Early Intervention for Children With Autism Spectrum Disorder Under 3 Years of Age: Recommendations for Practice and Research

abstract

This article reviews current evidence for autism spectrum disorder (ASD) interventions for children aged <3 years, based on peer-reviewed articles published up to December 2013. Several groups have adapted treatments initially designed for older, preschool-aged children with ASD, integrating best practice in behavioral teaching methods into a developmental framework based on current scientific understanding of how infants and toddlers learn. The central role of parents has been emphasized, and interventions are designed to incorporate learning opportunities into everyday activities, capitalize on "teachable moments," and facilitate the generalization of skills beyond the familiar home setting. Our review identified several comprehensive and targeted treatment models with evidence of clear benefits. Although some trials were limited to 8- to 12-week outcome data, enhanced outcomes associated with some interventions were evaluated over periods as long as 2 years. Based on this review, recommendations are proposed for clinical practice and future research. *Pediatrics* 2015;136:S60–S81

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ABBREVIATIONS

ABA—applied behavior analysis
ASD—autism spectrum disorder
ESDM—Early Start Denver Model
GRADE—Grading of Recommendations Assessment, Development, and Evaluation

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The ultimate goal of early detection and screening is to ensure that children with autism spectrum disorder (ASD) can access evidence-based interventions to provide the best opportunity for optimal development and outcomes.[1] With the advances reviewed by Zwaigenbaum et al[2,3] in this special issue of *Pediatrics,* and the growing evidence that ASD can be diagnosed accurately before 2 years of age,[4,5] the need for ASD treatment programs specifically designed for this age group has never been greater. Some authors have also argued that the second year of life is a particularly critical developmental period for children with ASD, for various reasons. First, the second year is a dynamic period of brain growth, during which increases in brain volume and atypical connectivity associated with ASD first emerge[6,7] but also a time of substantial neural plasticity providing greater potential to alter developmental course.[8] Second, a proportion of children with ASD reportedly regress in the second year. Recent research has indicated only modest agreement between retroactively reported regression and analysis of behavioral change as observed on serial home videos[9] and that acute skill loss may exist along a continuum of gradually declining trajectories of social and communicative behavior.[10,11] However, interventions during this period may counter the developmental cascade that contributes to progressive symptom development and ultimately prevent ASD-related impairments before they fully manifest.[8]

Intervention approaches for children aged <2 to 3 years need to be developmentally appropriate. We cannot assume that findings from treatment research involving older children with ASD will generalize to infants and toddlers, who differ with respect to the nature of their social relationships as well as their cognitive and communicative processes. Infants depend on experiential learning within their natural environments and on interactions rooted in social play that occur within the context of everyday caregiving activities.[1] Fortunately, over the past several years, a growing number of studies have evaluated interventions specifically designed for children aged <2 to 3 years. An updated review of these interventions may provide needed direction and guidelines to clinicians and policy makers.

METHODS

The working group conducted a search of the literature published online between 2000 and 2012 related to intervention programs provided to children with ASD aged <3 years. The working group summarized published research on interventions developed for use in children aged ≤36 months, even if the age range of samples of children being evaluated extended beyond age 3 years (Table 1). A PubMed search was conducted on June 30, 2010, for articles published since January 1, 2000, by using the search terms ("child developmental disorders, pervasive" or "autistic disorder/" or "autism [tw]" or "autistic [tw]") and ("Early Intervention/" or "intervention [tw]"), with an age filter ("infant, birth-23 months" or "Preschool child, 2-5 years") and limited to English-language articles. This search yielded 419 references, which were reviewed by Drs Zwaigenbaum and Bauman, who selected articles focusing on clinical trials of developmental/behavioral interventions (ie, not medications or trials of other biomedical therapies) that included children aged <36 months. Search results were complemented by additional publications identified by working group members. Hence, although the search strategy was comprehensive, selection of articles was not systematic, which is an important limitation. A scoping approach, with some discretion of the multidisciplinary expert working group, was used instead to select articles of highest relevance.

Each selected study was assessed, and working group members were asked to arrive at a consensus evaluation on each article after a detailed discussion. The search was updated by using the same strategy to add articles published to December 31, 2013, which yielded an additional 323 references; selection was again limited to clinical trials of developmental/behavioral interventions that included children aged <36 months. The working group reviewed and approved the final wording of the summary and recommendations.

We recognize that in addition to comprehensive early intervention programs, the management and treatment of young children with ASD often involves speech and language and occupational and physical therapies, as well as management of comorbid conditions such as associated medical disorders (eg, sleep, gastrointestinal),[12] anxiety, and challenging and maladaptive behaviors. However, a review of these targeted interventions was beyond the scope of the current initiative.

LITERATURE REVIEW

Table 1 summarizes the key features and outcomes of 24 randomized controlled, quasi-experimental, and open-label studies involving children with ASD aged <3 years reviewed by the working group.[13–38] Because few studies focused exclusively on this age group, studies in which participants included some children aged >3 years were assessed as long as there was sufficient information to draw inferences about younger children. The group reviewed additional reports, which have not been listed in Table 1, including single-subject studies,[39–44] other relevant studies,[16,45–50] meta-analyses,[51,52] and reviews.[53–56]

TABLE 1 Selected Intervention Studies Involving Children Aged <3 Years (2000–2013)

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
Rogers et al,[14] 2012	*N* = 98 with ASD (screen-positive on the ITC and ESAT and diagnosis by using ADOS-T and clinical judgment) Aged 12–24 mo (mean: 21.0 mo); 76 boys	RCT	1 h parent training per week × 12 wk, plus self-instruction manual for parent to review	Comprehensive	ESDM (see Dawson et al,[17] below), adapted as briefer parent training model	No main treatment effects on parent acquisition of ESDM intervention skills nor improvement in child development or ASD symptoms Stronger working alliance with primary therapist in ESDM group compared with community intervention controls	Implemented by parents	Both groups showed improvement in child outcomes, related to hours of intervention and older child age at baseline	Moderate/high	Weak
Carter et al,[15] 2011	*N* = 62 with ASD symptoms or at risk (STAT) Aged 15–25 mo (mean: 20.3 mo); 51 boys	RCT	1 group session with parents per week × 8 wk, plus 3 at-home individualized sessions for parent and child All sessions completed by 3.5 mo	Targeted	Hanen recommendations: parent training in small groups plus 1:1[a] "Business as usual"[b]	No main treatment effects on parent responsivity or child communication outcomes immediately or 5 mo after treatment (although moderate to large effect sizes for parent responsivity gains) In children with low baseline levels of object interest, ↑ gains in child communication 5 mo posttreatment In those with high baseline object interest, attenuated growth in communication	Implemented by parents	Missing data precluded ITT analysis Internal study validity questioned by authors Size of parent groups smaller than Hanen recommendations	Moderate/high	Weak
Landa et al,[16] 2011	*N* = 48 with ASD	RCT	10 h/week × 6 mo	Targeted	Social curriculum (5:3,[a] DTT, routines-based interactions) added to comprehensive classroom-based intervention (AEPS)	Significant (P = .02) between-group difference for socially engaged imitation (moderate effect size at 6 mo, large effect size at 12 mo)	Implemented by interventionists But there was home-based parent training (1.5 h/mo × 6 mo) and parent education classes (38 h)	Control group without social curriculum nevertheless received some imitation and JA intervention	Moderate/high	Weak

TABLE 1 Continued

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
	Aged 21–33 mo (mean: 28.6, 28.8 mo); 40 boys				AEPS curriculum (developmental approach) without added intervention	NS between-group differences in IJA and shared positive affect (moderate or large effect sizes at 6 and 12 mo) NS between-group differences in expressive language or nonverbal cognition (moderate effect sizes at 6 and 12 mo)				
Dawson et al,[17] 2010	*N* = 48 with ASD	RCT	20 h/week × 2 y (therapists) plus ≥5 h/wk × 2 y (parents)	Comprehensive	ESDM: 1:1,[a] home-based, ABA and developmental approaches; plus other available therapies[c]	Significant between-group differences in IQ and adaptive behavior after 2 y	Delivered by therapists and parents	Group differences larger than those in studies of comparable developmental behavioral approaches of shorter duration and fewer hours of delivery per week	Moderate/high	Strong
	Aged 18–30 mo (mean: 23.9, 23.1 mo); male-to-female ratio 3.5:1		Actual mean: 15.2 h/wk (therapists) plus 16.3 h/wk (parents) Mean: 9.1 h/wk individual therapy plus 9.3 h/wk group		Assess and monitor: referrals by community-based providers	ESDM group maintained rate of adaptive behavior growth compared with normative sample of TD children, and the comparison group showed further lag				
Green et al,[18] 2010	*N* = 152 with AD	RCT	4 h/month × 6 mo, then 2 h/month × 6 mo	Targeted	PACT: intervention to increase parent sensitivity and responsiveness; 1:1[a] with child present; plus treatment as usual[d]	NS between-group difference in child autism symptom severity, language measures, or adaptive functioning in school at 13 mo	Parent mediated	ADOS-G, used as primary outcome, may not be sensitive measure of change	Moderate/high	Strong (per parent report)

TABLE 1 Continued

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
	Aged 24–60 mo (M: 45); 138 boys				Treatment as usual (local services)[d]	Large effect size for parent synchronous response to child; small effect sizes for other parent–child interaction measures (child initiations with parent, parent-child shared attention)				Weak (per child measures)
Ingersoll,[19] 2010	*N* = 21 with AD	RCT	3 h/week × 10 wk	Targeted	Behavioral intervention (RIT): laboratory setting, naturalistic techniques	Significantly more gains in elicited ($P < .05$) and spontaneous ($P < .02$) imitation, in both object ($P < .05$), and gesture ($P < .01$) imitation compared with controls	Implemented by therapists	Groups not matched pretreatment (better imitation in RIT group)	Moderate/high	Strong
	Aged 27–47 mo (mean: 41.4, 37.2 mo); 18 boys				"Treatment as usual" in community					
Kasari et al,[20] 2010	*N* = 38 with AD	RCT	2 h/wk (three 40-min sessions) × 8 wk	Targeted	Immediate JA intervention: instructing caregiver–child dyad during play routines; combined developmental and ABA approach; laboratory setting	At 8 wk, significant ($P < .05$) between-group differences in level of joint engagement, child responsiveness to JA, and diversity of functional play acts (generally large effect sizes) At 1-y follow-up, treatment gains were maintained or improved	Caregiver mediated	Concurrent early intervention (9–40 h/wk) received by both groups (no differences in dose or type)[e]	Moderate/high	Strong
	Aged 21–36 mo (mean: 30.8); 29 boys				Delayed JA intervention (wait-listed group)	Quality of caregiver involvement, but not treatment fidelity, predicted child outcome				

TABLE 1 Continued

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
Oosterling et al,[21] 2010	*N* = 75 with ASD	RCT	Year 1: Group sessions 2 h/wk × 4 wk, then home visits 3 h/wk every 6 wk	Targeted	Parent training by psychologists or sociotherapists (nonintensive, home-based, called "focus parent training") plus care as usual[f]	After 12 mo:	Parents as everyday therapists	Modeled on the intervention of Drew et al,[37] 2002 (see below)	Moderate to low/ very low	Weak
								Flawed randomization of first 26 participants		
	Aged 12–24 mo (mean: 34.4 mo); 52 boys		Year 2: Home visits every 3 mo plus plenary sessions every 6 mo		Care as usual[f]	No between-group differences in language development, global clinical development, or mediating outcomes (ie, child engagement, early precursors of social communication, parental skills)		Treatment integrity not formally verified		
Zachor and Ben-Itzchak,[22] 2010	*N* = 78 with ASD	Quasi-experimental	20 h/wk × 1 y	Comprehensive	ABA-based intervention: 1:1,[a] child-centered; part of community center–based ASD-specific preschool program (40 h/wk)	NS between-group differences in change in ASD diagnostic classification, cognitive abilities, or adaptive skills	Stronger parent involvement in eclectic group	Groups not randomly assigned	Moderate	Weak
	Aged 15–35 mo (mean: 25.4); 71 boys		19 h/wk × 1 y		ED: mix of developmental, DIR, and TEACCH; 7:5[a]; part of same preschool program (40 h/wk)	In subgroup with less severe baseline ASD symptoms, eclectic >ABA in adaptive skills				
Ben-Itzchak and Zachor,[23] 2009	*N* = 68 with AD	Open	35 h/wk × 1 y	Comprehensive	ABA-based early intervention as part of center-based autism-specific preschool; 1:1[a]	NS effect of type of intervention on change in autism severity (~20% in each group changed diagnostic classification at 1 y)	Implemented by therapists and special education teachers		Moderate	Strong

TABLE 1 Continued

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
	Aged 18–35 mo (mean: 25.4 mo); 62 boys				Eclectic as part of center-based autism-specific preschool; mix of treatment approaches, small groups	Compared with children with unchanged status ($n = 53$), those with improved classification ($n = 15$) gained significantly more in cognitive abilities ($P < .01$), adaptive skills ($P < .05$ for communication scores), and stereotyped behaviors ($P < .05$)	But parent training is part of eclectic programs			
Eikeseth et al,[24] 2009	*N* = 20 with AD	Open	Range of supervision intensity: 2.9–7.8 h/month (M: 5.2)	Comprehensive	EIBI (UCLA/Lovaas model): home-based, 1:1[a]; mean: 34.2 h/wk × 50 wk, parent-managed service	Intensity of supervision significantly ($P < .05$) correlated with changes in IQ and visual-spatial IQ after 14 mo	Implemented by tutors	3 children excluded from data analysis (2 withdrew from study; 1 required increased supervision)	Very low/low	Weak
	Aged 28–42 mo (mean: 34.9 mo)					NS correlation with adaptive functioning	But parent training on ABA methods	Study designed to find only association between supervision intensity and outcome		
	Of 23 who entered study, 17 boys									
Ben-Itzchak and Zachor,[25] 2007	*N* = 25 with AD	Open	≥35 h/wk × 1 y	Comprehensive	Intensive ABA-intervention: center-based, 1:1,[a] addressing developmental and behavioral areas	Significant ($P < .001$) improvements after 1 y in imitation, receptive/expressive language, nonverbal communication, play skills, and stereotyped behaviors	Implemented by therapists	No control group	Low/moderate	Weak
	Aged 20–32 mo (mean: 26.6 mo); 23 boys					Children with higher IQ or fewer social interaction deficits before treatment showed better acquisition of receptive/expressive language and play skills	Parent training on how to use behavioral methods at home			

TABLE 1 Continued

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
Goin-Kochel et al,[26] 2007	*N* = 29 with ASD	Open	≥30 h/wk × 12–18 mo	Comprehensive	EIBI: ASD-specific preschool program in private school setting; ABA-based (ABLLS[g]) curriculum; 1:1[a] plus small groups	Significant group progress over time across multiple skills ($P < .001$ for all ABLLS domains[g])	Parents "required" to provide EIBI at home, 10 h/wk, to supplement school-based intervention	No control group	Low	Weak
	Aged 29.6–61.4 mo (mean: 45.7 mo); 27 boys					Baseline ABLLS[g] score and rate of learning during first 6 mo best predicted outcome 9/16 discharged to inclusive kindergarten or first grade with assistance of aide; all needed special education services		Access to archival school data only (not known whether other interventions were received)		
Magiati et al,[27] 2007	*N* = 44 with ASD	Quasi-experimental	18–40 h/wk × 2 y (M, 33.2 at end of 2 y)	Comprehensive	EIBI in community setting: home based; 1:1[a]; DTT and, in 2 families, verbal behavior	NS group differences in cognitive ability, language, play skills, or ASD severity at 2 y	In 23 of 28 families, 1 parent trained as a therapist	Groups not randomly assigned	Low/moderate	Weak
	Aged 23–54 mo (mean: 38.0, 42.5); 39 boys					Moderate to large effect sizes for adaptive behaviors; moderate effect size for ASD severity		Treatment fidelity not assessed directly		
			15–30 h/wk × 2 y (M, 27.4 at end of 2 y)		ED (including PECS, SPELL, and TEACCH) in autism-specific nurseries: 1:1 to 3.3:1[a]	Baseline IQ and language level best predicted overall progress	Nursery programs emphasized "close liaison with parents"			
Reed et al,[28] 2007	*N* = 27 with ASD	Quasi-experimental	20–40 h/wk (M, 30.4) × 9–10 mo	Comprehensive	Home-based, high-intensity ABA programs, mostly 1:1[a] and in natural settings:	Significant ($P < .01$) between-group differences in educational functioning	Some involvement by family members	Groups not randomly assigned	Low/moderate	Weak
	Aged 31–48 mo (mean: 42.9, 40.8 mo); all boys				UCLA/Lovaas model	NS between-group differences in intellectual functioning, adaptive behavior, and ASD severity		Within the high-intensity groups, ↑ temporal input (h/wk) was not associated with ↑ gains		

TABLE 1 Continued

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
					CABAS: emphasizing teacher–student interaction as unit of analysis	Large effect sizes for high-intensity group in intellectual and educational functioning; moderate effect sizes for low-intensity group				
					Verbal behavior: focusing on developing verbal responses	Small effect sizes for all groups in adaptive behavior				
			11–20 h/wk (mean: 12.6) × 9–10 mo		Home-based, low-intensity, generic ABA program	Of 3 high-intensity programs, CABAS had best effect sizes				
Remington et al,[29] 2007	*N* = 44 with AD	Quasi-experimental	18.4–34.0 h/wk (mean: 25.6) × 2 y	Comprehensive	EIBI: ABA-based; home setting; delivered by multiple service providers; plus "usual" treatments[h]	Significant main effects of group for IQ, daily living skills, and motor skills; significant differences in language abilities at 1 and 2 y favoring EIBI	EIBI delivered by therapists and parents	Groups not randomly assigned	Moderate	Strong
	Aged 30–42 mo (mean: 35.7, 38.4 mo)					Effect sizes at 2 y: large for IQ, moderate for adaptive behaviors		Potential examiner bias		
					"Treatment as usual": no intensive or predominantly 1:1[a] intervention[h]; publicly funded education provision	At 2 y, more children in EIBI group attended mainstream schools (17/23 compared with 10/21)		Investigators could not control practical aspects of interventions		
						Response to EIBI predicted by higher baseline intellectual functioning, more baseline problem behaviors, more severe ASD symptoms				
Zachor et al,[30] 2007	*N* = 39 with ASD	Quasi-experimental	35 h/wk × 1 y	Comprehensive	ABA-based early intensive intervention: center-based, 1:1,[a] DTT, naturalistic techniques	ABA > ED in improvements in language and communication ($P < .01$) and reciprocal social interaction ($P = .07$): only ABA showed significant improvement in former domain; ABA had larger effect size in latter	Implemented by therapists	ADOS used to measure changes in ASD core symptoms	Low	Weak

TABLE 1 Continued

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
	Aged 22–34 mo (mean: 27.7, 28.8 mo); 37 boys		35 h/wk × 1 y		ED approach: center-based, mix of methods[i]; focused on teaching imitation and awareness of social interactions; 1:1[a] plus small groups	ABA > ED in changes in diagnostic classification ($P < .05$)				
Cohen et al,[31] 2006	*N* = 42 with ASD	Quasi-experimental	35–40 h/wk × 47 wk/y × 3 y[j]	Comprehensive	EIBI (UCLA/Lovaas model): community based, 1:1[a] home instruction, DTT; plus classroom-based regular education preschool	Significant differences in IQ ($P = .03$) and adaptive behavior ($P = .01$) favoring EIBI	Implemented by tutors	Groups not randomly assigned	Very low/low	Weak
	Aged 20–41 mo (mean: 30.2, 33.2 mo); 35 boys					IQ and adaptive behavior gains in EIBI group tended to plateau after 1 y	EIBI: parent training; parents encouraged to participate actively in intervention (no set number of hours required)	Significantly ($P < .05$) more children with AD in EIBI group		
						NS between-group difference in language comprehension or nonverbal skills		Treatment fidelity not assessable in comparison group		
			≤15–25 h/wk × 3 y (for 17 of 21 children)		Special education classes at local public schools (mixed approaches; 1:1 to 3:1[a])	At year 3, 17 of 21 EIBI children in regular education (6 without support) vs 1 of 21 in comparison group		At year 3, EIBI children trained in advanced social skills		
Kasari et al,[32] 2006	*N* = 58 with AD	RCT	2.5 h/wk × 5–6 wk	Targeted	JA intervention: child-centered ABA and milieu teaching strategies added to EIP; laboratory setting	After 6 wk:	Children directly taught by trained interventionists	After 5–6 wk, children transitioned off EIP to community services without JA or SP intervention	Moderate/high	Strong
Kasari et al,[33] 2008	Aged 3–4 y (mean: 43.2, 42.7, 41.9 mo); 46 boys		2.5 h/wk × 5–6 wk		SP intervention using same strategies, added to same EIP; laboratory setting	↑ JA skills in JA group and ↑ diversity and sophistication of play in SP group compared with controls (large effect sizes)		Control group then received more hours of intervention services than former JA ($P < .05$) and SP ($P < .01$) groups		

TABLE 1 Continued

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
			EIP: 30 h/wk × 5–6 wk		Control group: Same EIP without JA or SP intervention: hospital day-treatment program for children with developmental disabilities and/or behavioral disorders; 1:1 or 1:2 ABA-based techniques; adult-centered, response-oriented approach to teaching	Acquired skills generalized to play with mothers (large effect sizes for JA and SP) Some general effects of therapy (JA, functional play skills) in JA and SP groups At 12-mo follow-up: Significantly ($P < .01$) greater growth in expressive language for JA and SP (moderate effect sizes for JA and SP versus control) Children with lowest language levels pretreatment had significantly ($P < .001$) better language outcomes with JA than with SP or EIP (moderate to large effect sizes for JA) JA and SP groups continued to show growth and generalization in skills and outperform control group				

TABLE 1 Continued

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
Wetherby and Woods,[34] 2006	*N* = 17 with ASD	Quasi-experimental	2 home visits/wk × 1 y	Targeted	ESI: family training to follow child's focus of attention and build child's skills in daily routines (developmental approach, natural environment)	Significant improvements from baseline for ESI group in 11 of 13 social communication measures (large effect sizes for 12 CSBS DP behavioral sample measures, moderate effect size for 13th measure)	Implemented by parents	Not known whether groups were matched at baseline (age 2 y)	Very low/low	Weak
	Aged 12–24 mo (mean: 18.2 mo); 15 boys		Plus 1 supervised parent–child play group (including TD children) per week × 9 wk × 1 y			At age 3 y, ESI > contrast group in social communication (large effect size for 8 of 13 CSBS DP measures)		Actual intervention intensity not documented		
	n = 18 with ASD				No-treatment contrast group at third year					
	Aged 25–36 mo (mean: 31.6 mo); 14 boys									
Yoder and Stone,[35] 2006	*N* = 36 with ASD	RCT	1 h/wk (three 20-min sessions) × 6 mo	Targeted	University clinic–based PECS: 6 instructional phases conducted by speech-language pathologists	RPMT > PECS in facilitating frequency of generalized IJA (in children with some pretreatment IJA) and generalized turn taking (large and moderately large effect sizes, respectively)	Parent training (up to 15 h) to support intervention use outside clinic	Examiners conducting pre/post assessments not blinded to treatment status	Moderate/high	Weak
	Aged 18–60 mo; 31 boys				University clinic–based RPMT: 1:1[a]; can advance to Milieu Language Teaching; Hanen curriculum for parent support	In children with little pretreatment IJA, PECS > RPMT in facilitating generalized requests (large effect size)				
Howard et al,[36] 2005	*N* = 61 with ASD	Quasi-experimental	25–40 h/wk × 14 mo	Comprehensive	EIBI: 1:1[a]; home, school, or community setting	EIBI > AP: significantly higher group mean scores for IQ, nonverbal, language, overall communication, and social skills	Delivered by trained tutors	Groups not randomly assigned	Very low/moderate	Weak

TABLE 1 Continued

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
	Aged <48 mo (mean: 30.9, 37.4, 34.6 mo); 54 boys		25–30 h/wk × 14 mo		Intensive, eclectic, autism-specific educational programming (AP): 1:1 or 2:1[a]; public school classroom-based; including DTT, PECS, and TEACCH	NS differences in group mean scores between AP and GP	Parents to implement programs outside of scheduled intervention hours	No direct group comparison; statistical analysis of group mean scores		
			15 h/wk × 14 mo		Nonintensive generic educational programming (GP): 6:1[a]; community based; mix of methods	↑ Learning rates at 14 mo ($P \leq .05$) for EIBI versus other 2 groups in all domains except motor skills (normal or above-normal rates, especially in acquisition of language skills)		Many techniques not operationally defined		
Drew et al,[37] 2002	*N* = 24 with AD	RCT	3 h/wk every 6 wk × 12 mo	Targeted	Parent training (home-based) that focused on joint attention skills; plus available community services	NS group differences in child language development after 12 mo	Parent mediated	Groups not matched on baseline nonverbal IQ	Very low/low/moderate[l]	Weak/moderate
	Aged <24 mo (mean: 22.5 mo); 19 boys					NS group differences in nonverbal IQ and symptom severity after 12 mo	Parents to use learned techniques during daily routines and in set-aside joint play sessions (30–60 min/d)	No data on parent training implementation		
						Language ability in both groups still severely compromised at 12 mo		Total intervention hours higher ($P = .07$) in control group		
					Available community services only[k]		Sometimes entirely delivered by therapists, sometimes parent involvement	Reliance on parent report for language outcomes		

TABLE 1 Continued

Reference	*N*, Chronological Age, Gender	Design	Dose	Treatment		Outcomes	Degree of Parental Involvement	Comments	GRADE Quality of Evidence[13]	GRADE Recommendation[13]
				Content	Approach					
Smith et al,[38] 2000	*N* = 28 with ASD	RCT	30 h/wk × 2–3 y (decreasing in later years with progress by child)	Comprehensive	EIBI (UCLA/ Lovaas model): home-based 1:1,[a] then shifting to classroom setting; ABA-based	Significant ($P < .05$) between-group differences at age 7–8 y in IQ, visual spatial skills, and language development favoring EIBI	Intensive treatment implemented by therapists	Lacked standardized diagnostic instrument	Moderate/high	Strong
	Aged 18–42 mo (mean: 35.8, 36.1 mo); 23 boys		5 h/wk parent training × 3–9 mo plus 10–15 h/wk of special education for children		Parent training in same treatment approaches; plus special education classes for children	No differences in adaptive functioning or behavior problems	In both groups, parents asked to provide 5 h/wk of intervention	Skewed distribution of scores precluded some statistical analyses		
						Improved school placement in intensive treatment group				

ABLLS, Assessment of Basic Language and Learning Skills; AD, autistic disorder; ADOS, Autism Diagnostic Observation Schedule; ADOS-G, Autism Diagnostic Observation Schedule–Generic; ADOS-T, Autism Diagnostic Observation Schedule–Toddler Module; AEPS, Assessment, Evaluation, and Programming System for Infants and Children; AP, intensive eclectic autism-specific educational programming; CABAS, Complete Application of Behavior Analysis to Schools approach; CSBS DP, Communication and Symbolic Behavior Scales Developmental Profile; DIR, Developmental, Individual Difference, Relationship; DTT, discrete trial training; ED, eclectic-developmental; EIBI, early intensive behavioral intervention; EIP, Early Intervention Program; ESAT, Early Screening of Autistic Traits questionnaire; ESI, Early Social Interaction Project; GP, non-intensive generic educational programming; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IJA, initiating joint attention; ITC, Infant/Toddler Checklist; ITT, intention-to-treat; JA, joint attention; PACT, Preschool Autism Communication Trial; PECS, Picture Exchange Communication System; RCT, randomized controlled trial; RIT, reciprocal imitation training; RJA, responding to joint attention; RPMT, Responsive Education and Prelinguistic Milieu Teaching; SP, symbolic play; SPELL, Structure, Positive (approaches and expectations), Empathy, Low (arousal), and Links framework; STAT, Screening Tool for Autism in Two-Year-Olds; TD, typically developing; TEACCH, Treatment and Education of Autistic and Related Communication Handicapped Children; UCLA, University of California, Los Angeles.

[a] Child-to-teacher ratio.

[b] Carter et al,[15] 2011: "Business as usual" interventions not specified in publication.

[c] Dawson et al,[17] 2010: Including speech, developmental preschool.

[d] Green et al,[18] 2010: Treatment as usual included group-based autism psychoeducation, communication-focused intervention, Portage therapy, speech and language therapy, and (for 1 child each in PACT group) home-based EIBI and Son-Rise therapy.

[e] Kasari et al,[20] 2010: Concurrent early interventions involved mostly ABA/educational services and speech and occupational therapy; study investigators did not coordinate with providers of these services.

[f] Oosterling et al,[21] 2010: Care as usual, including speech and language therapy, motor therapy, music therapy, play therapy, and parental counseling.

[g] Goin-Kochel et al,[26] 2007: ABLLS is a curriculum guide for children with language delays and a comprehensive behavioral assessment; ABLLS domains, language, social/play, academics, self-help, motor.

[h] Remington et al,[29] 2007: Treatment-as-usual interventions in both groups included PECS, TEACCH, speech therapy, dietary intervention, and prescription medications.

[i] Zachor et al,[30] 2007: ED approach included speech and language, occupational, and music therapies, plus structured cognitive teaching (DIR, TEACCH, and ABA techniques).

[j] Cohen et al,[31] 2006: 35 to 40 hours per week for children aged >3 years; 20 to 30 hours per week for children aged <3 years.

[k] Drew et al,[37] 2002: Children in control group received mix of speech and language therapy, occupational therapy, and preschool services. Within 3 mo of initial assessment, 3 children in control group started on intensive, home-based ABA interventions (UCLA/Lovaas model, 1:1, mean of 32.9 h/week for 12 months).

[l] Drew et al,[37] 2002: Reflects different assessments of 3 reviewers.

Compared with early intervention models evaluated for preschool-aged children (aged 3–5 years), programs for children aged <3 years were more likely to use developmental approaches, more intensively involve parents, and target social communication. These studies varied in sample size and severity of diagnosis, dose (level of intensity/frequency of service delivery), duration, agent (parent, therapist, or a combination), and format of delivery (parent-managed/home-based and/or center-based in a clinic or school) of the intervention. Some interventions were comprehensive, defined as addressing multiple core ASD deficits, while others targeted specific areas of functioning. A word of caution is warranted when interpreting any 1 interventional study or model. In some cases, elements of a particular programmatic approach varied from study to study (eg, the addition of training in advanced social skills in 1 early intensive behavioral intervention program).[31] Furthermore, reported group differences may not reflect the range of individual responses in any 1 study, and participants who demonstrated gains in some end points may have continued to show impairment in others.

Six randomized controlled trials were considered to produce strong recommendations and an assessment that the desirable effects of an intervention clearly outweighed the undesirable effects. Only 2 studies focused solely on children aged <3 years; 1 was related to a comprehensive treatment approach,[17] and 1 was a targeted intervention program.[20] The remaining 4 studies included preschool-aged children as well as some children aged <3 years or focused on developmental tasks of infancy. Two of these studies evaluated the same sample of children aged 3 or 4 years at the beginning of treatment.[32,33]

To briefly summarize these 6 studies[17–20,32,33,38]: both of the comprehensive intervention programs (Early Start Denver Model [ESDM] and the UCLA/Lovaas model) and the 4 targeted interventions (focusing on social communication or imitation skills) exhibited significantly improved outcomes relative to comparison groups after therapeutic durations of 8 weeks to 2 to 3 years. Several of the 6 studies reported effect sizes: large effect sizes after 6 and 8 weeks of therapy for increases in joint attention skills,[20,32] a moderate effect size after 12 months for expressive language growth,[33] and small effect sizes after 13 months for parent–child interaction measures.[18] It is notable that targeted interventions generally focused on outcomes related to ASD-specific characteristics, whereas the comprehensive models included teaching to the core deficits but often did not measure changes in these core deficits (or obtained nonsignificant findings); they instead focused on gains in general functioning (eg, cognitive and/or adaptive skills). Two nonrandomized controlled studies were rated as producing strong recommendations: comprehensive applied behavior analysis (ABA)-type interventions were associated with significantly improved outcomes relative to the comparison group after 2 years (compared with publicly funded educational services)[29] and with significantly improved outcomes in a subset of participants after 1 year (compared with an eclectic mix of treatments).[23]

Although other studies included in the present review exhibited less than moderate quality of evidence and/or produced weak recommendations, it was agreed that the findings in these studies might nevertheless inform treatment options as well as future research. Specifically, there were studies rated as having a strong quality of evidence but equivocal findings.[16] For example, a recent trial evaluated the ESDM in a brief format: 1 hour per week of parent training for 12 weeks, as opposed to the original ESDM, which involved 20 hours per week of therapist involvement plus additional parent-mediated intervention for 2 years.[14] The study failed to detect improvements in parental intervention skill acquisition and child-related outcomes relative to community intervention controls.

Based on expert opinion that arose from the review and discussion of the existing evidence, members of the working group agreed on several summary statements intended to guide clinical practice and future research. Practice recommendations are highlighted in statements 1 through 4; consensus regarding future research directions is highlighted in statements 5 through 9. Statement 10 focuses on the importance of considering the potential impact of medical comorbidities on treatment and developmental outcomes.

SUMMARY STATEMENTS

Statement 1: Current best practices for interventions for children aged <3 years with suspected or confirmed ASD should include a combination of developmental and behavioral approaches and begin as early as possible.

Based on current outcome data, the working group supported the provision of interventions targeted to the specific deficits of ASD (eg, language skills, joint attention, emotional reciprocity) (Table 1) for children aged <3 years that integrate both behavioral and developmental approaches. Behavioral interventions are techniques based on behavioral analysis of antecedents and consequences of specific behaviors, and they use principles derived from experimental psychology research to systematically change behavior. Developmental models of intervention use developmental theory to design approaches to target ASD deficits.[57] Developmental approaches often

underlie community services, such as public school programs implemented by special education specialists and speech and language pathologists.[56] However, the distinction between behavioral and developmental strategies may not be very helpful, as many intervention programs blend features of both approaches. The curricula of a behavioral intervention may be developmentally informed and based on developmental sequences, whereas a developmental program could use behavioral techniques to teach a curriculum.

Our analysis supports the effectiveness of integrated developmental and behavioral interventions, outside of the laboratory setting, in improving developmental quotients, adaptive functioning, and language skills.[17,29]

In line with the American Academy of Pediatrics, the working group recommended initiating interventions as soon as a diagnosis of ASD is seriously considered or determined.[57] Data available since 2001 support the fact that early intensive education and therapies can yield significantly improved developmental outcomes. In addition, it has been suggested that interventions initiated before 3 years of age may have a greater positive impact than those begun after the age of 5 years.[58–60]

Statement 2: Current best practices for children aged <3 years with suspected or confirmed ASD should have active involvement of families and/or caregivers as part of the intervention.

There is a consensus that effective early intervention includes a family and/or caregiver component.[57] For many intervention programs, this approach would mean parental involvement as a co-therapist, with appropriate supervision, training, and monitoring as part of the intervention. Specifically, parents should help set goals and priorities for their child's treatment, identify and locate needed support for themselves, and teach or reinforce their child's new skills at home and in the community.[60]

Active family involvement can have a positive impact on developmental outcomes. Parental or caregiver involvement increases the amount of intervention time delivered to the child inasmuch as children in this age range are likely to spend more time with their parents in their home and neighborhoods than in other settings. Furthermore, parents and caregivers can capitalize on teachable moments as they occur, provide learning opportunities during daily routines, and facilitate the generalization of learned skills across environments.[15] Family involvement is also likely to be cost-effective and increases the sense of empowerment on the part of parents and caregivers. In the 2 comprehensive developmental/behavioral programs for which we have moderate or high evidence of effectiveness,[17,29] parents were supported in complementing educators and therapists in the delivery of the interventions because of the importance of, and challenges inherent in, carrying over services and generalizing skills across multiple settings. Importantly, the concept of parental involvement is consistent with the recommended broader best practices that support working with young children in natural environments. Several parent-mediated interventions have shown positive parent and/or child outcomes. However, the extent to which these interventions are as effective as therapist-mediated interventions or are more effective when added into comprehensive child services, or with the combination of therapist plus parent mediated interventions, requires further study.[18,20]

Statement 3: Interventions should enhance developmental progress and improve functioning related to both the core and associated features of ASD, including social communication, emotional/behavioral regulation, and adaptive behaviors.

Many behavioral interventions for ASD focus on cognitive, behavioral, and language outcomes, but interventions also need to address social communication challenges central to the diagnosis. Sensory dysregulation, challenging behaviors, and motor skills are also common in children with ASD and should be targeted by interventions when needed.

Despite an apparent lack of change on standardized measures of social communication symptoms in 2 randomized controlled trials,[17,37] a growing body of research describes the beneficial effects early intervention has on the development of communication and social functioning. (This lack of change may reflect the utilization of symptom measures such as the Autism Diagnostic Observation Schedule, which, as a diagnostic tool, was designed to be relatively stable; measures specifically designed and validated as being sensitive to change are needed.) Specifically, targeted interventions have been associated with gains in imitation,[16,19] joint attention,[16,20,32,34] social engagement,[20,32,33] other social communication measures,[34] and functional and symbolic play.[20,32]

Impaired effortful control (ie, a reduced ability to regulate attention, emotions, and behavior to achieve goals) has been reported in children with ASD as early as at 24 months of age.[61] Interventions dealing with attention regulation in young children with ASD have not yet been reported, but in typically developing children, short-term training has improved attention control measures associated with effortful

control.[62] Comprehensive interventions that blend developmental and behavioral approaches have successfully improved adaptive functioning in many studies.[17,23,29,31] Thus, future intervention studies should address and assess various developmental domains as intervention and outcome targets.

Statement 4: Intervention services should consider the sociocultural beliefs of the family and family dynamics and supports, as well as economic capability, in terms of both the delivery and assessment of factors that moderate outcomes.

Socioeconomic status, family characteristics, and cultural factors may present barriers to service provision. Families with lower socioeconomic status are likely to have less access to services. Because cultural values and differences can affect the goals and priorities of the family and may in some cases lead to misunderstandings, clinicians and other service providers should aim to understand the values, beliefs, and accompanying practices of families of differing cultures and assimilate that knowledge into their practice parameters as it relates to autism occurring in ethnically diverse populations. Culturally competent care extends beyond fluency in a non-English language. As a minimum, culturally appropriate program materials should be developed for families. In addition, training programs should be created that can help service providers learn how to promote culturally responsive assessment and intervention services.[56]

Management of a child with ASD should focus on the family as well as on the child.[57] Important considerations for the clinician include the well-being of each person in the family, the comfort and support of each family member, the lifestyle that has evolved around the child with ASD, and the unmet needs among family members or problem areas that might otherwise go unaddressed.[56] Service providers can be of assistance by monitoring the physical and mental health of the family as well as that of the child with ASD. Finally, respect for the perceptions, priorities, and preferences of family members is an important "family-centered" tenet to bear in mind when working with children on the autism spectrum and their complex needs.[63]

Statement 5: Intervention research should include socially and culturally diverse populations of participants and evaluate familial factors that may affect participation, acceptability, and outcomes of therapeutic approaches as well as willingness to participate in investigative studies.

Parents are expected to play a prominent role in supporting optimal development and thus intervention program delivery for their children, particularly at a very young age. An important focus of intervention research should therefore include factors such as cultural background and other family characteristics that may influence participation in treatment programs and interventional results. Due to attitudes concerning childhood rearing and independence, shame regarding developmental delays and ASD, or other societal and cultural beliefs, parents may be reluctant to enroll a child in a research study. Cumulatively, such decisions can diminish the generalizability and clinical applicability of reported interventions. In addition, when there is participation, cultural differences and language barriers might influence and moderate treatment effects.

In addition to any cultural issues, when parents are expected to be the therapeutic provider, assessment should focus on more than just fidelity of implementation and adherence to intervention goals. The quality of a parent's involvement, consideration of a parent's other responsibilities and roles,[20] and potential family stressors[15] arising from fulfilling their role in an intervention or from coping with care for a child with ASD warrant examination to determine whether moderators of treatment are present or are needed. Apart from any possible reluctance by families to participate in research, there is also a need for investigators to make a particular effort to recruit as culturally diverse a research sample as possible.

Statement 6: Future research should prioritize well-defined sampling strategies, rigorous investigative design, fidelity of implementation, and meaningful outcome measurements.

The methodologic rigor of intervention trials in ASD is improving, but continued attention to key aspects of research design is needed to further develop the evidence base for toddlers.

Future directions include identifying characteristics of children and families who would benefit most from particular interventions to support a more individualized approach, as well as systematically varying components of multifaceted intervention programs to identify critical ingredients. Thorough characterization of research participants would help to define the subset of children and families who most strongly benefit from particular intervention approaches. In addition, to avoid systematic bias from confounding factors, research participants should be randomly allocated to the treatment approaches that are being compared, and each treatment (including

community-based "as-usual" treatment) should be thoroughly described. Although the optimal study design to minimize bias in treatment research is a randomized controlled trial, it is acknowledged that contexts occur in which other methods may be appropriate. For example, to determine whether an intervention holds promise, it is important that intervention procedures are carefully tested for feasibility and acceptability. Moreover, single case designs, carefully implemented and with attention to appropriate measurement, may also be informative.[64] Attention to and systematic evaluation of fidelity of implementation and selection of well-validated measures of key constructs (eg, joint attention, imitation, other indicators of age-appropriate social and communication skills and function) that are responsive to change are also essential.

Statement 7: Research is needed to determine the specific active components of effective interventions, including but not limited to the type of treatment provided, the agent implementing the intervention(s) (parent, therapist, teacher, or combination), consistency of service provision across environments and between providers, and duration of treatment and hours per week.

Information is lacking regarding the features of an intervention that drive its effectiveness, but progress is being made on identifying these active ingredients or mechanisms of change. Without appropriate study designs to carefully examine the effect of specific intervention strategies such as treatment type, dose, and agent, we may be unable to determine which of the potentially significant elements in an intervention model are responsible for change and for which subgroups. With such information, future intervention programs can be refined.

Intensity of intervention

The National Research Council has recommended a minimum intensity of 5 hours a day, 5 days a week, for interventions.[60] However, some recent studies have suggested the possibility of positive outcomes with fewer hours of direct therapist involvement for young toddlers with ASD, particularly when parents are actively engaged in the treatment process. For example, gains in some social communication skills (eg, play, joint attention, imitation) were demonstrated in some studies when directly targeted in interventions of relatively low intensity (based on hours per week or length of treatment).[16,18,20] Notably, the "real-life" intensity of the intervention may be influenced by the degree to which parents are implementing the strategies in natural routines throughout the day. The effectiveness of interventions is also likely to be influenced by whether training and ongoing supports allow parents to correctly implement the treatment strategies (ie, with fidelity to the treatment procedures as originally designed), as has been reported in the treatment of preschool-aged children with ASDs.[65] In addition, other factors can affect the extent to which such interventions are effective, including age, degree of impairment, and the extent to which the child receives other services.

Treatment content

A recent study in toddlers with ASD has attempted to determine the additive value of joint attention, imitation, and affect on an intervention when applied within 2 developmental/behavioral toddler classroom environments.[16] The investigators evaluated impact in 1 study group, and another group received the same overall comprehensive intervention but without the ingredient of interest. Few differences emerged in this study except for the apparent benefit of imitation in 1 group. Nonetheless, this research paradigm provides a possible model through which intervention research may be implemented. Similarly, other investigators have evaluated the additive effects of joint attention or play skills into an ABA program that did not include a focus on these developmental skills. Teaching these skills increased their spontaneous occurrence in generalized contexts and further predicted greater language outcomes compared with the children in the ABA program without a focus on play and joint attention.[33,59]

Incorporating teaching targets of joint attention, play, and imitation are clearly indicated for early intervention programs for ASD. However, given the heterogeneity of the disorder, it will be critical to determine how treatment strategies can be most effectively tailored to the needs of subgroups of children with ASD who have particular clinical profiles.

Statement 8: Adopting a common set of research-validated core measures of ASD symptoms (including but not limited to cognitive function, communication, and adaptive behavior) that can be used across multiple sites will facilitate comparisons across studies of children with ASD aged <3 years.

The interpretation of study findings is often hampered when investigators use different variables, or measures, to report outcomes. A consistent set of core measures relevant to the specific intervention goal(s) of interest should be adopted for studies of toddlers with ASD as well as for older children. Outcome measures do not need to be identical across studies, but agreement on a subset of standardized instruments to use (which may assess

changes in cognitive function, core autism symptoms, and adaptive and language behavior) would facilitate future comparisons. Some early developmental skills could yield "early-read" measures that are important to later developmental outcomes. These early-read measures may include joint attention, shared affect, and imitation skills, with the expectation that these early developmental tasks may predict better functioning in later cognition, language, and adaptive behavior. Early-read measures may provide important information on the effectiveness of short-term interventions and may also offer information on active ingredients essential to include in comprehensive intervention programs. Additional measures related to the impact that having a child with ASD has on family life and parental stress would also be important.

Statement 9: Future research should examine biological and behavioral heterogeneity as moderators of individual responses to interventions.

In any sample population, positive responses to an intervention can range from dramatic to extremely limited. Factors that underlie such heterogeneity—possible moderators of individual responses—can include age at onset of intervention, patient characteristics (eg, baseline stage of development of cognitive function, language and preverbal skills, adaptive behavior, sociocultural characteristics), and symptom severity. As important, however, is the increasing appreciation that ASD is a heterogeneous disorder—etiologically, biologically, and clinically. Given this heterogeneity, it is highly likely that specific subsets of individuals with ASD may respond to specific interventions more effectively than to others, perhaps based on etiology and underlying biological factors alone. Thus, there is a critical need to begin to identify subtypes of individuals with ASD, to understand the cause of their disorder as well as the associated neurobiological mechanisms at work in each case, and to be able to offer more directed interventions depending on the biological subtype when available and present.

A number of genetic and neurobiological subgroups are already known to be associated with ASD. The most well-known groups are children with fragile X syndrome, tuberous sclerosis, and duplication 15q. Other genetic disorders have been identified as being associated with ASD features, and a growing number of candidate genes are being explored. For example, Campbell et al[66] reported that children with ASD and MET gene mutations were more likely to have gastrointestinal disorders, raising the possibility that medical comorbidities in children with ASD could index underlying genetic heterogeneity. It is thus important for future research to determine both biological and clinical subtypes within the autism spectrum that may ultimately affect the effectiveness of treatment and intervention.

To date, few studies have been designed or powered for analysis of heterogeneous effects.[67] Treatment modifiers were recently identified in 2 studies based on appropriate study design and statistical analysis. In both studies, a measure developed to index the level of initial object exploration determined the extent to which a child would benefit more from 1 language-based intervention versus another[35] or the extent to which children had better communication outcomes from a parent-mediated intervention.[15] Object exploration can reflect a child's flexibility in play and play level, both of which may influence later cognitive and language outcomes.[59] Further studies like these are needed before we can make informed choices and personalize the treatment of each individual child.

Statement 10: Intervention providers should consider medical disorders that may affect a child's clinical presentation (especially behavior) and response to an intervention and should refer to appropriate health care providers as indicated.

It has become increasingly evident in the ASD population that changes in behavior may be associated with an underlying medical condition.[13] For example, clinical experience would suggest that a child with ASD exhibiting behavioral changes might be experiencing pain or discomfort owing to a medical problem such as otitis media, a dental abscess, or constipation. Frequently encountered medical factors in ASD include: seizures, particularly in children who also have severe intellectual disability, motor deficits, or a positive family history of epilepsy[68,69]; other gastrointestinal symptoms[57,70]; and sleep disturbances affecting daytime functioning. The full effect of medical factors on the clinical presentation of children aged <3 years with ASD is not known, nor has the association between medical factors and maladaptive behaviors such as aggression and self-injury been well studied in general in ASD. Nevertheless, best practices would indicate that a patient with a potential medical comorbidity be referred to a medical specialist for appropriate evaluation, diagnosis, and management. It is important that future research address these and other potential medical factors, how they may be more reliably identified (especially in nonverbal or hypo-verbal ASD individuals), and what effect treatment of these conditions may have on behavior, developmental trajectory, and learning.

ACKNOWLEDGMENTS

The conference chairs and working groups acknowledge the preconference contributions of Tony Charman, PhD, and Gary Mesibov, PhD, who were unable to attend the conference. We also acknowledge the

efforts of Katherine F. Murray, BSN, RN, Massachusetts General Hospital for Children, in coordinating the forum and subsequent conference report process, and Sifor Ng in the conference report process.

The meeting and consensus report were sponsored by the Autism Forum. An important goal of the forum is to identify early indicators of ASDs that may lead to effective health care services. Autism Forum programs are developed under the guidance of its parent organization, the Northwest Autism Foundation. For this project, the Autism Research Institute provided financial support.

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Drs Zwaigenbaum and Bauman initiated a literature review, co-chaired the meeting that generated the consensus recommendations outlined in this article, and drafted the initial manuscript; Drs Choueiri and Kasari co-chaired the working group that conducted the detailed literature review, generated initial recommendations that were discussed at the consensus meeting, and provided critical input to subsequent drafts of the manuscript; Drs Carter, Granpeesheh, Mailloux, Smith Roley, and Wagner were members of the working group that reviewed selected publications, contributed to initial recommendations that were reviewed at the consensus meeting, and critically reviewed the manuscript; Drs Fein, Pierce, Buie, Davis, Newschaffer, Robins, Wetherby, Stone, Yirmiya, Estes, Hansen, McPartland, and Natowicz contributed to the consensus meeting that formed the basis for the manuscript and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-3667E

doi:10.1542/peds.2014-3667E

Accepted for publication Aug 3, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: Dr Zwaigenbaum was the site Principal Investigator of a study sponsored by SynapDx (he received operating funds but no honoraria). Drs Fein and Robins are co-owners of M-CHAT, LLC, which licenses use of the Modified Checklist for Autism in Toddlers in electronic products. Dr Stone is the author of the Screening Tool for Autism in Two-Year-Olds and receives a share of royalties from sales of this instrument. The authors received an honorarium as well as travel expenses from Autism Forum for contributing to the expert panels.

FUNDING: Sponsored by the Autism Forum under the guidance of the Northwest Autism Foundation and with the support of the Autism Research Institute.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.