Autism Spectrum Disorder: Research and Implications for Treatment in Children and Adolescents

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January 12, 2013  PAL Conference
Objectives for Today

1. To review the description of autism (autism spectrum disorders—ASDs) and evolution of diagnostic criteria over time.

2. To review proposed changes to the diagnostic criteria for ASD as currently planned for DSM-5.
Diagnostic challenges in Autism
--who is in and who is out?

how wide a spectrum?

how to capture heterogeneity?

how does this influence treatment selection?
Sanity and Insanity.

By CHARLES MERCIER, M.B.,
Lecturer on Insanity at the Westminster Hospital Medical School, and at the Medical School for Women.

WITH ILLUSTRATIONS.

London: WALTER SCOTT, LTD., PATERNOSTER SQUARE. CHARLES SCRIBNER'S SONS, 153-157 FIFTH AVENUE, NEW YORK.
fact has impressed itself upon me that it is fruitless to endeavour to draw up an elaborate scheme of classes, orders, and genera, into which cases of insanity are to be grouped. No such divisions exist in nature, and to create them would be a highly artificial proceeding, and one that would not accurately represent the facts. Certain it is, that there are wide differences between different cases, but equally certain is it that the differences are not abrupt, and that any scheme of division, that shall correspond with the facts, must separate the cases into but a few broad and comprehensive groups, and must recognize that between these groups no exact line of demarkation can be drawn. Cases will always occur partaking pretty equally of the nature of two adjoining groups, and other cases will occur which exhibit at one time the features of one group, and at another time those of another. Nevertheless, it is certain that cases of insanity
The Autism Spectrum Quotient: Children’s Version (AQ-Child)

Bonnie Au yeung · Simon Baron-Cohen · Sally Wheelwright · Carrie Allison

Abstract

The Autism Spectrum Quotient—Children’s Version (AQ-Child) is a parent-report questionnaire that aims to quantify autistic traits in children 4–11 years old. The range of scores on the AQ-Child is 0–150. It was administered to children with an autism spectrum condition (ASC) \((n = 540)\) and a general population sample \((n = 1,225)\). Results showed a significant difference in scores between those with an ASC diagnosis and the general population. Receiver-operating-characteristic analyses showed that using a cut-off score of 76, the AQ-Child has high sensitivity (95%) and specificity (95%). The AQ-Child showed good test–retest reliability and high internal consistency. Factor analysis provided support for four of the five AQ-Child design subscales. Future studies should evaluate how the AQ-C performs in population screening.
Barr (1904) Case Report: “Kirtie”

Unique among 2500 children in institution
Male: 22 years old (intelligence at 5 y/o)
No Family History of nervous/mental disease
Parents of exceptional refinement and intelligence
Unusually large head
Normal development until 16 months of age
Developed epilepsy at age of 4
Learned to talk normally, but developed a habit of peculiar repetition.
Precocious memory and need to have nursery rhymes repeated to him daily.
Liked the presence of other children but did not join in their play
Would spend hours apart amusing himself with blocks or weaving strings.
Entered school with difficulty and talked constantly using made up phrases.
Nervous, restless, self-willed, would work himself into a fury when thwarted.
Spent great deal of time twirling and untwirling a string.
Has phenomenal memory: recalls the names of people he hasn’t seen in years.
Is extravagantly fond of blocks
Would deliberately tear his clothes to pieces
Speaks of himself in the 3rd person
Mutters vacant repetitions; speech is automatic
"Since 1938, there have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far, that each case merits—and, I hope, will eventually receive—a detailed consideration of its fascinating peculiarities."
Kanner Syndrome Highlights

1. A profound lack of affective contact with other people.
2. An anxiously obsessive desire for the preservation of sameness.
3. A fascination for objects, which are handled with skill in fine motor movements.
4. Mutism, or a kind of language that does not seem to be intended to serve interpersonal communication.
5. The retention of an intelligent and pensive physiognomy and good cognitive potential, manifested, in those who can speak, by feats of memory and, in the mute children, by their skill on performance tests.
In what follows, I will describe a particularly interesting and highly recognisable type of child.¹ The children I will present all have in common a fundamental disturbance which manifests itself in their physical appearance, expressive functions and, indeed, their whole behaviour. This disturbance results in severe and characteristic difficulties of social integration. In many cases the social problems are so profound that they overshadow everything else. In some cases, however, the problems are compensated by a high level of original thought and experience. This can often lead to exceptional achievements in later life. With the type of personality disorder presented here we can demonstrate the truth of the claim that exceptional human beings must be given exceptional educational treatment, treatment which takes account of their special difficulties. Further, we can show that despite abnormality human beings can fulfil their social role within the community, especially if they find understanding, love and guidance. There are many reasons for describing in detail this type of abnormally developing child. Not the least of them is that these children raise questions of central importance to psychology and education.
CLINICAL MANIFESTATIONS OF AUTISM AND SCHIZOPHRENIA IN CHILDHOOD

DANIEL CAPPON, M.B., M.R.C.P.,* Toronto
Currently, “autistic behavior” is characterized in the literature by reference to extreme preoccupation, a highly personalized and stereotyped approach to inanimate objects, and unrelatedness to people. In Kanner’s initial descriptive study of early infantile autism he felt that his sample of 11 children presented two major primary symptoms: extreme interpersonal aloneness and a marked desire for the preservation of sameness. Utilizing these specific diagnostic guidelines, a wide number of clinical disorders that display autistic reactions in young children has been reported. The range of these reported clinical disorders is noted in Table 4.1.
Table 4.1 Causative Factors Reported in Autistic Reactions of Childhood

<table>
<thead>
<tr>
<th>Acute situational stress reactions</th>
<th>Deprivation: maternal, sensory, and affective</th>
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<tbody>
<tr>
<td>Central language disorders</td>
<td>Early infantile autism</td>
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<td>Childhood schizophrenia</td>
<td>Idiot savant</td>
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<td>Chronic brain syndromes of</td>
<td>Mental retardation</td>
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<tr>
<td>Diverse etiologies</td>
<td>Parental overprotection with infactilization</td>
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<td>Constitutional factors</td>
<td>Precipitate of severe parental psychopathology</td>
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<td>Convulsive disorders</td>
<td></td>
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<tr>
<td>Deafness</td>
<td></td>
</tr>
</tbody>
</table>

Menolascino, FJ. Challenges in Mental Retardation: Progressive Ideology and Services 1977
Diagnostic Criteria for Autism through the Diagnostic and Statistical Manual of Mental Disorders

1952
1968
1980
1987
1994
2000

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DSM III
(1980)

• Infantile Autism

• Childhood Onset Pervasive Developmental Disorder

• Atypical Pervasive Developmental Disorder
• Infantile Autism

A. Onset before 30 months of age
B. Pervasive lack of responsiveness to other people (autism).
C. Gross deficits in language development.
D. If speech is present, peculiar speech patterns such as immediate and delayed echolalia, metaphorical language, pronomial reversal.
E. Bizarre responses to various aspects of the environment, e.g., resistance to change, peculiar interest in or attachments to animate or inanimate objects.
F. Absence of delusions, hallucinations, loosening of associations, and incoherence as in Schizophrenia.
DSM III

• Childhood Onset Pervasive Developmental Disorder

– **At least 3 of the following:**

1. Sudden excessive anxiety manifested by such symptoms as free-floating anxiety, catastrophic reactions to everyday occurrences, inability to be consoled when upset, unexplained panic attacks

2. Constricted or inappropriate affect, including lack of appropriate fear reactions, unexplained rage reactions, and extreme mood lability
DSM III

3. resistance to change in the environment (e.g., upset if dinner time is changed), or insistence on doing things in the same manner every time (e.g., putting on clothes always in the same order).

4. oddities of motor movement, such as peculiar posturing, peculiar hand or finger movements, or walking on tiptoe

5. abnormalities of speech, such as questionlike melody, monotonous voice

6. hyper- or hypo-sensitivity to sensory stimuli, e.g., hyperacusis

7. self-mutilation, e.g., biting or hitting self, head banging
C. Onset of the full syndrome after 30 months of age and before 12 years of age.

D. Absence of delusions, hallucinations, incoherence, or marked loosening of associations.
Autistic Disorder

≥ 8/16 items [≥2 from (A) and 1 from (B) and (C)]:

A. Qualitative impairment in reciprocal social interaction as manifested by the following:
   1. marked lack of awareness of the existence or feelings of others (e.g., treats a person as if he or she were a piece of furniture; does not notice another person’s distress; apparently has no concept of the need of others for privacy)
DSM-IV
(1994)
Autistic Disorder
Asperger’s Disorder
Childhood Disintegrative Disorder
Rett’s Disorder
Pervasive Developmental Disorder
Not Otherwise Specified

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Asperger’s Disorder

C. The disturbance causes clinically significant impairments in social, occupational, or other important areas of functioning.

D. There is no clinically significant general delay in language e.g., single words used by age two years, communicative phrases used by age three years).

E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.

F. Criteria are not met for another specific pervasive developmental disorder or schizophrenia.

PDD NOS

The essential features of PDD-NOS are severe and pervasive impairment in the development of reciprocal social interaction or verbal and nonverbal communication skills; and stereotyped behaviors, interests, and activities.

The criteria for Autistic Disorder are not met because of late age onset; atypical and/or sub-threshold symptomatology are present.

This category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction or verbal and nonverbal communication skills, or when stereotyped behavior, interests, and activities are present, but the criteria are not met for a specific Pervasive Developmental Disorder.
Did Asperger’s Cases Have Asperger Disorder? A Research Note

Judith N. Miller and Sally Ozonoff
University of Utah, Salt Lake City, U.S.A.

With publication of the fourth edition of the Diagnostic and statistical manual of mental disorders (DSM–IV), standardized criteria for Asperger Disorder, a putative subtype of Pervasive Developmental Disorder, are now available. This paper examines the four cases Asperger originally presented in his seminal paper (1991/1944), using DSM–IV criteria to determine whether a diagnosis of Autistic or Asperger Disorder is most appropriate. We found that all four cases met DSM–IV criteria for Autistic Disorder, rather than Asperger Disorder. This suggests that the syndrome Asperger originally described may not be captured by present diagnostic criteria. Implications for future research are discussed.

Keywords: Autism, Asperger Disorder, subtype validity, diagnostic criteria.

Abbreviations: HFA: High-functioning autism; PDD: Pervasive Developmental Disorder.
### Table 1

<table>
<thead>
<tr>
<th>Number of Symptoms of DSM-IV-defined Autistic Disorder Demonstrated by Asperger's Original Cases</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>1. Impairment in Social Interaction</td>
</tr>
<tr>
<td>a. Impaired use of nonverbal communication*</td>
</tr>
<tr>
<td>b. Poor peer relationships*</td>
</tr>
<tr>
<td>c. Lack of sharing*</td>
</tr>
<tr>
<td>d. Lack of social/emotional reciprocity*</td>
</tr>
<tr>
<td>2. Impairment in Communication</td>
</tr>
<tr>
<td>a. Delayed language development</td>
</tr>
<tr>
<td>b. Impaired ability to initiate or sustain conversations</td>
</tr>
<tr>
<td>c. Stereotyped, repetitive or idiosyncratic language</td>
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<tr>
<td>d. Social play below developmental level</td>
</tr>
<tr>
<td>3. Restricted Behavior or Interests</td>
</tr>
<tr>
<td>a. Encompassing preoccupation*</td>
</tr>
<tr>
<td>b. Inflexible adherence to routines*</td>
</tr>
<tr>
<td>c. Stereotyped and repetitive motor mannerisms*</td>
</tr>
<tr>
<td>d. Repetitive use of objects*</td>
</tr>
</tbody>
</table>

*These symptoms are common among people with autism and Asperger's Disorder.
How stable are autism diagnoses over time?
Residual Language Deficits in Optimal Outcome Children with a History of Autism

Elizabeth Kelley · Jennifer J. Paul · Deborah Fein · Letitia R. Naigles

Published online: 8 August 2006
© Springer Science+Business Media, Inc. 2006
<table>
<thead>
<tr>
<th>Child (random initials)</th>
<th>Age at Dx by author in months</th>
<th>Diagnosis given by author at this time</th>
<th>Original diagnosis</th>
<th>Age at current testing in months</th>
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<td>38</td>
<td>PDD-NOS</td>
<td>Autistic disorder</td>
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<td>PDD-NOS</td>
<td>PDD-NOS</td>
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<td>D.K.</td>
<td>64</td>
<td>Asperger's</td>
<td>Autistic disorder</td>
<td>77</td>
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<tr>
<td>P.B. (f)</td>
<td>44</td>
<td>PDD-NOS</td>
<td>Autistic disorder</td>
<td>79</td>
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<tr>
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<td>Autistic disorder</td>
<td>80</td>
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<td>C.B.</td>
<td>58</td>
<td>Autistic Disorder</td>
<td>PDD-NOS</td>
<td>82</td>
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<tr>
<td>N.E.</td>
<td>77</td>
<td>PDD-NOS</td>
<td>Autistic disorder</td>
<td>86</td>
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<tr>
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<td>52</td>
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<tr>
<td>M.S.</td>
<td>51</td>
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<td>Autistic disorder</td>
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<td>PDD-NOS</td>
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<td>T.M.</td>
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<td>U.N.</td>
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<tr>
<td>T.B.</td>
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<td>Autistic Disorder</td>
<td>Autistic disorder</td>
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<tr>
<td>Q.K.</td>
<td>92</td>
<td>PDD-NOS (mild)</td>
<td>PDD-NOS</td>
<td>109</td>
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</tbody>
</table>

f = female
Is Pervasive Developmental Disorder Not Otherwise Specified Less Stable Than Autistic Disorder? A Meta-Analysis

Emélie Rondeau · Leslie S. Klein · André Masse · Nicolas Bodeau · David Cohen · Jean-Marc Guilé

Published online: 14 December 2010 © Springer Science+Business Media, LLC 2010

Abstract  We reviewed the stability of the diagnosis of pervasive developmental disorder not otherwise specified (PDD-NOS). A Medline search found eight studies reiterating a diagnostic assessment for PDD-NOS. The pooled group included 322 autistic disorder (AD) and 122 PDD-NOS cases. We used percentage of individuals with same diagnose at Times 1 and 2 as response criterion. The pooled Relative Risk was 1.95 ($p < 0.001$) showing that AD diagnostic stability was higher than PDD-NOS. When diagnosed before 36 months PDD-NOS bore a 3-year stability rate of 35%. Examining the developmental trajectories showed that PDD-NOS corresponded to a group of heterogeneous pathological conditions including prodromic forms of later AD, remitted or less severe forms of AD, and developmental delays in interaction and communication.

Keywords  Validity · Diagnosis · Autistic disorder · Pervasive developmental disorder · Autism · Meta-analysis

Introduction

Over the past 15 years, there has been increasing interest in the early identification of autism spectrum disorders (ASD). In that respect, several studies have examined the stability of early diagnosis (Lord 1995; Cox et al. 1999; Moore and Goodson 2003; Charman et al. 2005). In keeping with those studies, we conducted a meta-analysis focusing on the stability of the diagnosis of pervasive developmental disorder not otherwise specified (PDD-NOS), when diagnosed for the first time in young children.
Fig. 3 Developmental trajectories within the autism spectrum. *AD* autistic disorder, *PDD-NOS* pervasive developmental disorder not otherwise specified, *non ASD* non autism spectrum disorder. Numbers within brackets refer to the discussion part of the text.
Is there genetic support for categorical subtypes?

Do specific autism subtypes track within families?
Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study

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¹Centre for Basic Psychiatric Research, Psychiatric Hospital in Aarhus, Aarhus University Hospital, Denmark; ²National Centre for Register-based Research, University of Aarhus, Denmark

Background: The etiology of autism is unknown. A strong genetic component has been detected but non-genetic factors may also be involved in the etiology. Methods: We used data from the Danish Psychiatric Central Register and the Danish Civil Registration System to study some risk factors of autism, including place of birth, parental place of birth, parental age, family history of psychiatric disorders, and paternal identity. Results: A total of 943,664 children younger than ten years were followed from 1994 to 2001; of those, 818 children developed autism. The highest risks of autism were found in siblings of children with autism, or Asperger’s syndrome and other pervasive developmental disorders (PDDs), with relative risks of 22 and 13, respectively. The relative risk of autism in the child was about twice as high if the mother had been diagnosed with a psychiatric disorder. The risk of autism was associated with increasing degree of urbanisation of the child’s place of birth and with increasing paternal, but not maternal, age. An increased relative risk of 1.4 was found if the mother was born outside Europe, and in children of parents who were born in different countries. Conclusions: The highest risk of autism was found in families with a history of autism, or Asperger’s syndrome and other PDDs in siblings, supporting the commonly accepted knowledge that genetic factors are involved in the etiology of autism. Keywords: Autism, Asperger’s syndrome, PDD, family history, risk factors, place of birth, maternal age, paternal age, parental age, psychiatric disorders, immigrants.
Results: A total of 943,664 children younger than ten years were followed from 1994 to 2001; of those, 818 children developed autism. The highest risks of autism were found in siblings of children with autism, or Asperger’s syndrome and other pervasive developmental disorders (PDDs), with relative risks of 22 and 13, respectively.

Furthermore, we found gradations in the relative risk for autism in siblings from families with the sibling affected with autism to families with the other PDDs in the child and this provides evidence from an epidemiological study that PDDs are spectrum disorders with the same genetic liability.
Is there genetic support for categorical subtypes?

Does specific autism subtype (e.g. severity) track within families?
Recurrence Risk for Autism Spectrum Disorders: A Baby Siblings Research Consortium Study
Sally Ozonoff, Gregory S. Young, Alice Carter, Daniel Messinger, Nurit Yirmiya, Lonnie Zwaigenbaum, Susan Bryson, Leslie J. Carver, John N. Constantino, Karen Dobkins, Ted Hutman, Jana M. Iverson, Rebecca Landa, Sally J. Rogers, Marian Sigman and Wendy L. Stone

*Pediatrics* 2011;128;e488; originally published online August 15, 2011;
DOI: 10.1542/peds.2010-2825
The age of the infant at study enrollment, the gender and functioning level of the infant’s older sibling, and other demographic factors did not predict ASD outcome.
Advances in autism genetics: on the threshold of a new neurobiology

Brett S. Abrahams & Daniel H. Geschwind

Nature Reviews Genetics 9, 341-355 (May 2008)
Is there genetic support for categorical subtypes?

Do specific autism subtypes track within “homogeneous” genetic subgroups?
Autism Profiles of Males With Fragile X Syndrome

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M.I.N.D. Institute and Department of Pediatrics, University of California at Davis Medical Center

David Hessl, Beth Goodlin-Jones, and Jessica Ferranti
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Susan Bacalman
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Ingrid Barbato
Neurogene Clinical Laboratory (Florianopolis, Brazil)

Flora Tassone and Paul J. Hagerman
Department of Biochemistry and Molecular Medicine, University of California at Davis School of Medicine

Kristin Herman and Randi J. Hagerman
M.I.N.D. Institute and Department of Pediatrics, University of California at Davis Medical Center

Abstract

Autism, which is common in individuals with fragile X syndrome, is often difficult to diagnose. We compared the diagnostic classifications of two measures for autism diagnosis, the ADOS and the ADI-R, in addition to the DSM-IV-TR in 63 males with this syndrome. Overall, 30% of the subjects met criteria for autistic disorder and 30% met criteria for PDD-NOS. The classifications on the ADOS and DSM-IV-TR were most similar, whereas the ADI-R classified subjects as autistic much more frequently. We further investigated the relationship of both FMRP and FMRI mRNA to symptoms of autism in this cohort and found no significant relationship between the measured cognitive and molecular features, including FMRP, FMRI mRNA, and CGG repeat number.
Group Classifications for Individual Measures and Overall Group Assignment

(n = 63 males with Fragile X Syndrome)

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Fragile X mutation

Autism

PDD-NOS

Other developmental/behavioral conditions

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PAL Conference
Fragile X mutation

- Autism
- PDD-NOS
- Other developmental/behavioral conditions

Autism

- PDD-NOS
- Other developmental/behavioral conditions
Speech delays and behavioral problems are the predominant features in individuals with developmental delays and 16p11.2 microdeletions and microduplications

Jill A. Rosenfeld · Justine Coppinger · Bassem A. Bejjani · Santhosh Girirajan · Evan E. Eichler · Lisa G. Shaffer · Blake C. Ballif

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than the microduplications. Although 16p11.2 abnormalities have mostly been identified in ASD cohorts, our cohort demonstrates a phenotypic range from behavioral problems that were not considered autistic to formal diagnoses of PDD-NOS in three individuals, suggestive of a spectrum of developmental and speech delays and behavioral issues that overlaps with ASD. The disparity in numbers of individuals with ASD among cohorts may be the result of differences in study inclusion criteria. Because the microdeletion and
than the microduplications. Although 16p11.2 abnormalities have mostly been identified in ASD cohorts, our cohort demonstrates a phenotypic range from behavioral problems that were not considered autistic to formal diagnoses of PDD-NOS in three individuals, suggestive of a spectrum of developmental and speech delays and behavioral issues that overlaps with ASD. The disparity in numbers of individuals with ASD among cohorts may be the result of differences in study inclusion criteria. Because the microdeletion and
A Multisite Study of the Clinical Diagnosis of Different Autism Spectrum Disorders

Catherine Lord, PhD; Eva Petkova, PhD; Vanessa Hus, MSc; Weijin Gan, MS, MD; Feihan Lu, MA; Donna M. Martin, MD, PhD; Opal Ousley, PhD; Lisa Guy, PhD; Raphael Bernier, PhD; Jennifer Gerdts, MA; Molly Algermissen, PhD; Agnes Whitaker, MD; James S. Sutcliffe, PhD; Zachary Warren, PhD; Ami Klin, PhD; Celine Saulnier, PhD; Ellen Hanson, PhD; Rachel Hundley, PhD; Judith Piggot, MD, PhD; Eric Fombonne, MD; Mandy Steiman, PhD; Judith Miles, MD, PhD; Stephen M. Kanne, PhD; Robin P. Goin-Kochel, PhD; Sarika U. Peters, PhD; Edwin H. Cook, MD; Stephen Guter, MA; Jennifer Tjernagel, MS; Lee Anne Green-Snyder, PhD; Somer Bishop, PhD; Amy Esler, PhD; Katherine Gotham, PhD; Rhiannon Luyster, PhD; Fiona Miller, PhD; Jennifer Olson, PhD; Jennifer Richler, PhD; Susan Risi, PhD

Arch Gen Psychiatry 2012;69:306-313.
Table 2. Summary of Variation Between Sites With Respect to Diagnostic Scales and Continuous Demographic and Behavioral Characteristics

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<thead>
<tr>
<th></th>
<th>Ranges Across Sites</th>
<th>Variance</th>
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<tr>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
<td>Mean</td>
<td>SD</td>
<td>Overall Mean (SD)</td>
<td>Within Sites</td>
<td>Between Sites</td>
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<td>48-51</td>
<td>209-216</td>
<td>101.8-117.3</td>
<td>38.5-45.0</td>
<td>107.2 (42.1)</td>
<td>1770.0</td>
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<tr>
<td>No control</td>
<td>5-13</td>
<td>138-167</td>
<td>72.4-85.4</td>
<td>27.5-33.4</td>
<td>79.3 (30.5)</td>
<td>918.4</td>
<td>13.1</td>
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<td>Control for verbal mental age</td>
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<tr>
<td>Nonverbal IQ</td>
<td>9-30</td>
<td>133-161</td>
<td>79.7-89.8</td>
<td>22.0-27.7</td>
<td>86.1 (25.3)</td>
<td>635.1</td>
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<td>Control for nonverbal mental age</td>
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<td>Autism Diagnostic Interview—Revised</td>
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<tr>
<td>Social interaction</td>
<td>8-9</td>
<td>30</td>
<td>18.5-22.6</td>
<td>5.1-6.1</td>
<td>20.1 (5.7)</td>
<td>31.8</td>
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<td>Verbal communication</td>
<td>6-8</td>
<td>24-26</td>
<td>15.6-18.4</td>
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<td>0-3</td>
<td>14</td>
<td>8.2-10.3</td>
<td>3.1-3.6</td>
<td>9.1 (3.4)</td>
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<td>0.5</td>
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<tr>
<td>Restricted/repetitive behavior</td>
<td>0-2</td>
<td>12</td>
<td>5.8-7.1</td>
<td>2.2-2.7</td>
<td>6.5 (2.5)</td>
<td>6.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Autism Diagnostic Observation Schedule</td>
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<td></td>
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<tr>
<td>Calibrated severity score</td>
<td>4-4</td>
<td>10</td>
<td>6.8-8.1</td>
<td>1.6-1.8</td>
<td>7.4 (1.7)</td>
<td>2.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Social and communication</td>
<td>4-7</td>
<td>22-24</td>
<td>12.1-14.7</td>
<td>3.8-4.6</td>
<td>13.3 (4.2)</td>
<td>17.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Social affect</td>
<td>3-6</td>
<td>19-20</td>
<td>10.3-12.7</td>
<td>3.7-4.3</td>
<td>11.0 (4.0)</td>
<td>16.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Restricted/repetitive behavior</td>
<td>0-0</td>
<td>8</td>
<td>3.4-4.5</td>
<td>1.8-2.3</td>
<td>3.9 (2.0)</td>
<td>4.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Vineland-II composite</td>
<td>27-52</td>
<td>95-115</td>
<td>68.9-75.9</td>
<td>9.3-14.4</td>
<td>73.8 (11.7)</td>
<td>134.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Aberrant Behavior Checklist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>0-0</td>
<td>28-42</td>
<td>8.4-13.1</td>
<td>6.8-9.2</td>
<td>11.3 (8.6)</td>
<td>72.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>0-1</td>
<td>37-48</td>
<td>13.1-18.0</td>
<td>8.9-11.0</td>
<td>16.5 (10.5)</td>
<td>107.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Sample size, No.</td>
<td>97</td>
<td>229</td>
<td>175</td>
<td>38</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: ICC, intraclass correlation coefficient; Vineland-II, the second edition of the Vineland Adaptive Behavior Scales.\(^{23}\)

The ratio of between-site variance to total variance.

The highest possible score (ie, ceiling) on the instrument.
Best-estimate clinical diagnoses across 12 university-based sites for 2102 probands assigned to 3 autism spectrum disorder diagnostic categories
Evidence of spectrum nature of the PDD diagnoses

• Genetics – twin, family, genetic studies:
  – No relationship between severity of symptoms in the two sibs with ASD (Ozonoff et al, baby sibs consortium, 2011).
  – Sibs of children with Asperger’s have a 13 fold increase in diagnosis of full AD (common genetic basis) Lauritson et al, 2005).
  – Variability (spectrum) in context of shared genetic etiology/risk (e.g., Fragile X, others).

• Changing picture over time (diagnosis can change in same individual).

• Inter-rater agreement at the supra-ordinate level and with AD and lack of agreement with the subcategories.

• Lack of solid evidence of differences at the cognitive, brain, and genetic levels of analysis.
MEMBERS
- Gillian Baird
- Ed Cook
- Francesca Happe
- James Harris
- Walter Kaufmann
- Bryan King
- Catherine Lord
- Joseph Piven
- Rosemary Tannock
- Sally Rogers
- Sarah Spence
- Susan Swedo, chair
- Amy Wetherby
- Harry Wright

ADVISORS
- Jim Bodfish
- Martha Denckla
- Ann Kummer
- Maureen Lefton-Grief
- Sally Ozonoff
- Diane Paul
- Eva Petkova
- Daniel Pine
- Alya Reeve
- Mabel Rice
- Joseph Sergeant
- Bennett & Sally Shaywitz
- Audrey Thurm
- Keith Widaman
- Warren Zigman
Scientific Publications Citing ASD v PDD in the Title

<table>
<thead>
<tr>
<th>Year</th>
<th>ASD</th>
<th>PDD</th>
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</thead>
<tbody>
<tr>
<td>2006</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td>2007</td>
<td>81</td>
<td>23</td>
</tr>
<tr>
<td>2008</td>
<td>106</td>
<td>16</td>
</tr>
<tr>
<td>2009</td>
<td>130</td>
<td>15</td>
</tr>
<tr>
<td>2010</td>
<td>171</td>
<td>17</td>
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<tr>
<td>2011</td>
<td>184</td>
<td>17</td>
</tr>
<tr>
<td>2012</td>
<td>197</td>
<td>9</td>
</tr>
</tbody>
</table>
Criteria A, B, & C must be met, by current presentation or by history. A. Persistent deficits in social communication and social interaction, manifest across multiple contexts by deficits in the following (examples are illustrative not exhaustive):

1. Social-emotional reciprocity; ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, affect and response to total lack of initiation of social interaction, etc.

2. Nonverbal communicative behaviors used for social interaction; ranging from poorly integrated verbal and nonverbal communication, through abnormalities in eye contact and body-language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures, etc.

3. Developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends, to an apparent absence of interest in people, etc.
B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following:

1. Stereotyped or repetitive speech, motor movements, or use of objects (such as simple motor stereotypies, echolalia, repetitive use of objects, or idiosyncratic phrases)

2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change (such as motoric rituals, insistence on same route or food, repetitive questioning, rigid thinking or extreme distress at small changes)

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

4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment (such as apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, unusual vestibular/proprioceptive responses evident in motor behaviors, excessive smelling or touching of objects, fascination with lights or spinning objects).
C. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities, and may be masked by compensation in later life).

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

Specify if:
With or without loss of established skills
Age of first concern

Specify if:
With or without accompanying intellectual impairment
With or without accompanying structural language impairment
Associated with a known medical/genetic or environmental/acquired condition
Associated with another neurodevelopmental, mental, or behavioral disorder

January 12, 2013
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<table>
<thead>
<tr>
<th>Severity Level</th>
<th>Social Communication</th>
<th>Restricted, repetitive behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 3</strong></td>
<td>Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning; very limited initiation of social interactions and minimal response to social overtures from others. E.g. someone with around 20 words of intelligible speech, rarely initiates interaction, and when does so makes unusual approach to meet needs only, responds to only very direct social approach.</td>
<td>Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.</td>
</tr>
<tr>
<td></td>
<td>‘Requiring very substantial support’</td>
<td></td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td>Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions and reduced or abnormal response to social overtures from others. E.g., a person who speaks simple sentences, interaction limited to narrow special interests, markedly odd nonverbal communication.</td>
<td>Inflexibility of behavior, difficulty coping with change, or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.</td>
</tr>
<tr>
<td></td>
<td>‘Requiring substantial support’</td>
<td></td>
</tr>
<tr>
<td><strong>Level 1</strong></td>
<td>Without supports in place, deficits in social communication cause noticeable impairments. Has difficulty initiating social interactions and demonstrates clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions. E.g., a person able to speak in full sentences, engages in communication but to-and-fro of conversation fails, attempts to make friends are odd and unsuccessful.</td>
<td>Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.</td>
</tr>
<tr>
<td></td>
<td>‘Requiring support’</td>
<td></td>
</tr>
</tbody>
</table>
DSM 5:
A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:

1. **Deficits in social-emotional reciprocity**; ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction,

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

3. **Deficits in developing and maintaining relationships, appropriate to developmental level** (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people
Redefining Autism

In a preliminary analysis, three researchers estimate that far fewer people with autism or a related disorder would meet the criteria for autism spectrum disorder after a change proposed for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, or D.S.M.

Related Article »

Current definitions (D.S.M.-IV)  Percentage who would qualify under new definition

Classic autism  76%

Asperger syndrome  24%

P.D.D.-N.O.S.*  16%

Proposed definition (D.S.M.-V)

Autism spectrum disorder
Revised criteria improve specificity but exclude a substantial portion of cognitively able individuals and those with ASDs other than autistic disorder.
### DSM-5 Criteria

#### A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:

1. **Deficits in social-emotional reciprocity;** ranging from abnormal social approach and failure of normal back-and-forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction

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

3. **Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers);** ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in getting friends to an apparent absence of interest in people

---

### Field Trial Checklist Items

- Relative failure to initiate or sustain conversational interchange (at whatever level of language skills are present) in which there is no reciprocal to and from responsiveness to the communications of the other person

  - **or**

- Lack of shared enjoyment in terms of vicarious pleasure in other people’s happiness and/or a spontaneous seeking to share their own enjoyment through joint involvement with others

  - **or**

- Markedly impaired awareness of others

  - **or**

- Lack of social-emotional reciprocity

- Markedly abnormal nonverbal communication, as in the use of eye-to-eye gaze, facial expression, body posture, or gestures to initiate or modulate social interaction (e.g., does not anticipate being held, stiffens when held, does not greet parents or visitors, has a fixed stare in social situations)

- Failure to develop peer relationships as appropriate to developmental level

  - **or**

- No or abnormal social play (e.g., does not actively participate in simple games; prefers solitary play activities; involves other children in play only as “mechanical aids”)
Field Trials
<table>
<thead>
<tr>
<th>Pediatric Sites</th>
<th>Completed V1</th>
<th>Completed V2</th>
<th>Completed V3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford</td>
<td>158</td>
<td>148</td>
<td>40</td>
</tr>
<tr>
<td>The Children's Hospital</td>
<td>216</td>
<td>193</td>
<td>124</td>
</tr>
<tr>
<td>Baystate Medical Center</td>
<td>164</td>
<td>145</td>
<td>59</td>
</tr>
<tr>
<td>Columbia/Cornell</td>
<td>127</td>
<td>120</td>
<td>70</td>
</tr>
<tr>
<td><strong>Pediatric Sites</strong></td>
<td><strong>665</strong></td>
<td><strong>606</strong></td>
<td><strong>293</strong></td>
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</tbody>
</table>

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# Test-Retest Reliability of DSM-5 Diagnostic Criteria Tested at Child Sites – Autism Spectrum Disorder

<table>
<thead>
<tr>
<th>DSM-5 Diagnostic Criteria tested (strata N/total N)</th>
<th>Site (Dx N)</th>
<th>Intraclass Kappa (95%CI)</th>
<th>Prevalence DSM-IV/DSM-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism Spectrum Disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baystate (34/145)</td>
<td>Baystate (48)</td>
<td>0.66 (0.51, 0.81)</td>
<td>0.23/0.25</td>
</tr>
<tr>
<td>Stanford (30/148)</td>
<td>Stanford (36)</td>
<td>0.72 (0.54, 0.86)</td>
<td>0.26/0.20</td>
</tr>
<tr>
<td><strong>Pooled Estimate</strong></td>
<td><strong>0.69</strong> (0.58, 0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinician’s Dimensional Rating of:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autism Spectrum (Global)</td>
<td>Pooled Estimate</td>
<td>0.64 (0.57, 0.71)</td>
<td></td>
</tr>
<tr>
<td>Repetitive Behavior</td>
<td>Pooled Estimate</td>
<td>0.68 (0.61, 0.74)</td>
<td></td>
</tr>
<tr>
<td>Social Communication</td>
<td>Pooled Estimate</td>
<td>0.66 (0.59, 0.73)</td>
<td></td>
</tr>
</tbody>
</table>
Specificity and Sensitivity of DSM-5 ASD Criteria are comparable to DSM-IV (did not include “by history” threshold).
Implications for Treatment
Medication Use Among Children with Autism-Spectrum Disorders

Donald P. Oswald, Ph.D., and Neil A. Sonenklar, M.D.

ABSTRACT

The study characterizes the use of psychoactive medications among children and youth with autism-spectrum disorders over the course of a calendar year. Eighty-three percent of the sample had at least one drug claim during the year. Prescribed drugs came from 125 different therapeutic classes. The seven most frequently prescribed classes of psychoactive drugs were antidepressants, stimulants, tranquilizers/antipsychotics, anticonvulsants, hypotensive agents, anxiolytic/sedative/hypnotics, and benzodiazepines. The data on other relevant diagnoses indicate that children and youth are frequently treated with medication under an autism-spectrum diagnosis, even though the target symptoms may be commonly associated with other mental disorders. Age data indicate that a number of children with autism-spectrum disorders age 8 yr and up receive some form of psychoactive medication in a given year.
Autism

ADHD

ADHD

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DSM Trumping rules

ADHD: symptoms do not occur exclusively during the course of a PDD, Schizophrenia, or other psychotic disorder, etc.
Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder

Nanda N. J. Rommelse • Barbara Franke • Hilde M. Geurts • Catharina A. Hartman • Jan K. Buitelaar

Received: 12 August 2009 / Accepted: 8 January 2010 / Published online: 11 February 2010
© The Author(s) 2010. This article is published with open access at Springerlink.com
Overview of single nucleotide polymorphisms (SNPs) among the top-findings of GWAS in ADHD possibly also involved in ASD

<table>
<thead>
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<th>SNP</th>
<th>Chr</th>
<th>Position</th>
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<tr>
<td>rs272000</td>
<td>2</td>
<td>Within 50 kb downstream of DPP10</td>
</tr>
<tr>
<td>rs10049246</td>
<td>3</td>
<td>Intron of AK309325</td>
</tr>
<tr>
<td>rs6791644</td>
<td>3</td>
<td>Intron of FHIT</td>
</tr>
<tr>
<td>rs10983238</td>
<td>9q33.1</td>
<td>Intron of ASTN2</td>
</tr>
<tr>
<td>rs1764178</td>
<td>9</td>
<td>Coding exon of DMRT2</td>
</tr>
<tr>
<td>rs3893215</td>
<td>11p15.1</td>
<td>Intron of KCNC1</td>
</tr>
<tr>
<td>rs874426</td>
<td>11</td>
<td>Intron of NAV2</td>
</tr>
<tr>
<td>rs7995215</td>
<td>13q31.3</td>
<td>Intron of GPC6</td>
</tr>
<tr>
<td>rs2360997</td>
<td>14</td>
<td>Within 25 kb upstream of ESRRB</td>
</tr>
<tr>
<td>rs7164335</td>
<td>15q23</td>
<td>ITGA11</td>
</tr>
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<td>rs2677744</td>
<td>15q26.1</td>
<td>Intron of MAN2A2</td>
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<tr>
<td>rs1471225</td>
<td>15</td>
<td>Within 30 kb downstream of KIAA0574</td>
</tr>
<tr>
<td>rs7495052</td>
<td>15</td>
<td>Intron of SLCO3A1</td>
</tr>
<tr>
<td>rs7187223</td>
<td>16</td>
<td>Intergenic, within 203 kb upstream from CDH13</td>
</tr>
<tr>
<td>rs6565113</td>
<td>16</td>
<td>Intron of CDH13</td>
</tr>
<tr>
<td>rs4810685</td>
<td>20</td>
<td>Intron of SULF2</td>
</tr>
</tbody>
</table>
Overall, stimulants appeared ineffective and poorly tolerated for the majority of patients with PDDs.
Randomized, Controlled, Crossover Trial of Methylphenidate in Pervasive Developmental Disorders With Hyperactivity

Research Units on Pediatric Psychopharmacology (RUPP) Autism Network

Arch Gen Psychiatry. 2005;62:1266-1274
Randomized, Controlled, Crossover Trial of Methylphenidate in Pervasive Developmental Disorders With Hyperactivity

- Methylphenidate responders: 48%
- Placebo responders: 19%
- Non-responders: 12%
- Dropouts due to AE's: 18%
- Dropouts: 3%

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RUPP v. MTA methylphenidate

**RUPP**
- MPH responders: 48%
- Placebo responders: 19%
- Non responders: 12%
- Drop outs due to AE’s: 18%
- Drop outs: 3%

**MTA**
- MPH responders: 69%
- Placebo responders: 11%
- Non responders: 9%
- Drop outs due to AE’s: 1%
- Drop outs: 10%

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Arch Gen Psychiatry. 1999 Dec;56(12):1073-86.
Summary

Methylphenidate is more effective than placebo for the treatment of ADHD symptoms in children with autism.

The response rate (49%) is less than that for typically developing children with ADHD (70-80%).

Rate of adverse events associated with methylphenidate is higher in children with autism than for those with ADHD alone.
A Treatment Study of Children with Autism and Hyperactivity

Study Description:
We’re doing a research study to learn more about a medicine called Guanfacine. We want to know if Guanfacine helps treat hyperactivity and impulsive behavior in children with autism spectrum disorders (PDD-NOS, Asperger’s, Autism). We’re looking for volunteer families with children ages 5 – 13 who have both autism and hyperactivity.

Study Process:
Part 1 (8 weeks): Participants will receive treatment with Guanfacine or Placebo (not active medication) for their hyperactivity.
Part 2 (8 weeks): Participants who initially receive Guanfacine or Placebo and

For more information about this study, please contact the study coordinator, Denise Ward:
(206) 884-1168 or email denise.ward@seattlechildrens.org
Investigator: Dr. Bryan King
Division of Child and Adolescent Psychiatry and Behavioral Medicine
University of Washington, Seattle
Role for metabotropic glutamate receptor 5 (mGluR5) in the pathogenesis of fragile X syndrome

Gül Dölen¹,² and Mark F. Bear¹

¹Howard Hughes Medical Institute, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA
²Brown Medical School, Providence, RI, USA

Metabotropic glutamate receptors (mGluRs) have been implicated in a diverse variety of neuronal functions. Studies reviewed here indicate that exaggerated signalling through mGluR5 can account for multiple cognitive and syndromic features of fragile X syndrome, the most common inherited form of mental retardation and autism. Since a reduction of mGluR5 signalling can reverse fragile X phenotypes, these studies provide a compelling rationale for the use of mGluR5 antagonists for the treatment of fragile X and related disorders.

(Received 3 January 2008; accepted after revision 11 January 2007; first published online 17 January 2007)

Corresponding author M. F. Bear: Howard Hughes Medical Institute, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA. Email: mbear@mit.edu
Figure 1. Model for the pathogenesis and correction of FXS
Figure 1. Model for the pathogenesis and correction of FXS
ASD/FXS pathophysiology: Synaptic excitation: inhibition imbalance

Inhibition  Excitation
Normal

Inhibition  Excitation
ASD/FXS

Insufficient inhibition  Excitation

GABA inhibition at excitatory synapses

Presynaptic axon terminal  Postsynaptic dendritic spine
GABA$_B$R  Glutamate  GABA$_B$R

Insufficient GABA inhibition at excitatory synapses

Presynaptic axon terminal  Postsynaptic dendritic spine
GABA$_B$R  Glutamate  GABA$_B$R

Altered signaling

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ASD/FXS pathophysiology:
Synaptic excitation: inhibition imbalance

- Insufficient inhibition
- Excitation

ASD/FXS

- Re-established inhibition
- Excitation

Treated

Insufficient GABA inhibition at excitatory synapses

STX209 normalized GABA inhibition at excitatory synapses

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Arbaclofen (STX209)
Arbaclofen (R-baclofen, STX209)

• Active isomer of racemic baclofen
  – PK similar to racemic baclofen
  – $t_{1/2} = 5$ hours

• Racemic baclofen used for spasticity
  o Approved for ages 12 and up
  o Safety is well-established
  o Used very frequently in younger ages for cerebral palsy

• Mechanism of action: selective GABA-B agonist
  o R:S isomer potency ratio 10-100:1

• Potential clinical superiority of arbaclofen vs. racemic baclofen
  o Possible antagonistic effect of S-baclofen in animal models
  o Historical trial of arbaclofen vs. racemic in trigeminal neuralgia
Rationale for arbaclofen

• Hypothesized mechanisms
  
  ○ I:E imbalance in ASD (Rubinstein & Merzenich, 2003)
    - Enhancement of inhibitory tone by GABA-B agonism

  – mGluR theory of Fragile X syndrome (FXS)
    - GABA-B agonism results in decreased glutamate release
    - Relevance of FXS and synaptic plasticity to ASD

• Anecdotal clinical experience (racemic baclofen) in FXS and ASD
Effects of STX209 (Arbaclofen) on Neurobehavioral Function in Children and Adults with Fragile X Syndrome: A Randomized, Controlled, Phase 2 Trial

Elizabeth M. Berry-Kravis,¹ David Hessl,² Barbara Rathmell,³ Peter Zarevics,³ Maryann Cherubini,³ Karen Walton-Bowen,³ Yi Mu,⁴ Danh V. Nguyen,⁴ Joseph Gonzalez-Heydrich,⁵ Paul P. Wang,⁵ Randall L. Carpenter,³ Mark F. Bear,⁶ Randi J. Hagerman²

Research on animal models of fragile X syndrome suggests that STX209, a γ-aminobutyric acid type B (GABA_B) agonist, might improve neurobehavioral function in affected patients. We evaluated whether STX209 improves behavioral symptoms of fragile X syndrome in a randomized, double-blind, placebo-controlled crossover study in 63 subjects (55 male), ages 6 to 39 years, with a full mutation in the FMR1 gene (>200 CGG triplet repeats). We found no difference from placebo on the primary end point, the Aberrant Behavior Checklist—Irritability (ABC-I) subscale. In the other analyses specified in the protocol, improvement was seen on the visual analog scale ratings of parent-nominated problem behaviors, with positive trends on multiple global measures. Post hoc analysis with the ABC—Social Avoidance scale, a newly validated scale for the assessment of fragile X syndrome, showed a significant beneficial treatment effect in the full study population. A post hoc subgroup of 27 subjects with more severe social impairment showed improvements on the Vineland II—Socialization raw score, on the ABC—Social Avoidance scale, and on all global measures. STX209 was well tolerated, with an 8% incidence of sedation and headache as the most frequent side effects. In this exploratory study, STX209 did not show a benefit on irritability in fragile X syndrome. Nonetheless, our results suggest that GABA_B agonists have potential to improve social function and behavior in patients with fragile X syndrome.
Subjects with ABC-LSW $\geq 8$ at screening and baseline ($P = 0.03$).
Medication Use Among Children with Autism-Spectrum Disorders

Donald P. Oswald, Ph.D., and Neil A. Sonenklar, M.D.

Age data indicate that about 70% of children with autism-spectrum disorders age 8 yr and up receive some form of psychoactive medication in a given year.
Medication Use Among Children with Autism-Spectrum Disorders

The study characterized autism-spectrum disorder (ASD) sample had at least one of therapeutic classes. The antidepressants, stimulants, tranquilizers/antipsychotics, anticonvulsants, miscellaneous, hypotensive agents, anxiolytic/sedatives/hypnotics indicate that children with autism-spectrum diagnosis, especially developmental disorders age 8 yr and up receive some form of psychoactive medication in a given year.

### Table 2. Most Common Therapeutic Classes of Drugs

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>768</td>
</tr>
<tr>
<td>Stimulants</td>
<td>641</td>
</tr>
<tr>
<td>Tranquilizers/antipsychotics</td>
<td>561</td>
</tr>
<tr>
<td>Anticonvulsants, miscellaneous</td>
<td>343</td>
</tr>
<tr>
<td>Hypotensive agents</td>
<td>285</td>
</tr>
<tr>
<td>Anxiolytic/sedative/hypnotic</td>
<td>139</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>100</td>
</tr>
</tbody>
</table>
Fragile X

5p14.1 cadherin

5p15 SEMA5A

2p16.3 NRXN1

Tuberous sclerosis complex

16p11.2 SEZ6L2

AUTISMS

January 12, 2013
PAL Conference
Reversal of learning deficits in a $Tsc2^{+/−}$ mouse model of tuberous sclerosis

Dan Ehninger¹, Sangyeul Han², Carrie Shilyansky¹, Yu Zhou¹, Weidong Li¹, David J Kwiatkowski³, Vijaya Ramesh² & Alcino J Silva¹

Tuberous sclerosis is a single-gene disorder caused by heterozygous mutations in the $TSC1$ (9q34) or $TSC2$ (16p13.3) gene¹,² and is frequently associated with mental retardation, autism and epilepsy. Even individuals with tuberous sclerosis and a normal intelligence quotient (approximately 50%)³⁵ are commonly affected with specific neuropsychological problems, including long-term and working memory deficits⁶,⁷. Here we report that mice with a heterozygous, inactivating mutation in the $Tsc2$ gene ($Tsc2^{+/−}$ mice)⁸ show deficits in learning and memory. Cognitive deficits in $Tsc2^{+/−}$ mice emerged in the absence of neuropathology and seizures, demonstrating that other disease mechanisms are involved⁵,⁹–¹¹. We show that hyperactive hippocampal mammalian target of rapamycin (mTOR) signaling led to abnormal long-term potentiation in the CA1 region of the hippocampus and consequently to deficits in hippocampal-dependent learning. These deficits included impairments in two spatial learning tasks and in contextual discrimination. Notably, we show that a brief treatment with the mTOR inhibitor rapamycin in adult mice rescues not only the synaptic plasticity, but also the behavioral deficits in this animal model of tuberous sclerosis. The results presented here reveal a biological basis for some of the cognitive deficits associated with tuberous sclerosis, and they show that treatment with mTOR antagonists ameliorates cognitive dysfunction in a mouse model of this disorder.
Sleep disturbance

Anxiety

Sensory sensitivity

Aggression

Hyperactivity

Self-injury

Associated conditions

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“Autism” is a disorder (we) defined by a set of behaviors that occur in the context of a complex interplay of genetic and environmental and developmental factors.
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There are many pathways in to the disorder(s) which are now frequently recognized as “autisms”. It may ultimately be that the pathways become the focus and not the destination.
Parting thoughts

- The lives of individuals with autism, like everyone else, are dynamic and complex—we do not understand all of the variables.
- The population with autism is clearly heterogeneous—not only may autism be different from one person to another, but the cause and treatment of associated symptoms may also vary.
- Any potentially efficacious intervention will also have side-effect(s). No exceptions.
- There is an urgent need for us to formally test promising treatments, to identify and advance potential new therapeutics, and to retire those that do not deliver.