main outcome measure in RCTs involving medications) or other outcome measures (ie Parenting Stress Index) are parent reports. Parents cannot be blind in studies, especially studies that last 2 years. Blindness can be maintained with extraordinary efforts for professional based assessments of outcomes, but it may also be broken easily. In addition, we do not know what learning effects take place when parents are asked to repeat the same questionnaire several times over relatively short periods of time. Moreover, in studies that span the age range of 2 to 5 or 6, investigators have often to rely on different tests or measures to evaluate change in the same underlying construct. Thus, repeating the ADOS requires to change modules and combining or differencing scores becomes a much more difficult matter. The same applies to IQ tests for example, where a measure (eg the Mullen scale of Early Learning, a proxy test for IQ) is used in young children and other tests (Stanford-Binet, WPSSI etc..) at a later time point. This creates challenges to assess change over time, an issue which is not specific to ASD research per se but has complicated developmental research for decades. Adding to this, a further problem is evaluating change or developmental gains is that young children with ASD usually fare poorly on standardized tests at baseline (a floor score of 49 on the MSEL is common) when symptoms are at their worse; later, with more skills to tap into, their scores would be higher. This would create a positive change that may simply reflect measurement error in repeated assessments, a form of regression towards the mean effect. Of course, in an RCT, there is no reason to believe that regression towards the mean effect would be differential across treatment modalities and therefore it should not bias the assessment of treatment effect in the RCT. But I want to make 2 points following this measurement difficulty considerations. First, because of the complexity of measurements over time in RCTs that span longer periods of time, the measurement errors described above are likely to decrease the precision in general and will result in a bias towards the null hypothesis, in general. Unless this is compensated by larger sample sizes, it is my opinion our imperfect measures results in today's research in underestimating treatment effects. Second, the example given above also cautions against reliance on N-of-1 approaches for assessing change. The regression effect described above results in imprecision in a

comparative analysis between 2 groups where the same degree and direction of measurement operate. It will result in bias in an N-of-1 approach in showing again that can be wrongly interpreted.

i. Studies have not addressed the sustainability of treatment effects over time with a few exceptions. Nor do we know if treatment must be maintained (and if yes for how long and with which intensity) or if treatment discontinuation would lead to relapse or set-back. There are many clinical opinions on these issues (most of them being reasonable) but the data to support them are often lacking.

j. Studies do not exist that address the question of which treatment should be offered to those children who do not progress with a standard 'ABA-type' treatment package. Nor do we know when an 'ABA-type' treatment should be discontinued for lack of response. It is crucial to appreciate that the developmental nature of autism is such that failure to respond to ABA treatment cannot be defined solely as 'no change'. Change and improvement occur as part of maturation and of the natural developmental progression in all children with or without ASD impairments. For children with ASD, much before special education or ABA-type interventions existed, follow-up studies showed progresses in many children (and substantial ones in about 10-20% of them) in the absence of modern intervention approaches. Thus, failure to respond to ABA-treatment should be positively defined as the absence of predicted/expected gains as a function of the specific intervention under scrutiny, over and beyond gains/changes that will arise from maturation alone. In fact, developmental trajectories in ASD children included as controls in treatment efficacy studies could be used to calibrate what a minimal gain from 'ABA-type' treatment should look like. This remains to be done. The concern we should have is that the mere documentation of some changes or progress in a child should not be regarded as demonstration that treatment currently delivered 'works'. In autism as well as other areas of practice in child psychiatry, many therapists naively ascribe any change in their patients to their own activity without entertaining competing hypotheses as should be done. This is one example of why N-of-1 studies (although they are methodologies that contribute to knowledge in their own right) are not sufficient in themselves, simply as they fail to control for maturation and are usually based on non-blind evaluations.

k. Most studies show huge individual variability in treatment outcomes (see slide 8 from ESDM study by Dawson et al. 2009; the error bars are much wider at the end of the treatment and they also overlap substantially between the 2 conditions; and see my Pediatrics E-letter). This heterogeneity in treatment response and outcome has been reported in autism research for about every characteristic. The natural history, long-term adult outcomes, response to drug treatment, and to other interventions have been consistently difficult to predict at the individual level and characterized by a huge variability. In turn, this poses substantial challenges for investigators that conduct RCTs. The longer the

duration of the treatment, the larger the variability in the measurement of the outcome, which in turn decreases the power to detect true treatment effects. Increasing the sample size would be a natural remedy but, as noted in the previous committee session, most studies of ABA efficacy has relied on small sample sizes. This is not specific to behavioral research, however. For example, RCTs for drug evaluation in autism have been very hard to conduct with most studies having samples size way below a total of 100. One of the largest study to date took 5 years to complete in a multisite network, and enrolled at the end only 149 subjects (citalopram study by King et al., 2009). And this was for an 8-week DBPC design, eg not a huge commitment for participants. It takes a serious personal effort for investigators to conduct RCTs on ABA or similar types of treatment for 2 years, and authors should be commended for their dedication.

l. As indicated above, there are very different treatment package approaches available in the US (ESDM, Lovaas-ABA, PRT, RDI, Jaspers etc..). There has been thus far no head to head comparisons between these different treatment modalities although studies are under way.

m. Because duration of EIBI in RCTs is usually 18 months to 2 years, it is not possible to conduct these trials with a non effective (placebo) condition. Thus, recent study designs have used "treatment as usual" that are a mixed bag of professional interventions (SLT, OT) associated with behavioral support in pre-school environments, and various other measures. In the Dawson et al 2009 RCT of ESDM, the control group received a high weekly number of hours of intervention (as I recall about 20 hrs/week; see also my Commentary). It is in this context that treatment gains showed in RCTs in favour of ABA-manuelized treatments need to be interpreted. The treatments are compared to active albeit less structured and comprehensive interventions, a point that stresses the significance of the positive findings.

IV. Adverse effects

In the previous committee session, comments were made about the lack of adverse effects of ABA, adverse effects being ascribed solely to psychopharmacology studies. As an experienced clinician with psychopharmacology expertise, I agree there are well documented adverse effects of medications that we use at times to treat co-occurring behavioral problems in autism, and in other groups. The point is that we know them, we measure them and we are mandated to investigate them in our RCTs.

ABA treatments have been associated with adverse effects although their systematic documentation has been far from satisfactory. Lovaas, in his seminal study (1987) used contingent aversives (eg thigh slapping of children) that have been widely criticized later in the professional community. Lovaas also requested that parents would give up their

employment during the first year of treatment to enhance the generalizibity of learning acquired in treatment sessions to the home environment. These were obviously two very concerning features of Lovaas' ABA intervention. His follower corrected this (and see Smith admission of these changes; see slide 6), and it can be safely assumed than most ABA therapists today, with adequate training, do not rely on such debatable approaches. Yet, the field of ABA therapies have developed rapidly, certified ABA professionals are scarce and they often manage crews of therapist with variable levels of training, understanding and experience. As many other practitioners, I have come across several situations where a rigid and mechanical application of behavioral techniques by undertrained and undersupervised therapists have led to distress in the child and his family. Whilst these observations do not necessarily invalidate the underlying principles or usefulness of these treatments, they call for a tight regulation of the training of therapists, both of those who devise the treatment and of those who deliver it under their guidance. Moreover, as parents are usually incorporated in the treatment plan as 'co-therapists', there is a potential for them to be blamed, or to blame themselves, in the absence of (sufficient) progress in their child. These issues are not necessarily specific to behavioral interventions with ASD children; in fact, they permeate all psychosocial interventions (and psychotherapies) currently used to treat behavioral/emotional problems in children. The fact that these issues have not been documented in the ASD ABA literature (with the exception of Lovaas, as indicated above) does not mean that they do not exist. Simply, they are just not measured and/or reported in existing treatment studies that have been so far conducted by those who developed the treatments. The issue should not be simply dismissed and pushed under the carpet as being one issues of the past, or one that is fully address by training and supervision of staff. There are complex issues at stake regarding families and individual patients'rights and needs for protection, and more generally of fit between ABA models of teaching and learning and family cultures and sensitivities.

V. Social inequalities and 'ABA'

In most countries, the demand by parents and advocates for ABA-like treatments has surged so fast that access to treatment has been problematic, and remains so. Even in countries with a well-funded public service that covers all or most expenses (like the UK or Canada) for EIBI, waiting lists and times have been the rule. In those contexts, and in communities where access to treatment is through a network of private fee-paying providers, wealthy families have privileged access to more extensive services and at an earlier age. In the US, it is well established through CDC surveys that children with ASD from disadvantaged backgrounds (poorer or less educated parents, Black or Hispanic families) are underdetected and diagnosed at a later age; similarly, prevalence of ASD is higher in high SES families reflecting better access to care for these families (a US association, not reported in

European countries). ABA treatments typically cost about $50,000/year for a child in preschool years. Wealthy families are therefore more likely to secure treatment for their child than those from more disadvantaged backgrounds. This social differential (for both detection, diagnosis and access to early intervention) creates an added layer of risk , a social risk that is amenable to change. Reducing this inequality through measures that make access to treatment more universal, such as providing systematic insurance coverage, is an important dimension of the work of you committee.

I wanted to address more specifically the questions of your list but I do not have the time now. Also, it seems at first glance that my previous comments provide some answers to these questions.

I wish your committee a productive session. I am available for further discussions if needed.

Respectfully submitted,

Eric Fombonne MD

Article: Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The Early Start Denver Model

Geraldine Dawson, Sally Rogers, Jeffrey Munson, Milani Smith, Jamie Winter, Jessica Greenson, Amy Donaldson, and Jennifer Varley

Pediatrics January 2010; 125:1 e17-e23; published ahead of print November 30, 2009, doi:10.1542/peds.2009-0958

Abstract

Full Text

Full Text (PDF)

1. **Young preschoolers with autism: evidence for efficacy of early intervention**

    - **Eric Fombonne, Canada Research Chair in Child Psychiatry**

McGill University

Dear Editor:

Dawson and colleagues published a highly important study which provides much-needed evidence for the efficacy of early behavioral interventions for preschoolers with autism spectrum disorders under the age of 30 months. There has been much speculation and belief that the earlier the intervention, the better the outcome, but robust data to support this assumption were thus far lacking. This study therefore fulfills a knowledge gap that will have wide implications for service providers worldwide. Not only will the study provide an evidence-based treatment for preschoolers who are diagnosed at increasingly earlier stages, but it will also inform practitioners on interventions that are required for children who present atypical developmental trajectories without meeting full criteria for ASD, such as siblings of autistic probands who are at risk and are now frequently followed closely from an early age.

The strengths of this study are numerous. The authors have combined the principles of applied behavioral analysis with more developmental and relationship-based approaches that are likely to be appealing to a wide community of professionals as well as being more user-friendly for most families. The design was a randomized clinical trial, with a manualized treatment, properly trained therapists, and fidelity of treatment delivery was measured throughout. In addition, outcome was measured with blind assessors over two time points using the most up-to-date, standardized measures; and minimal attrition after 2 years of intervention was registered.

Nevertheless, a number of issues sprung to mind when reading the manuscript that pertain to the internal and external validity of the study findings.

Despite a relatively small sample size, treatment effects reached statistical significance. However, relative to the control group, cognitive gains (2/3 of SD) in the experimental treatment were of

moderate magnitude. Similarly, Vineland scores in the experimental group certainly indicated gains of skills as a function of age, but as the standardized scores did not change, there was no real catch up in developmental rates compared to typically developing children. Most gains appeared attributable to language improvements with other domains showing minimal gains and some declines.

The statistical analysis of the trial data was conducted on treatment completers only while it might have been useful to include the 3 dropouts from the control group, using the classical approach of the last observation carried forward (LOCF). Despite remaining low, dropping-out occurred differentially across treatment modalities, and the relatively small sample size and magnitude of treatment effects may render the findings sensitive to this analysis. As a result, differences between the two interventions may have been either attenuated or inflated, depending on the clinical status of the drop-outs when exiting the study.

Next, with the exception of those obtained in cognitive testing sessions, direct observational measures of the children were limited, especially to evaluate outcome in less structured settings. Thus, most of the outcome measures relied on parental reports and, even though assessors were blind to treatment status, parents could not blind to group membership. More independent and naturalistic assessments of participants' behaviors would have strengthened the ecological validity of the study.

Intriguingly, gains reported in the experimental group were mostly achieved during the first year of treatment while subsequent improvements in the second year of treatment were much less impressive. It may be that there is a critical age at which treatment effects are maximal, in which case treatment response in the EDSM group should be larger in those participants who started treatment earlier. Alternatively, true time differences in treatment administration may have existed, either because treatment goals and methods were more efficacious in younger children beginning the treatment or because treatment intensity decayed over time. Or, it may be that the chosen outcome measures are age-dependent in their sensitivity for capturing change. Finally, sleeper or lagged treatment effects might be considered, with an opportunity for treatment gains to increase later should a post-treatment natural follow-up become available. The latter possibility is perhaps illustrated in the actual first 2 years of the trial where cognitive/language scores increased sharply during the first year, with adaptive behavior improvements occurring only in the subsequent year. These competing hypotheses can probably be empirically tested although the sample size will limit this possibility.

Treatment subjects were randomized between the two groups, but there was a noticeable difference in the intensity of treatment received in both groups. Adding up all hours of weekly treatment for each modality, the ESDM group received weekly 36.7 hours of treatment as compared to 18.5 hours for the controls. Therefore, one must question whether or not the more pronounced improvements in the experimental group reflect specific treatment effects of the ESDM as opposed to more general, non-specific, effects due to uncontrolled differences in treatment time or intensity.

Further examination of the variance in the outcome measures (Vineland scale, Mullen Scales of Early Learning) in the Early Start Denver Model group shows that, despite equal variances between groups at baseline, the variance was much larger in the experimental group at 1-year follow up for the MSEL, and

at 2-year for both measures. The much larger heterogeneity observed in the experimental group suggests that responders and non- responders within the experimental group should be further compared in order to identify individual-level factors which might predict treatment response or mediate treatment effects.

The final comment concerns the customary limitations to the external validity of studies of this nature. As is usually the case in tightly controlled randomized trials, children with some co-occurring medical conditions (epilepsy) or identified genetic anomalies (fragile X) were excluded in an attempt to increase sample homogeneity, the assumption being here that treatment effects maybe otherwise masked by noise due to heterogeneity. However, as rapidly accumulating findings of new and different genes involved in the etiology of autism tell us, the “idiopathic” group of children with autism is unlikely to represent a pure, etiologically homogeneous, group. Therefore, the classical exclusion rules for studies of autism, especially for treatment studies, should be reconsidered soon in order to enlarge the universe to which results can be generalized and to avoid leaving a rapidly growing proportion of children with ASD orphan from evidence-based knowledge. Moreover, including children with a wider range of genetic abnormalities may prove necessary in future treatment studies to tease apart the aforementioned variability in treatment response, provided that genetic information is brought in the design and analysis of randomized clinical trials.

All studies have points that require further examination and other important manuscripts will undoubtedly flow from this critical study. Needless to say, the study provides important and immediately clinically relevant information, particularly at a time when universal screening for ASD in 18-month-olds has been proposed.

Dr. Eric Fombonne Canada Research Chair in Child Psychiatry McGill University Montreal, January 25th 2010

Conflict of Interest:

None declared

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When there is no cure...

there are thousands treatments

Pseudo-”treatments” for autism

- dolphin therapy
- auditory integration training
- scotopic sensitivity training
- holding therapy
- gentle teaching
- sensory integration
- cranial osteopathy
- hyperbaric oxygen chamber
- Vit B6/Mg2+
- communication facilitated
- pet therapies
- Doman-Delacato method
- Daily Life Therapy (Higashi)
- Option method
- music therapy
- brushing
- GFCF diet
- chelation

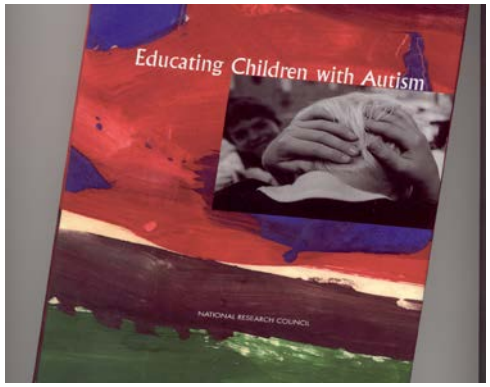
Educational and behavioral approaches

- TEACCH method (Schopler, 1970s)
  - Teacch classroom, one-on-one structured teaching sessions
  - Classroom environment structured to capitalize on strengths (visuo-spatial) and limit the effects of core deficits
  - Parental involvement to facilitate generalization

- Lovaas ABA studies (1987,1989,1993)
  - intensive (40h/wk) behavioral treatment, 1:1, manuelized, with supervision, mean age:32 months, mean IQ=53, (N=19);
  - controls: low intensity treatment (10h/wk), community treatment (N=21)
  - Claim of recovery in 47% of cases with intensive (40 hrs/week) of ABA home-based intervention. However:
    - Study did not use randomization;
    - No actual count of hours in treatment
    - No fidelity measurement
    - Outcome measures non standardized (recovery loosely defined)

- Later replication by Smith et al. (2000) in an RCT showed :
  - More modest effects
  - Tx intensity: 25 hrs/week
  - IQ gains smaller, and still in the impaired range
  - Most gains are seen in the PDDNOS group, <u>not in</u> the Autistic disorder group

National Research Council, 2001



- intervention should begin <u>as early as possible</u>
- at least 25 hours/week with year-round programming
- repeated and planned teaching opportunities *(with time intervals appropriate to developmental level)* should be implemented with one-on-one and small-group instruction to meet individual goals
- family involvement, parent education
- low student-teachers ratios in classrooms
- ongoing program evaluation and assessments with appropriate adjustments based on data

Randomized Trial of Intensive Early Intervention for Children With Pervasive Developmental Disorder

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Young children with pervasive developmental disorder were randomly assigned to intensive treatment or parent training. The intensive treatment group (7 with autism, 8 with pervasive developmental disorder not otherwise specified—NOS) averaged 24.52 hours per week of individual treatment for one year, gradually reducing hours over the next 1 to 2 years. The parent training group (7 with autism, 6 with pervasive developmental disorder NOS) received 3 to 9 months of parent training. The groups appeared similar at intake on all measures; however, at follow-up the intensive treatment group outperformed the parent training group on measures of intelligence, visual-spatial skills, language, and academics, though not adaptive functioning or behavior problems. Children with pervasive developmental disorder NOS may have gained more than those with autism.

Intensive treatment group. The goal of intensive treatment was to maximize children's intellectual, adaptive, and socioemotional functioning and, thereby, reduce their subsequent need for special education services. For our purposes in the present study, *intensive treatment* was defined as 30 hours per week of intervention for each child for 2 to 3 years. Children received treatment from teams of 4 to 6 student therapists working under our close supervision. Each child's primary caregiver was asked to conduct 5 hours per week of treatment, working alongside a student therapist, for the first 3 months of treatment.

At the outset of treatment, student therapists relied primarily on a one-to-one, discrete trial format, implemented in children's homes, so that they could provide highly individualized interventions that maximized children's successes. At this stage, the children were not yet attending school. Once they spoke in

Donahoe, and Davis, in press, for additional details on transitioning to school and terminating services from the UCLA Young Autism Project).

The treatment in the present study was less intensive than that provided by Lovaas (1987) in four respects: First, the aim was to provide 30 rather than 40 hours per week of intervention, as done by Lovaas (1987). Second, treatment was phased out after 18 months for children who were progressing slowly (as defined in the preceding paragraph), rather than continuing for up to 10 years, as Lovaas (1987) did. Third, fewer requirements were placed on parents, who, in the Lovaas (1987) study, were asked to take a year off from their jobs to participate in their children's treatment. Finally, though contingent aversives were employed briefly with the first 4 children, they were then stopped for all children, whereas Lovaas (1987) employed this intervention more extensively.

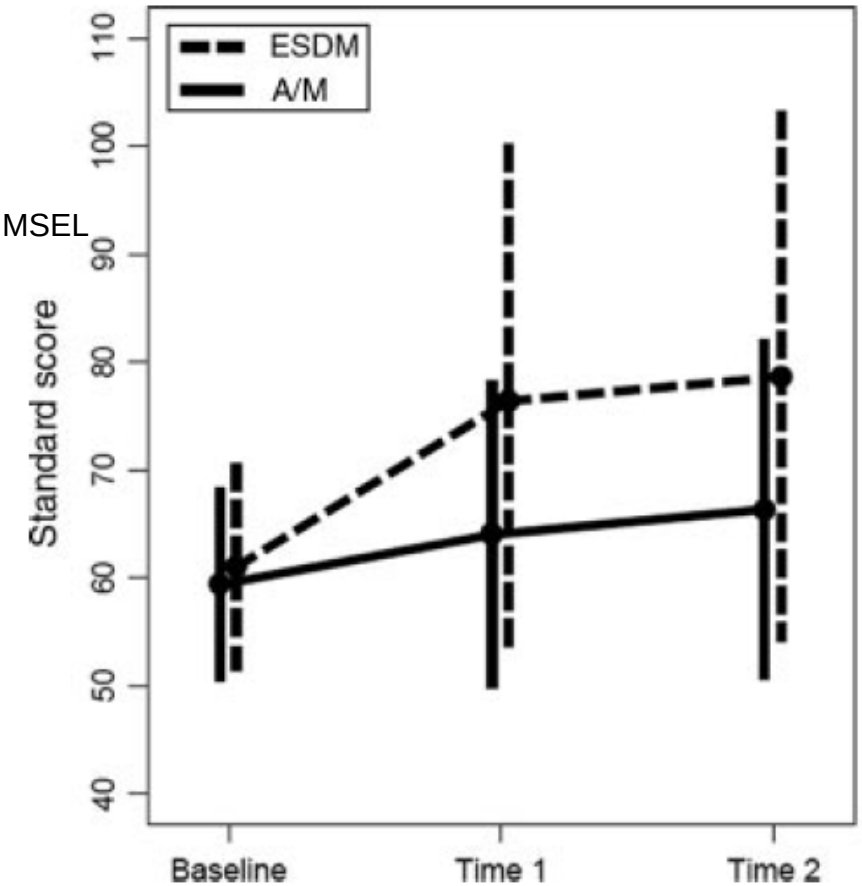
Table 2
Means and *SD*s of Children's Standardized Test Scores by Group and Time

	Intensive treatment						Parent training					
	Autism		PDD NOS[a]		Total		Autism		PDD NOS		Total	
Measure	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
IQ[a]												
Intake	51.00	13.94	50.13	9.11	50.53	11.18	50.71	14.24	50.67	14.79	50.69	13.88
Follow-up	55.29	24.09	76.25	20.69	66.49	24.08	52.57	22.83	47.13	17.89	49.67*	19.74
Merrill-Palmer[b]												
Intake	21.29	4.65	21.88	4.64	21.60	4.49	23.57	6.11	20.00	4.43	21.92	5.50
Follow-up	54.43	23.60	68.63	13.41	64.33	18.74	45.67	23.64	52.67	20.60	49.17*	21.43
Reynell[b]												
Comprehension												
Intake	15.14	4.91	12.00	0.00	13.47	3.60	14.86	4.88	12.33	0.82	13.69	3.73
Follow-up	39.00	26.00	46.25	19.98	42.87	22.29	32.14	19.04	34.20	15.66	33.00	16.86
Expressive												
Intake	15.29	0.76	15.00	0.00	15.13	0.52	17.00	3.46	15.50	1.2	16.31	2.69
Follow-up	40.57	25.13	48.00	23.05	44.53	23.48	32.14	20.93	41.00	22.3	36.23	21.19
Total (Rec+Exp)												
Intake	30.43	5.59	27.00	0.00	28.60	4.07	31.86	8.32	27.83	2.04	30.00	6.34
Follow-up	79.57	41.99	94.25	41.99	87.40	46.21	64.29	39.25	57.20	21.48	61.33*	31.88
Vineland[c]												
Communication												
Intake	61.00	5.69	55.75	4.40	58.20	5.56	62.29	5.74	61.67	7.06	62.00	6.11
Follow-up	66.14	33.97	69.38	28.55	67.87	30.08	64.43	15.72	56.50	19.44	60.77	17.26
DLS[d]												
Intake	75.57	8.62	65.00†	4.11	69.93	8.37	68.43	8.66	73.17	14.59	70.62	11.50
Follow-up	65.57	30.85	63.88	22.49	62.33	25.76	64.71	15.89	61.00	19.47	63.00	16.97
Socialization												
Intake	66.00	8.17	59.25	6.40	62.40	7.82	69.14	3.76	69.17	12.98	69.15	8.75
Follow-up	66.57	28.50	66.13	23.06	66.33	24.78	67.00	15.33	71.12	19.88	68.92	16.94
Composite												
Intake	68.86	11.16	59.2	4.99	63.44	9.35	65.00	9.54	65.40	10.41	65.17	9.44
Follow-up	62.14	32.84	60.44	25.11	61.19	29.72	61.86	16.83	53.80	16.84	58.50	16.58

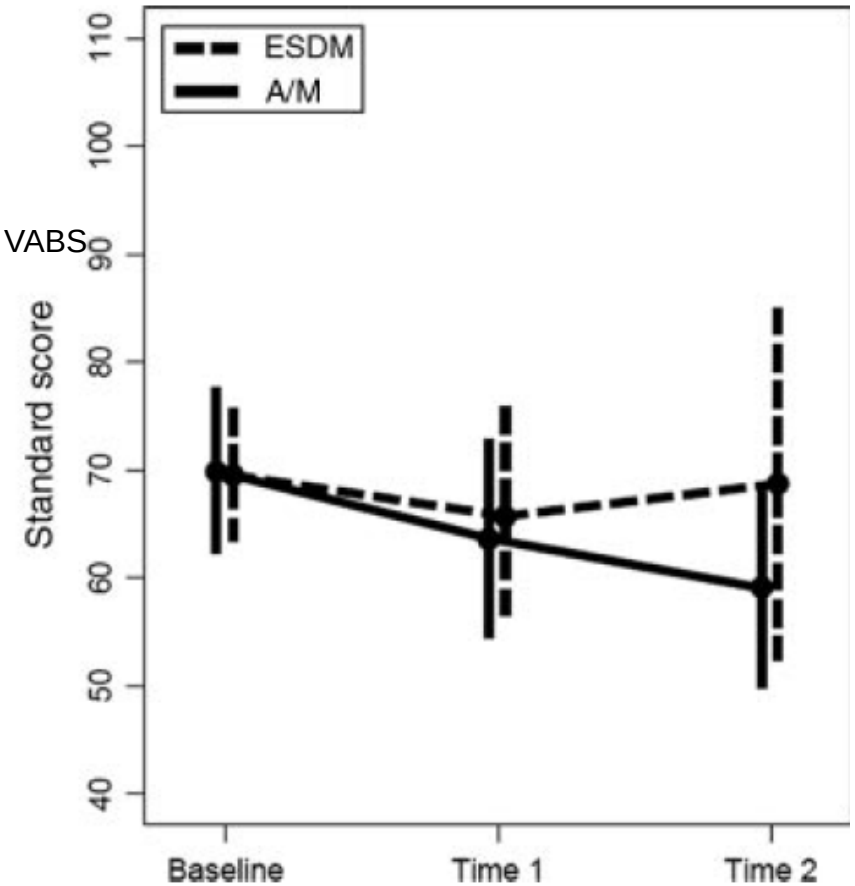
[a]Bayley scored as ratio IQ, Stanford-Binet as deviation IQ. [b]Developmental age (months). [c]Standard score (population *M*[*SD*] = 100(15)).

RCT of Early Intervention at age 18 months+

MSEL



VABS



Dawson et al., 2010; Pediatrics

RCT of P-ESDM in 12-24months ASD toddlers

98 at risk subjects; low-intensity (1 hr/wk of therapist contact), 12 weeks duration, parent-mediated ESDM; control= community TAU

TABLE 2 Means and Standard Deviations for All Time 1 and Time 2 Child Variables, With Effect Sizes, by Group

	P-ESDM Group		P-ESDM Group		P-ESDM Group	Community Group		Community Group		Community Group
	Visit 1		Visit 2			Visit 1		Visit 2		
Measures	Mean	SD	Mean	SD	Cohen's d	Mean	SD	Mean	SD	Cohen's d
Modified ADOS Social Affect	29.45	9.16	26.61	10.14	−0.37	34.14	8.69	27.33	10.62	−0.63
ADOS–Restrictive and Repetitive	3.92	2.01	3.96	1.86	0.02	4.31	1.92	3.82	2.04	−0.22
Mullen DQ	64.88	17.22	69.82	17.9	0.44	63.08	15.93	67.92	17.93	0.37
Mullen Verbal DQ	47.78	22.19	56.65	23.65	0.56	44.45	20.37	54.35	21.94	0.53
Mullen Nonverbal DQ	80.96	16.68	81.98	14.82	0.08	80.73	15.51	80.57	18.45	−0.01
MCDI Part I: Phrases Understood	8.22	7.02	12.73	9.11	0.62	9.38	7.95	14.77	8.14	0.87
MCDI Part I: Vocabulary Comprehension	64.53	65.73	106.51	96.81	0.66	70.31	78.34	125.72	106.39	0.84
MCDI Part I: Vocabulary Production	12.24	35.6	42.27	61.99	0.69	12.44	39.72	38.87	73.71	0.57
MCDI Part II: Total Gestures	19.89	10.12	28.02	12.62	0.83	20.33	11.15	29.79	13.51	1.02
VAB II: Communication	67.66	13.19	72.55	12.06	0.69	67.29	11.05	74.29	14.55	0.84
VAB II: Daily Living Skills	83.07	12.4	82.25	13.82	−0.08	83.21	10.6	84.04	13.5	0.08
VAB II: Socialization	76.68	8.74	77.32	9.19	0.08	77.95	8.01	78.67	10.78	0.07
VAB II: Adaptive Behavior Composite	76.76	10.3	77.43	9.59	0.1	78.22	8.88	80.33	11.34	0.29
Imitative Sequences	3.78	3.12	4.58	3.45	0.22	2.53	2.6	3.76	3.44	0.37
Mean Social Orient I	0.47	0.33	0.47	0.28	−0.02	0.41	0.29	0.43	0.35	0.06
Mean Nonsocial Orient	0.65	0.3	0.74	0.28	0.27	0.62	0.35	0.6	0.37	−0.06
Mean Orient to Joint Attention	0.35	0.35	0.34	0.29	−0.03	0.28	0.33	0.34	0.34	0.18

Note: ADOS = Autism Diagnostic Observation Schedule; DQ = Developmental Quotient; MCDI = MacArthur-Bates Communicative Development Inventory; P-ESDM = Parent Delivery—Early Start Denver Model; VAB II = Vineland Adaptative Behavior Scales—II.

Promising results showing larger developmental gains and reduction in autistic symptoms if treatment is more intensive and younger age at initiation

Rogers et al., 2012