SHAKE RATTLE AND ROLL: THE PEDIATRIC BRAIN (PART 2)

Regina Rosace, MD, FAAP
AVP Medical Director
Scor Global Life Americas
Chardon, OH
rrosace@scor.com

Executive Summary *This is part 2 of a two-part series on the pediatric brain. The described illnesses, conditions and syndromes may be seen on insurance applications and attending physician statements of children and young adults. Part 2 involves psychiatric and behavioral syndromes that are diagnosed relatively frequently in adolescents and young adults. Most psychiatric disorders have a higher implication at younger ages. Alcohol and substance abuse particularly raise mortality rates, especially as a comorbidity with other mental illnesses. Autism is addressed, including increased prevalence and mortality predictors. And finally, the recent mortality data on ADHD is reviewed.*

Psychiatric Impairments

Why review pediatric psychiatric impairments? If potential insureds are children or young adults, there is a high probability that the underwriter will encounter a pediatric psychiatric disorder. According to the National Health and Nutrition Examination Survey (NHANES) National Youth Fitness Survey 2012 by the Centers for Disease Control (CDC), the 12-month prevalence for 8-15-year-old children to carry the diagnoses of a pediatric psychiatric disorder is 13.1%.

Serious Mental Illness

Chang et al. published an article in *BMC Psychiatry 2010* assessing all-cause mortality in people with serious mental illness. A population in London, aged 15 years and older, between the years 2007 - 2009, was evaluated, and standardized mortality ratios were calculated.

Serious mental illness (SMI) in this case includes all of the listed disorders in Table 1. Clearly, there is increased mortality with all of these disorders, but most so in substance use disorder.

When patients are broken down by age, as noted in Table 2 (next page), the SMR is much higher in younger people with mental illness compared to those older. It is evident that there is higher risk in the younger population, especially with substance use disorder.

Table 1

Diagnosis	Male	Female	Total
SMI	2.47	1.89	2.15
Schizophrenia	2.78	1.74	2.25
Schizoaffective	2.35	2.88	2.52
Bipolar	1.76	2.21	1.95
Substance use	3.60	4.67	4.17
Depressive	1.53	1.18	1.29

SMI = all serious mental illness
Units = standandized mortality ratios (SMR)

Table 2

Diagnosis	15-44 yo	45-64 yo	65+ yo
SMI	4.47	3.10	1.60
Schizophrenia	4.73	3.44	1.63
Schizoaffective	3.96	2.71	2.10
Bipolar	4.09	2.58	1.51
Substance Abuse	6.81	4.40	1.91
Depressive	3.21	1.75	1.18

SMI = all serious mental illness
Units = standardized mortality ratios (SMR)

Eating Disorders

The prevalence in the US for eating disorders is about 3% of 13-18-year-olds with females affected more often than males. The prevalence among models, athletes and dancers is much higher, with dancers' prevalence as high as 16%. The definitions of the different eating disorders are as follows:

Anorexia Nervosa

- Restricting caloric intake leading to maintenance of body weight <85% of that expected or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected.
- Intense fear of gaining weight or becoming fat, even though underweight.
- Disturbance in the way one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.

Bulimia Nervosa

- Recurrent episodes of binge eating characterized by both:
  - Eating, in a discrete period of time, an amount of food that is definitely larger than most people would eat.
  - A sense of lack of control over eating during the episode.
- Recurrent inappropriate compensatory behavior to prevent weight gain.
  - i.e., vomiting, laxatives, fasting, excessive exercise.
- The binge eating and inappropriate compensatory behavior both occur, on average, at least once a week for 3 months.
- Self-evaluation is unduly influenced by body shape and weight.

Binge Eating Disorder (previously listed as Eating Disorders NOS)

- Recurrent episodes of binge eating characterized by both:
  - Eating, in a discrete period of time, an amount of food that is definitely larger than most people would eat.
  - A sense of lack of control over eating during the episode.
- The binge eating occurs, on average, at least once a week for 3 months.
- Accompanied by feelings of guilt, embarrassment or disgust.

A meta-analysis of 36 studies from 1966-2010 by Arcelus et al. in *Archives in General Psychiatry* 2011 calculated the SMR of the different diagnoses (Table 3, next page).

Table 3

Standardized Mortality Rates	
Anorexia Nervosa	5.86
Bulimia	1.93
Eating Disorders NOS	1.92

Table 4

Age of diagnosis of Anorexia Nervosa and Mortality	
Age at Diagnosis	Standardized Mortality Rate
<15 yo	3
15-19 yo	10
20-29 yo	18
30+ yo	6

In addition, this study demonstrated that the age of diagnosis of anorexia nervosa is a significant predictor of mortality (Table 4).

Of note, 1 in 5 anorexia nervosa deaths were from suicide.

Diagnosis, age at diagnosis, treatment and treatment response all factor into the risk in eating disorders.

Autism Spectrum Disorder

Autism spectrum disorder (ASD), autism or being "on the spectrum" are all terms for a condition that has a wide range of symptoms and abilities/disabilities. Autism is a term describing a group of neurodevelopmental disorders that affect social interactions and communication challenges. Individuals can be mildly affected, where many acquaintances and friends may not even realize a problem exists, vs. those who are quite severely affected. There has been an apparent increase in prevalence over the last 30 years of autism diagnoses, which has led many in the media to declare an "autism epidemic." The number of autism diagnoses has clearly increased; however, this appears to be the result of broadened diagnostic criteria; increased surveillance by families, educational and medical professionals; and heightened public awareness.

The incidence of autism spectrum disorder in the US according to the Centers for Disease Control is indicated in Table 5.

Table 5

Prevalence of Autism Spectrum Disorder (ASD) in 8-year Olds (2012)		
		About 1 in every "x" children
	Overall	1 in 68
Sex	Boys	1 in 42
	Girls	1 in 189
Race	White	1 in 65
	Black	1 in 76
	Asian/Pacific Islander	1 in 88
	Hispanic	1 in 99

NIH — Data courtesy of CDC

The vast changes in the 2013 Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 diagnostic criteria of autism have allowed the inclusion of many children who would not have fit into the 1980s DSM III criteria, nor the interceding DSM IV or DSM IV TR.

2013 DSM 5 Autism Spectrum Disorder definition:

- Persistent deficits in social communication and social interaction across multiple contexts.
  - i.e., deficits in social-emotional reciprocity, nonverbal communication, maintaining or understanding relationships, ...
- Restricted, repetitive patterns of behavior, interests, or activities (at least two) currently or historically.
  - i.e., Repetitive movements or speech, inflexibility, highly fixated interests, hyper- or hyporeactivity to sensory input, ...
- Symptoms must be present in the early developmental period.
- Symptoms cause clinically significant impairment.
- These disturbances are not better explained by intellectual disability or global developmental delay.

In comparing some aspects of the DSM III 1980 definition of Infantile Autism to the DSM 5 2013 definition of Autism Spectrum Disorder, the differences become more evident. Of note, there were intermediary changes that included the diagnoses Asperger's Syndrome and Pervasive Developmental Delay, not otherwise specified (PDDNOS) which are now defunct. Rett Syndrome has been removed from the autism category and the DSM altogether because

it has been found to have a single gene etiology. This removal seems to be a dangerous precedent, as autism is not a single entity but appears to be a group of entities which are classified together because of similar symptoms.

DSM III – 1980 Infantile Autism

- Onset, 30 months.
- Pervasive lack of responsiveness to other people.
- Gross deficits in language development.
- If speech is present, peculiar speech patterns such as immediate and delayed echolalia, metaphorical language, pronominal reversal.
- Bizarre responses to various aspects of the environment.

DSM V – 2013 Autism Spectrum Disorder

- Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies later in life).
- Deficits in social-emotional reciprocity must be present or have been present earlier in development. However, these can include abnormal social approach, failure of normal back and forth conversation through reduced sharing of interests, emotions or affect, to total lack of initiation of social interaction.
- ASD can be with or without accompanying language impairment.
- "Peculiar speech patterns" are not required for a diagnosis. However, echolalia and idiosyncratic phrases are considered examples of restricted repetitive behaviors.
- Two or more restricted repetitive behaviors must be present currently or earlier in development.

With all of the above being said, one must realize that any long-term studies of mortality have been calculated with individuals affected using one of the older diagnostic criteria. However, there are some generalities that appear to remain true. There is a male predominance with male to female ratio ~ 4:1. Children with autism can have behaviors that improve or deteriorate over time, with 20-30% deteriorating in adolescence. Approximately 40% have a comorbid psychiatric disorder, and 20-33% have comorbid epilepsy. Adaptive behavior is usually markedly lower than intelligence, and as a result, independent living is often compromised. There is an increased mortality rate for children on the spectrum, with mortality greatest from epilepsy, accidents and "cause unknown," although if accompanied by severe intellectual disability, respiratory death is frequent.

A study published by Shavelle et al. in the *Journal of Autism and Developmental Disorders* in 2001 looked at 13,111 ambulatory Californians diagnosed with autism between 1983-1997, with the following results (Table 6). The units are standardized mortality ratio (SMR), and the male to female ratio is 3.9:1.

Table 6

Autism Mortality Rate				
Male	**Female**	**High IQ**	**Low IQ**	**Overall**
1.7	5.5	1.4	3.1	2.4

This study was done using only autism as a diagnosis. Rett syndrome, Down syndrome or any non-ambulatory patients were excluded. Comparable studies have been done in Utah and Sweden with similar findings. Of note, the SMR of autism comorbid with epilepsy is six times that of autism alone. As can be observed, autism with a higher intellectual disability (lower IQ) holds more risk than autism with a lower intellectual disability (higher IQ). Females appear to have a higher risk, not because autism is more virulent in females, but because females' baseline mortality is much lower than males.

Suicide

In 2014, suicide was the 10th leading cause of death in the US, with 13 deaths/100,000. Alarmingly, it is the second leading cause of death in the 10-14-year-old, 15-24-year-old, and 25-34-year-old age groups, behind only unintentional injury. We are discussing it in this article about psychiatric disorders because >90% of people who succeed in killing themselves have a diagnosable mental illness. Adults' risk factors for suicide include mood disorder, panic disorder and substance abuse, while children's risk factors include previous attempts and mood disorder, especially in combination with conduct disorder. Males have a strong association with suicide and alcohol/substance abuse.

Externalizing Disorders

Externalizing psychiatric disorders are characterized by a child's failure to control his or her behavior in a socially acceptable way, to the expectations of peers and to supervising adults including parents, teachers and legal authorities. This is in contrast to internalizing psychiatric disorders which primarily affect a child's internal world, such as anxiety or depression. In children more so than adults, there can be overlapping symptoms between the internalizing and externalizing disorders, and a diagnostician must prudently tease out the true etiology of the problem to make an accurate diagnosis.

The disorders addressed here include oppositional defiant disorder (ODD), conduct disorder (CD) and attention deficit hyperactivity disorder (ADHD), which are all highly heritable, as evidenced by twin studies of types of disruptive behavior. Epidemiologic studies show that the prevalence of ODD and CD are relatively consistent throughout different countries of the world, ranging in prevalence between approximately 4-9%. Externalizing psychiatric disorders tend to have a high amount of comorbidities with each other and with substance use disorders.

Oppositional Defiant Disorder
To meet criteria for ODD, one must have the following behaviors with a person (not a sibling):

- A pattern of the following behaviors lasting at least 6 months with at least four symptoms from the following categories, with at least one individual who is NOT a sibling.
  - Angry/irritable mood.
  - Argumentative/defiant behavior.
  - Vindictiveness.
- Causes distress in self or others or has a negative impact on social, educational or occupational functioning.
- Not a result of psychosis, mood disorder or substance abuse.

Conduct Disorder
To meet criteria for CD, one must have the following behaviors:

- Persistent pattern of behavior in the past 12 months where the basic rights of others or societal norms are violated with the presence of at least three items from 15 criteria from the following categories:
  - Aggression to people and animals.
  - Destruction of property.
  - Deceitfulness or theft.
  - Serious violation of rules.

- The behavior causes significant impairment in social, academic or occupational functioning.
- Often includes:
  - Lack of remorse or guilt.
  - Callousness – lack of empathy.
  - Unconcerned about performance.
  - Shallow or deficient affect.

A major concern with both ODD and CD is the risk of coexisting substance abuse.

Attention Deficit Hyperactivity Disorder
Attention deficit hyperactivity disorder (ADHD) is an oft talked about and frequently diagnosed disorder. The CDC reports that approximately 11% of children aged 4-17 years of age have been diagnosed with ADHD as of 2011. The prevalence of ADHD in 13-18-year-olds in the US is approximately 9%, with boys diagnosed more often than girls (boys 12.9% vs. girls 4.9%) according to Merikangas in *J Am Acad Child Adolesc Psychiatry* 2010. The 12-month prevalence of adults diagnosed with ADHD is 4.1% of the US adult population according to Kessler in *Archives of General Psychiatry* 2005. The average age at diagnosis is 7 years. Genetics plays an important role in etiology, as recent twins and sibling studies reveal. In addition to genetics, scientists are examining other possible causes and risk factors, including premature delivery, low birth weight, exposures to toxins in utero such as drugs or alcohol, brain injury, etc. Research does not support some popularly held views of the causes of ADHD such as too much sugar, too much TV, family chaos or lack of discipline, although all of the above could contribute to worsening symptoms and certainly do not help in alleviating symptoms.

The diagnosis ADHD in the DSM 5 encompasses both ADHD and the former attention deficit disorder (ADD). There are three presentations of ADHD: predominantly inattentive, predominantly hyperactive/impulsive, and combined. This change in categorization was made because it is believed that ADHD may look different at different stages of life. Several inattentive or hyperactive-impulsive symptoms must be present before age 12 years; they must be present in two or more settings; and there must be clear evidence that the symptoms interfer with the quality of social, school or work functioning.

Inattention
Six or more of the following symptoms must be present for children up to age 16 years, or five or more symptoms must be present for those 17 years or older; symptoms must be present for more than 6 months, and must be inappropriate for the developmental level of the individual.

- Often fails to give close attention to details or makes careless mistakes.
- Often has trouble holding attention on tasks or play activities.
- Often does not seem to listen when spoken to directly.
- Often does not follow through on instructions and fails to finish tasks.
- Often has trouble organizing tasks and activities.
- Often avoids, dislikes or is reluctant to do tasks that require mental effort over a long period of time.
- Often loses things necessary for tasks and activities.
- Is often easily distracted.
- Is often forgetful in daily activities.

Hyperactivity and Impulsivity

Six or more of the following symptoms must be present for children up to age 16 years, or five or more symptoms must be present for those 17 years or older; symptoms must be present for more than 6 months, and must be disruptive and inappropriate for the developmental level of the individual.

- Often fidgets with or taps hands or feet, or squirms in seat.
- Often leaves seat in situations when remaining seated is expected.
- Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).
- Often unable to play or take part in leisure activities quietly.
- Is often "on the go" acting as if "driven by a motor."
- Often talks excessively.
- Often blurts out an answer before a question has been completed.
- Often has trouble waiting his/her turn.
- Often interrupts or intrudes on others (e.g., butts into conversations or games).

A few different studies have been done evaluating the mortality rate in childhood and into adulthood of ADHD, both childhood and adult diagnosed forms. A retrospective study by Barbaresi et al. (2013) *Pediatrics* looking at 5718 records of children diagnosed with ADHD in Minnesota, born between 1976-1982, found a statistically significant increase in suicides in people diagnosed with childhood ADHD. They noted an increase in all-cause mortality and accidental death as well, but these two were not statistically significant. The prospective portion of the above study showed that of all of the children diagnosed with childhood ADHD, in adulthood 5.6% had only adult ADHD, 23.7% had adult ADHD and a psychiatric disorder, 33.2% had only a psychiatric disorder, and 37.5% had no diagnosed condition at all. This leads one to wonder if the symptoms of ADHD in childhood may occasionally be misclassified symptoms of other psychiatric disorders.

Dalsgaard et al. in *Lancet* 2015 followed 1.92 million Danish individuals born 1981-2011, from first birthday until 2013, including 32,061 with ADHD. Several points stand out in the conclusions:

1) The comorbidities of CD, ODD and/or substance use disorder increase the mortality of ADHD in a dose-response manner (Table 7).

2) When looking at ADHD without any comorbidities, the mortality rate ratio (MRR) is greater in females than in males (Table 8, next page). This may be due to a combination of causes. The mortality rate of females is normally lower than in males. Therefore, an increase in mortality would affect females disproportionately higher than males. Also, females are diagnosed with ADHD much less frequently than males, and one might hypothesize that the females who actually receive the diagnosis may have more severe and impairing symptoms.

3) The age at first diagnosis of ADHD is a mortality predictor (Table 9, next page).

4) The increased mortality is driven by deaths from unnatural causes, most commonly accidents.

Although ADHD alone increases mortality risk, the comorbidities of ODD, CD and substance use disorder greatly accentuate the affect. Common medications used for improved attention include stimulants such as methylphenidate (Ritalin, Focalin, Concerta, Metadate, Daytrana patch), amphetamines (dextroamphetamine, lisdexamfetamine, Vyvanse) and Straterra (a selective norepinephrine reuptake inhibitor). Less commonly used medications are generally reserved for patients in whom the common medications have failed. They include but are not limited to: clonidine (Catapres), guanfacine (Intuniv), various antidepressants, and atypical antipsychotics such as risperdone (Risperdal), ziprasidone (Geodon) and aripiprazole (Abilify).

Table 7

Diagnosis	Adjusted MRR
ADHD	1.50
ADHD + ODD or CD	2.17
ADHD + Substance Use Disorder	5.63
ADHD + ODD or CD + Substance Use Disorder	8.29
ODD or CD or Substance Use Disorder	3.55
Control	1.00

MMR = Mortality Rate Ratio

Table 8 - ADHD without ODD, CD, or substance use disorder, broken down by gender

Gender	MRR
Male	1.27
Female	2.85

MMR = Mortality Rate Ratio

Table 9 - 1.57 million children born at term, birthweight>2500 gm, 5 minute APGAR of 10, no congental malformations

Age at first ADHD dx (years)	Adjusted MRR
1-5	2.34
6-17	1.32
>17	4.77
No ADHD	1.00

MMR = Mortality Rate Ratio

Key Underwriting Points

- The SMR of serious mental illness is higher in younger ages compared to older ages.
- Substance use disorder increases SMR in all ages, with the greatest effect in the younger ages.
- Eating disorders affect certain avocation groups disproportionately, and although low in prevalence, can have high mortality implications.
- Autism spectrum disorder is a much broader category now than it was 30 years ago, containing individuals with many varying abilities and disabilities.
- Oppositional defiant disorder, conduct disorder and substance use disorder, if diagnosed during childhood, have very large mortality implications.
- ADHD alone, diagnosed in childhood, has a mild increase in mortality. When combined with ODD, CD or substance abuse, the mortality increases in a dose response fashion.
- Accidents are the primary cause of increased mortality in ADHD.

References

Arcelus, Jon, Alex J. Mitchell, Jackie Wales, and Søren Nielsen. "Mortality rates in patients with anorexia nervosa and other eating disorders: a meta-analysis of 36 studies." *Archives of General Psychiatry* 68, no. 7 (2011): 724-731.

Arcelus, J., Witcomb, G.L. and Mitchell, A., 2014. Prevalence of eating disorders amongst dancers: a systemic review and meta-analysis. *European Eating Disorders Review*, 22 (2), pp. 92 - 101.

Barbaresi, William J., Robert C. Colligan, Amy L. Weaver, Robert G. Voigt, Jill M. Killian, and Slavica K. Katusic. "Mortality, ADHD, and psychosocial adversity in adults with childhood ADHD: a prospective study." *Pediatrics* 131, no. 4 (2013): 637-644.

Bilder, Deborah, Elizabeth L. Botts, Ken R. Smith, Richard Pimentel, Megan Farley, Joseph Viskochil, William M. McMahon et al. "Excess mortality and causes of death in autism spectrum disorders: a follow up of the 1980s Utah/UCLA autism epidemiologic study." *Journal of Autism and Developmental Disorders* 43, no. 5 (2013): 1196-1204.

Chang, Chin-Kuo, Richard D. Hayes, Matthew Broadbent, Andrea C. Fernandes, William Lee, Matthew Hotopf, and Robert Stewart. "All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study." *BMC Psychiatry* 10, no. 1 (2010): 77.

Dalsgaard, Søren, Søren Dinesen Østergaard, James F. Leckman, Preben Bo Mortensen, and Marianne Giørtz Pedersen. "Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study." *The Lancet* 385, no. 9983 (2015): 2190-2196.

INSERM Collective Expertise Centre. "Conduct: Disorder in children and adolescents." (2005).

Shavelle, Robert M., David J. Strauss, and Jane Pickett. "Causes of death in autism." *Journal of Autism and Developmental Disorders.*

About the Author

Dr. Regina Rosace, MD, FAAP, is an AVP and Medical Director at Scor Global Life Americas. She graduated from Northeast Ohio Medical University, completed a pediatric residency in Phoenix, AZ, and spent 20 years practicing pediatric emergency medicine in Cleveland, OH. She is currently on the 2017 Program Committee and the Professional and Public Relations Committee for American Academy of Insurance Medicine, and is the secretary/treasurer for the Midwestern Medical Directors Association. Now that she has left clinical practice, she gets her "kid fix" hanging out with her nine children.