ARTICLE

Neurobehavioral Disorders in Children, Adolescents, and Young Adults With Down Syndrome

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The term dual-diagnosis refers to a person with mental retardation and a psychiatric disorder. Most children with Down syndrome (DS) do not have a psychiatric or neurobehavioral disorder. Current prevalence estimates of neurobehavioral and psychiatric co-morbidity in children with DS range from 18% to 38%. We have found it useful to distinguish conditions with a pre-pubertal onset from those presenting in the post-pubertal period, as these are biologically distinct periods each with a unique vulnerability to specific psychiatric disorders. Due to the increased recognition that psychiatric symptoms may co-occur with mental retardation, and are not inextricably linked to cognitive impairment, these conditions are considered treatable, in part, under a medical model. Improvement in physiologic regulation, emotional stability, and neurocognitive processing is one of the most elusive but fundamental goals of pharmacologic intervention in these disorders.

KEY WORDS: Down syndrome; dual-diagnosis; neurobehavioral disorder; psychiatric disorder; attention deficit hyperactivity disorder; oppositional defiant disorder; disruptive behavior disorder; autistic spectrum disorder; pervasive developmental disorder; stereotypy movement disorder; depression; obsessive-compulsive disorder; psychosis; aberrant behavior checklist; Reiss scales; Diagnostic & Statistical Manual IV

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NEUROBEHAVIORAL DISORDERS IN PERSONS WITH MENTAL RETARDATION AND DOWN SYNDROME

The term dual-diagnosis refers to a person with mental retardation and a psychiatric disorder [Lovell and Reiss, 1993]. In the past, the notion that persons with mental retardation (MR) could have co-existing mental illness was not generally accepted on theoretical grounds. It was widely held that all behavioral disturbances were inherently linked to cognitive impairment in persons with MR, and did not require further diagnostic consideration or evaluation. In recent decades, there has been wider recognition that persons with MR can also have a co-existing psychiatric disorder. Increasing interest from medical and mental health practitioners has resulted in practical guidelines on how to work with this population [Silka and Hauser, 1997; Aman et al., 2004; Summers et al., 2004]. An important implication of these efforts is the realization that psychiatric disorders are not inextricably linked to cognitive impairment, and are treatable, in part, using a medical model.

The prevalence of various psychiatric and behavioral disorders in children and adolescents with Down syndrome (DS) is available from small community, school, or clinic samples; which use different terminology, diagnostic criteria, and design to derive their data. A few case-reports and case-series focus on the presentation, diagnosis, and treatment of various psychiatric disorders in adults with DS. The existing literature however, fails to capture the complex background upon which these disorders may present, so there is little information regarding associated medical conditions, developmental attributes, or treatment outcomes in children with DS and any psychiatric disorder. This review, which focuses on children, adolescents, and young adults with DS, represents a distillation and synthesis of information from several sources including: the available literature on DS, dual-diagnosis in persons with MR, a growing body of literature in pediatric psychiatry and psychopharmacology, as well as our own clinical experience over the past 15 years.

PREVALENCE ESTIMATES OF PSYCHIATRIC AND BEHAVIORAL CO-MORBIDITY IN DOWN SYNDROME

The majority of children with DS do not have a coexisting psychiatric or

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behavioral disorder, and the available estimates of psychiatric co-morbidity range from 18% to 38% [Menolascino, 1965; Gath and Gumley, 1986; Gillberg et al., 1986; Myers and Pueschel, 1991; Coe et al., 1999; Dykens et al., 2002]. These estimates are greater compared to children from the general population, but probably lower compared to other children with similar levels of MR [Gath and Gumley, 1986].

Gath and Gumley sampled 193 children with DS from community schools and used the Rutter Behavioral Scale and parent interviews to estimate the prevalence of significant behavior problems at 38% (infantile autism 1%, childhood psychosis 9%, conduct disturbance 15%, emotional disturbance 3%, and hyperactivity disorder 9%) [Gath and Gumley, 1986]. Myers and Pueschel sampled 261 children with DS, ascertained from a large outpatient medical clinic, and used DSM-IIIR criteria to determine the prevalence of psychiatric disorders at 17.5% (infantile autism 1%, stereotypic-repetitive behaviors 4.5%, anxiety disorders 1.5%, conduct disturbance 12%, ADHD 6%) [Myers and Pueschel, 1991]. Kent et al. used the Childhood Autism Rating Scale, the Asperger Syndrome Screening Questionnaire, and ICD-9 criteria to estimate the prevalence of autism spectrum disorders at 7% in a small community-based sample of 33 children with DS [Kent et al., 1999].

Pueschel characterized a pattern of hyperactivity-impulsivity-inattention and stubbornness-disobedience in over half of the 40 school-age children with DS ascertained from an outpatient clinic sample [Pueschel et al., 1991]. Coe et al. surveyed the parents and teachers of 44 children with DS ascertained from school and community sources and determined the prevalence of behavior problems at 32%; identifying attention, conduct, psychotic behavior, and social withdrawal concerns as the most common [Coe et al., 1999]. Dykens et al. reported on 211 children with DS ascertained from community and clinical sources, and estimated the prevalence of maladaptive behavior at 20%; while an additional 15% were rated as borderline for significant behavior problems [Dykens et al., 2002]. Externalizing behaviors (aggression, delinquency) tended to decrease after onset of puberty, while certain internalizing behaviors (social withdrawal, secretiveness) increased in adolescents and teenagers. Clark and Wilson sampled the parents and teachers of 60 children with DS ascertained through an outpatient clinic and described an age-dependent increase in problems with attention deficit, anger/self-control, psychosis, and withdrawal [Clark and Wilson, 2003].

LEARNED BEHAVIOR AND PSYCHIATRIC SYMPTOMATOLOGY

It is too simplistic to dichotomize most atypical or maladaptive behaviors in persons with MR as exclusively behavioral or psychiatric, as neither adequately captures the complexity of most cases. Behavioral [Lowry and Sovner, 1991], psychiatric [Sovner, 1996], and integrated models [Gardner and Griffiths, 2004] have been advanced to explain the nature of maladaptive behaviors. Maladaptive behaviors, which come to clinical attention are often related to unrecognized disturbance(s) in social-psychological, developmental-physiological, or medical-psychiatric factors [Silka and Hauser, 1997].

Problem behaviors in young preschool and school-age children with DS frequently occur within a setting of atypical cognitive-language-social function, inconsistent progress in achieving or demonstrating developmental skills, and considerable caregiver anxiety or confusion. Distinguishing a component of psychiatric symptomatology within the setting of problem behavior is critical because it helps to prioritize and set realistic expectations for pharmacologic, behavioral, and educational treatments. Because the distinction between psychiatric symptom and learned behavior is not always straightforward in young children or those with low-level skills we have found it helpful to focus beyond overt behaviors in search of diagnostic clues, such as alterations in mood, arousal or activity level, physiologic disturbance, atypical development, or neurocognitive function. Table I summarizes some of the attributes of young children seen in our clinic with DS diagnosed with psychiatric disorder. In adolescents and young adults with DS who have achieved a previous stable level of function, the diagnostic process is only slightly less daunting. Guidelines to assist with diagnostic formulation in adults with MR have been proposed [Sovner and Lowry, 1990; Schwartz and Ruedrich, 1996], which caution against over reliance upon DSM criteria as too limiting, when used alone, to make a diagnosis [Sovner, 1986; Silka and Hauser, 1997].

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BEHAVIORAL STYLE AND COMMON CONCERNS IN YOUNG CHILDREN WITH DOWN SYNDROME

Preschoolers with DS can exhibit the full range of temperament styles; however, there may be qualitative differences on such traits as "response intensity", "threshold for stimulation," and "mood" when comparing toddlers with DS to mental-age-matched control children [Gunn and Berry, 1985]. There is a trend for infants with DS classified as "difficult" to become reclassified as "easy" as they become older [Ganiban et al., 1990], which is consistent with developmental theory which acknowledges the role of increasing biological maturation, cognitive organization, and capacity for self-regulation [Robarth and Derryberry, 1981]. The behavioral-temperamental traits commonly observed in young children with DS

TABLE I. Features Which may Suggest a Psychiatric Syndrome in Preschool Children With Down Syndrome

Behavior	New or sudden-onset Rapidly worsening in frequency, intensity or duration Associated with significant impairment in development, learning, or social function
Physiologic or emotional symptoms	Abnormal sleep pattern, increased or decreased activity-level, mood instability, increased irritability, unusual responding to sensory stimuli, repetitive movements, or self-injury
Neurocognitive symptoms	Abnormal gaze-preference, regulation of attention, cognitive-organization, play-routines, reciprocal social-interaction, or loss of established skills (developmental regression)
Family history	Major psychiatric disorder in 1st degree relatives: bipolar disorder, schizophrenia, OCD, autism

include a sociable-affectionate quality, cognitive inflexibility, and resistance to change. Some children demonstrate a rather stubborn-persistence, need-for-sameness, and repetitive or perseverative qualities [Evans and Gray, 2000].

Common behavior concerns in pre-school children with DS often include: (1) increased motor activity and impulsivity; (2) non-compliance or tantruming; (3) agitation, anxiety, or disruptiveness; (4) repetitive movements; (5) peculiar sensory responding; (6) atypical neurocognitive processing; and rarely (7) disinterest in social interaction. Sometimes these behaviors will occur infrequently only in certain settings or situations, and are generally mild or self-limited. In contrast, behaviors which result in significant impairment in learning or socialization or any dangerous behavior are a cause for concern at any age. Table II emphasizes some of the features helpful in distinguishing between common conditions of lesser significance, and serious

TABLE II. Common Behavior Concerns in Preschool Children With Down Syndrome

	Does not necessarily indicate a neurobehavioral disorder	May indicate a neurobehavioral or psychiatric disorder
General pattern	Occurs only in specific settings or situations, is mild or self-limited, does not interfere with learning or socialization	Occurs across multiple environments, is intense or frequent, results in impairments in learning or socialization
Increased motor activity and impulsivity	When excited or over-stimulated	Associated with unsafe or high-risk behaviors
Non-compliance or tantruming	When limits are set or a sudden transition occurs	Associated with aggression, self-injury or destructiveness
Agitation, anxiousness, or disruptiveness	When experiencing pain or physical discomfort	Results in physical harm to self or others or property destruction
Repetitive movements	Usually easy to interrupt, of brief duration; motor "stimming" may be seen when tired or bored, perhaps to regulate levels of arousal; motor "overflow" phenomena may be seen when overexcited	Performed in a variety of situations, and becomes a preferred activity which is difficult to interrupt
Peculiar sensory responding	Tactile defensiveness, auditory hypersensitivity, or oral-motor sensitivity resulting in aversion or mild agitation in response to sensory stimulation	Associated with agitation, anxiety, or autonomic symptoms
Atypical neurocognitive processing	With certain visual and hearing problems, or acute medical illnesses	Inability to attend to fun tasks or organize purposeful activity; atypical attention or gaze abnormalities; inability to process or understand spoken words or gestures
Disinterest in social interaction or play	With medical illnesses	Little peer interaction or interest imitating children at play; inability to engage in symbolic play or organized play activity

neurobehavioral or psychiatric disorders in preschool children with DS.

BEHAVIOR SCALES TO CHARACTERIZE NEUROBEHAVIORAL AND PSYCHIATRIC DISORDERS

Little research exists whereby a cohort of persons with DS diagnosed a priori with a psychiatric disorder are characterized according to some well-validated behavioral rating scale. These behavioral instruments could prove useful both in determining the symptom profile associated with specific psychiatric disorders, or as an outcome-measure of intervention. There are several easy to administer, informant-based questionnaires used to provide a snapshot of maladaptive behavior or psychiatric symptomatology in children and adults with mental retardation [Dykens, 2000; Rush et al., 2004].

One of the most widely used instruments for the assessment of persons with cognitive impairment and maladaptive behavior is the Aberrant Behavior Checklist (ABC) [Aman et al., 1985]. The ABC was developed to measure a variety of maladaptive behaviors and their response to treatment in persons with moderate to profound mental retardation. It has been used in children and adolescents with dual diagnosis [Rojahn and Helsel, 1991] and in children with DS [Capone et al., 2005]. The Reiss Scales for Children's Dual Diagnosis has been used for screening and diagnosis of maladaptive behaviors and psychiatric symptoms in children, adolescents, and young adults with mental retardation [Reiss and Valenti-Hein, 1994] and persons with DS [Clark and Wilson, 2003].

COMMON NEUROBEHAVIORAL AND PSYCHIATRIC DISORDERS IN CHILDREN WITH DOWN SYNDROME

Persons with DS are at risk for exhibiting neurobehavioral and psychiatric disorders. The current status of DS research does not allow us to determine why this is so. Although speculative, it appears that multiple etiologies are suspect, some common to all persons with developmental cognitive impairment, and others, biological, physiological, or medical, which are associated with trisomy 21. Table III organizes and summarizes some of the putative risk-factors which may predispose persons with DS to neurobehavioral and psychiatric disorders. When considering specific categories of disorders, we distinguish conditions with a pre-pubertal onset from those typically presenting in the post-pubertal period, as theyare considered biologically distinct periods with unique vulnerability to specific types of psychiatric disorder [Walker and Bollini, 2002].

Disorders With Pre-Pubertal Onset in DS

Most of the disorders of pre-pubertal children present prior to age 7 years, often earlier. Clinicians evaluating children with DS face the challenge of interpreting the significance of behavior within the context of an expanding array of psychosocial influences (parent-family-school); and expectation for increasingly sophisticated cognitive, behavioral, and adaptive skills, which is occurring against a background of delayed or atypical brain function and frequent medical illness. Upon observation, young children with DS frequently manifest atypical or an unusual combination of neurobehavioral symptoms rather than classic symptomatology. For those unfamiliar with evaluating young children with cognitive impairment, it is important to avoid falling into the trap of "diagnostic overshadowing" whereby the presence of MR is invoked to explain-away every type of behavior. In Table IV we consider primary diagnostic criteria, frequently associated behavioral and developmental attributes, medical considerations, treatment approaches and long-term concerns for each of the common categories of psychiatric disorder seen in pre-pubertal children with DS.

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Attention Deficit Hyperactivity Disorder

Definition, classification, and presentation. Attention deficit hyperactivity disorder (ADHD) is diagnosed by the presence of inattention, impulsivity, and hyperactivity disproportionate to mental age, which results in significant academic or social impairment. Hyperactivity and impulsivity with or without inattention may be seen in young children with DS before 36 months of age [Green et al., 1989]. Some degree of negativism and oppositional behavior in young DS children is not uncommon.

Associated behaviors and symptoms. Hyperactivity and impulsivity place DS children with cognitive impairment at especially high risk for accidental injury, wandering, running away, or becoming lost. In the general population, ADHD may become increasingly difficult to manage as a child gets older, especially if they have anxiety or other co-morbidities [Biederman et al., 1991; Aman et al., 1996].

Associated medical factors. Hyperthyroidism, hearing loss, sleep disturbance [Levanon et al., 1999] or sleep apnea [Marcus et al., 1991; Fallone et al., 2002; Blunden et al., 2005], and medication side effects (stimulants, SSRIs, antihistamines, adrenergic agonists, or caffeine) need to be considered as possible etiologic factors when evaluating children with DS + ADHD.

Oppositional-Defiant and Disruptive Behavior Disorders

Definition, classification, and presentation. We distinguish the related

TABLE III. Factors Which may Predispose Persons With Down Syndrome to Neurobehavioral or Psychiatric Disorders

Social	Psychological	Developmental	Neurophysiological	Medical
Pre-pubertal disorders				**All ages**
Parenting style: overly rigid, anxious or permissive Family stress or dysfunction	Temperament style: difficult, anxious Cognitive style: rigidity, need for sameness, perseveration, impulsiveness	Severe cognitive impairment Expressive speech: non-verbal Receptive language: poor comprehension Extreme food refusal	Developmental neurobiological dysfunction: neuroplasticity, synaptic function, cell-signaling	Recurrent hospitalizations Pre-existing or active seizures Hearing or visual impairment GE reflux-esophagitis Pain (ENT, dental GI, skeletal, menstrual) Primary sleep disorder (without apnea) Obstructive sleep apnea Hypo- or hyper-thyroidism
Post-pubertal disorders				
Awareness of being different Unrealistically high expectations Major life transitions Emotional loss, rejection, or trauma	Cognitive style: executive dysfunction (as above)	Expressive speech: non-verbal	As above Ongoing CNS impairment: amyloid, oxidative damage, mitochondrial dysfunction, inflammation, neurotoxicity Neural response to physiologic stress	

conditions, oppositional-deficit disorder (ODD) and disruptive behavior disorder (DBD), according to the severity, intensity, and pattern of negativistic, oppositional, disruptive, or aggressive behavior. Children with DS + ODD or DBD frequently have comorbid ADHD. Similarly, children with DS + ADHD and comorbid anxiety or mood disorder are frequently oppositional, disruptive, or aggressive. Taken together, DS + ADHD-ODD-DBD align themselves along a continuum of disruptive behavior or conduct disturbance. Oppositional behavior with ADHD may be seen in young DS children prior to age of 36 months, or oppositional behavior may develop in temperamentally vulnerable toddlers without obvious hyperactivity or impulse dyscontrol. Aggression in young DS children is very often impulsive or attention-seeking rather than malicious. Children with moderate-severe cognitive impairment are quite capable of manipulating their caretakers through the use of disruptive behavior. Thus, a long-standing pattern of undesirable behavior may become established which is difficult to change.

Associated behaviors and symptoms. Individuals in the general population who become increasingly disruptive or aggressive over time may have other associated conditions which contribute to their worsening problem, such as inadequate structure and discipline, unstable environmental factors, poor speech skills, learned behavioral responses, rigid-inflexible cognitive style, anxiety, rapid-cycling, or atypical mood disorder [Biederman et al., 1991; Dilsaver et al., 2003; Vance et al., 2005]. The degree of cognitive-language impairment is also an important prognostic factor to consider.

Associated medical factors. Physical pain (GI, ENT, headache, dental, musculoskeletal, menstrual), hyperthyroidism, sleep disturbance, or sleep apnea [Marcus et al., 1991; Chervin, 2003], and medication side effects need to be considered as possible etiologic factors-when evaluating children with DS + ODD or DBD.

Autistic Spectrum and Stereotypy Movement Disorders

Definitions and classification. The autistic spectrum disorders (ASD) and stereotypy movement disorder (SMD) are considered together because they may present similarly and are frequently confused with one another. Persons diagnosed with autism manifest qualitative impairment in reciprocal social and communication skills, along with restricted interests, and repetitive play-routines or movements. When this social-communication-stereotypy triad manifests prior to 36 months, a diagnosis of autism is made. Pervasive developmental disorder (PDD)—not otherwise specified is a term used when a child fails to meet clinical threshold of all three

core-criteria for autism, yet all the essential elements (must include social impairment) are present. In some children with DS, developmental regression occurs after 36 months, without a prior indication of atypical development. When significant impairments in social-language reciprocity result, such cases are thought to represent late-onset autism or childhood disintegrative disorder (CDD). In about 1/3 of our subjects with DS + ASD, there is a history given of lost cognitive-language-social skills without co-occurring clinical seizures.

Dyskinesia and stereotypic movements are common in persons with DS [Haw et al., 1996]. Children diagnosed with DS + SMD may at first glance be regarded as "autistic-like" because of their frequently intense repetitive behaviors or stereotypic movements, however they retain functional social-communication and reciprocity, thus excluding them from a label of ASD. When considered together however, DS + Autism-PDD-SMD appear to align along a continuum of cognitive-language-social impairment [Capone et al., 2005].

Presentation. Children may display unusual or atypical behaviors during infancy or the toddler years [Capone, 2002]. Social disinterest, lack of sustained joint attention, and little interest in signing or gestures may be noted. Behaviors often seen prior to 36 months include: repetitive motor behavior, head banging or self hitting, fascination and staring at lights or ceiling fans, episodic deviation of eye gaze, extreme food refusal, and unusual play with toys or other objects. Auditory processing impairments may cause the child to act as if deaf or produce little speech. In some children symptoms suggesting PDD have a slow and insidious onset, progressing over many months or years; or sometimes there is a distinct developmental regression in speech, language, and social skills between 3 and 6 years. Repetitive motor behaviors, anxiety, and sensory aversions may appear or intensify at that time.

Associated behaviors and symptoms. Some degree of increased sensory seeking or unusual sensory responding, anxiety, and sleep disturbance are often associated with DS + ASD [Ghaziuddin et al., 1992; Howlin et al., 1995]. Some children with DS + ASD also manifest significant impulsivity, cognitive disorganization, disruptive behavior or self-injury, while others may appear markedly inactive, withdrawn and self-absorbed. Agitation or disruptive behavior can result when children are transitioned away from preferred activities too abruptly. The severity of cognitive-language impairment and the presence of other co-morbidities are important prognostic factors to consider.

Associated medical factors. Children with DS and a history of difficult to control infantile spasms or myoclonic seizures are at risk for developing ASD [Goldberg-Stern et al., 2001; Eisermann et al., 2003], and should be monitored closely.

PRE-PUBERTAL CHILDREN: ABERRANT BEHAVIOR CHECKLIST

The outpatient DS Clinic at Kennedy Krieger Institute has evaluated over 200 children (<13 years) with DS and a neurobehavioral or psychiatric disorder since 1990. The Aberrant Behavior Checklist (ABC) is utilized to characterize behavioral profiles for clinical and research purposes. After obtaining informed consent from parents, a 58-item ABC is typically completed at the time of the child's initial evaluation. A comprehensive medical, developmental, behavioral and psychiatric history, and assessment is performed by a neurodevelopmental pediatrician (gc) after which a diagnosis is made. Our findings based on 190 children with DS, between 3 and 13 years, suggests that common psychiatric disorders have a characteristic profile on the ABC which permits them to be distinguished from each other, and "control" DS subjects without behavioral co-morbidity. We recently reported our findings using the ABC to characterize the neurobehavioral phenotype of children with DS + ASD, and DS + SMD [Capone et al., 2005]. Subjects with DS + ASD score significantly higher (>7 points average, $P < 0.0001$) on Hyperactivity, Irritability, Lethargy, and Stereotypy subscales compared with DS controls, while subjects with DS + SMD score significantly higher (>7 points average, $P < 0.0001$) on the Hyperactivity and Stereotypy subscales [Capone et al., 2005]. In another comparison, subjects diagnosed with DS + ADHD score moderately higher (3–7 points average, $P < 0.001$) on the Hyperactivity subscale, while those with DS + ODD and DS + DBD score significantly higher (>7 points average, $P < 0.0001$) on both the Hyperactivity and Irritability subscales compared with DS controls (Capone, unpublished).

PHARMACOLOGIC STRATEGIES IN PRE-PUBERTAL CHILDREN

The use of psychotropic medications for young children and adolescents with psychiatric disorders has grown dramatically during the past decade [DeBar et al., 2003; Zito et al., 2003]. Fewer research studies address children and adolescents with dual-diagnosis specifically, thus we know little about tolerability, safety, and long-term consequences of medication use in this population [Stavrakaki, 2004]. In 2004, an Expert Consensus Panel published its update on the "Treatment of Psychiatric and Behavioral Problems in Individuals with Mental Retardation" which is an excellent resource addressing diagnosis, assessment and psychosocial treatments and provides detailed guidance on medication selection and management in this population [Aman et al., 2004]. A summary of medications used to treat specific target symptoms in children with DS and dual diagnosis is provided in Table V.

DISORDERS WITH POST-PUBERTAL ONSET IN DS

Disorders of post-pubertal children typically present after 13 years of age.

TABLE IV. Diagnostic Considerations, Evaluation and Management of Childhood Psychiatric Disorders in Pre-Pubertal Children With Down Syndrome

Psychiatric disorder	DSMIV diagnosis	Associated features	Medical conditions	Treatment approaches	Long-term concerns
	Primary criteria and other considerations	Variable	Variable	Prioritize individually	
Attention deficit hyperactivity disorder	Inattention Impulsivity Hyperactivity Consider anxiety	(Developmental) Mild-moderate cognitive/adaptive impairment (Behavioral) Negativistic Defiant Anxious	Sleep apnea Sleep disturbance Hyperthyroidism Hearing loss Medication effects	(Child) Discipline Mental-age appropriate rules/expectations Behavior management Medications (Caregivers) Education, support	(Child) Academic failure Accidental injury Monitor for co-morbid disorders (Caregivers) Frustration, anxiety
Oppositional-defiant disorder	Negativistic Resistant Defiant Consider ADHD or anxiety disorder	(Developmental) Mild-moderate cognitive/adaptive impairment (Behavioral) Tantrums, argumentive, non-compliant, angry, runs away, stops-drops-plops Hyperactivity, impulsivity Anxiety	Sleep apnea Sleep disturbance	(Child) Discipline Mental-age appropriate rules/expectations Behavior management (Caregivers) As above	(Child) Academic failure Anxiety or mood-disorder in evolution? (Caregivers) As above
Disruptive disorder-NOS	Agitation, Aggression Disruptiveness Property destruction Consider ADHD, anxiety, OCD or mood disorder	(Developmental) Moderate-severe cognitive/adaptive impairment (Behavioral) Physical-injury to self or others Hyperactivity, impulsivity Mood-instability, anxiety Rigid-inflexible style	Sensory impairment Sleep apnea Occult pain Hyperthyroidism Medication effects	(Child) Medications Discipline Mental-age appropriate rules/expectations Behavior management (Caregivers) As above Training, respite	(Child) Academic failure Safety Social rejection Difficulty with medical/dental procedures Medication non-responder (common) (Caregivers) As above Depression Marital-family problems

Autism spectrum disorders	Qualitative impairment in social-communication reciprocity skills Narrowly restricted interests and repetitive motor acts or ritualized play Consider CDD if onset after 36 mo	(Developmental) Regression Inconsistent developmental progress Non-communicative Severe cognitive/adaptive impairment Dysphagia (Behavioral-Physiological) Self-injury Disruptiveness Anxiety, irritability Unusual vocalizations Food refusal Unusual sensory seeking/responding Cognitive disorganization Sleep disturbance	Infantile spasms or myoclonic seizures Visual or hearing impairment Occult pain, ENT, dental, GI, menstrual (If SIB or aggression is present) (Requires supportive evidence) CNS effects of chemotherapy? Autoimmune disorders?	(Child) Medications Functional communication Behavior management ABA-type curriculum Monitor sensory environment (Caregivers) Education, support, training, respite, waivers	(Child) Safety Constant supervision Low cognitive/adaptive function Difficulty with medical/dental procedures Medication non-responder (common) Medication side-effects (limiting) Residential placement (Caregivers) Frustration-anxiety, depression-guilt, isolation-despair Marital-family problems
Stereotypy movement disorder	Repetitive motor acts which impair function Consider PDD if socially impaired	(Developmental) Speech dyspraxia Moderate-severe cognitive/adaptive impairment Dysphagia (Behavioral-Physiological) Self-injury Unusual or atypical attention Disruptiveness Anxiety Unusual vocalizations Food refusal Unusual sensory seeking/responding Inconsistent social and communication skills Sleep disturbance	Occult pain, ENT, dental, GI, menstrual (If SIB or aggression is present)	(Child) Medications (SIB or anxiety) Monitor sensory environment, communication, educational progress (Caregivers) Education, Support?	(Child) ASD in evolution? Poor cognitive/adaptive function Poor developmental/academic skills (Caregivers) As above

TABLE V. Medication Guidelines for Children with Down Syndrome

Psychiatric syndrome	Common target behaviors	Initial considerations	Other considerations
Attention deficit hyperactivity disorder	Inattention	Stimulant/atomoxetine	Bupropion
	Hyperactivity-impulsivity	Guanfacine/clonidine	Stimulant/atomoxetine
	Insomnia	Guanfacine/clonidine	Melatonin
Oppositional-defiant disorder and disruptive disorder-NOS	ADHD	As above	Bupropion
	Defiance	Buspirone	Bupropion
	Physical aggression or destructiveness	Atypical neuroleptic	Mood stabilizer or beta-adrenergic antagonist
	Agitation-anxiety-irritability	Mood stabilizer or SSRI	Atypical neuroleptic
	OCD-like perseveration	SSRI	Atypical neuroleptic
Autism spectrum disorders or stereotypy movement disorder with complex features (SIB, ADHD, anxiety)	Social withdrawal and cognitive disorganization	Atypical neuroleptic	Second-atypical neuroleptic Atomoxetine
	Stereotypy (with SIB)	Atypical neuroleptic	Second-Atypical neuroleptic, mood stabilizer, SSRI
	Physical aggression or destructiveness	As above	As above
	Perseveration	Atypical neuroleptic	SSRI
	Anxiety	Buspirone	SSRI
	Distractibility	Stimulant/atomoxetine	Bupropion
	Hyperactivity	Guanfacine/clonidine	Stimulant/atomoxetine
	Insomnia	Atypical neuroleptic (HS)	Melatonin, guanfacine/clonidine
	Minor medical procedures (X-rays, phlebotomy, dental)	Benzodiazapine (Short-acting)	Atypical neuroleptic (sedation)

Clinicians evaluating adolescents and young adults with DS face the challenge of interpreting behavioral change within the context of personal transition in the family-school-workplace setting, and expectation for increasingly sophisticated socially appropriate function. While symptoms of mood, anxiety, or thought disorder can be seen across all levels of cognitive function, psychiatric symptoms are more noticeable in those with higher pre-morbid cognitive and adaptive function. In the MR population, individuals with severe cognitive impairment may present with "difficult-to-diagnose" behavior disorders [Mikkelsen and McKenna, 1999]. In Table VI we consider primary diagnostic criteria, frequently associated behavioral and developmental attributes, medical considerations, treatment approaches and long-term concerns for each of the common categories of psychiatric disorder seen in adolescents and young adults with DS.

DEPRESSIVE ILLNESS

Definition, Classification, and Presentation

Major depression and minor mood disturbance (dysthymia) are included here together. Depressed mood, crying, decreased interest, psychomotor slowing, fatigue, appetite/weight change, and sleep disturbance are the most common DSMIV criteria observed in persons with DS and major depression. Poor concentration, reduced speech, feelings of worthlessness or guilt and agitation may also be present [Cooper and Collacott, 1994; Myers and Pueschel, 1995]. Self-care routines may deteriorate, requiring assistance, or frequent prompting. In minor mood disturbances typically fewer than five of the above symptoms are present, and are less severe. Rarely individuals will present with hypomanic or mixed-mood state suggestive of a bipolar or atypical mood disorder [Pary et al., 1996, 1999]. Psychosocial stressors may precede the onset of mood disorder in adolescents and young adults with DS. Increasing awareness of being different, lack of acceptance by school peers and sudden change or loss in personal relationships are commonly cited occurrences. Bereavement, which often goes unrecognized, and hence untreated, may exacerbate symptoms of depression or anxiety in persons with DS who experience emotional loss [Dodd et al., 2005].

Associated Behaviors and Symptoms

Obsessions, compulsions, anxiety, and extreme social withdrawal are commonly associated with major depression in persons with DS [Myers and Pueschel, 1995; McGuire and Chicoine, 1996]. Premenstrual syndrome may occur in conjunction with menstrual cycles in females. Psychotic or catatonic-like

TABLE VI. Diagnostic Considerations, Evaluation and Management of Psychiatric Disorders in Adolescents and Adults With Down Syndrome

Psychiatric disorder	DSMIV diagnostic criteria	Associated features	Medical conditions	Treatment approaches	Long-term concerns
	Primary criteria and other considerations	Variable	Variable	Prioritize individually	
Depressive illness	Depressed mood Decreased interest Psychomotor slowing Fatigue Sleep disturbance Appetite, weight loss	Anxiety Obsessions, compulsions Mood fluctuation, PMS (females) Reduced speech Catatonic-like Psychosocial stressors, bereavement	Sleep apnea Sleep disturbance Hypothyroidism Chronic pain Visual or hearing impairment	(Adolescent/adult) Treat medical concerns Medications Reduce stressors Counseling (Caregivers) Education, Support	Medication non-responder Medication side-effects Risk for weight gain, metabolic syndrome, OSA Employability, quality of life Ageing parents
Obsessive-compulsive disorder	Compulsions Obsessions Anxiety Consider PTSD	Agitation, disruptiveness Mood disturbance Verbal perseveration Stuttering, stammering Tics, mannerisms EPS, cogwheel rigidity Obsessional slowness Physical-emotional trauma	PANDAS (especially if pre-pubertal onset)	(Adolescent/adult) Treat medical concerns Medications Maintain routines Reduce stressors Behavior management Counseling (Caregivers) Education, training, support	Medication non-responder Medication side-effects Risk for weight gain, metabolic syndrome, OSA Employability, quality of life Ageing parents
Psychotic-like disorder	Positive symptoms: Delusions-hallucinations Negative symptoms: Cognitive and behavioral disorganization Social withdrawal Reduced speech Affective blunting Apathy Psychomotor slowing	Major depression Anxiety, paranoia Sleep disturbance Fatigue Appetite, weight loss EPS, cogwheel rigidity Catatonic-like Dementia Psychosocial stressors	Sleep apnea Sleep disturbance Hypothyroidism Basal ganglia calcifications	(Adolescent/adult) Treat medical concerns Medications Reduce stressors Maintain stable environment (Caregivers) Education, support	Medication non-responder Medication side-effects Risk for weight gain, metabolic syndrome, OSA Employability, quality of life Ageing parents

features may further complicate the interpretation of symptoms and their treatment in some individuals. A history of daytime somnolence, frequent yawning, and excessive fatigue should raise the suspicion of obstructive sleep apnea (OSA) or sleep disturbance.

Associated Medical Factors

Occult OSA or primary sleep disorders are common in adolescents and adults with DS [Marcus et al., 1991; Resta et al., 2003]. Disturbance of sleep architecture related to frequent microarousals can have a significant impact on mood, attention, cognition, and motivation level [Andreou et al., 2002; Means et al., 2003]. Individuals with both depression and OSA are not uncommon. A full response to anti-depressant medication may not be achieved until the sleep abnormality is recognized and treated successfully. Chronic pain, sudden loss of hearing or vision and hypothyroidism can occasionally trigger symptoms of mood disturbance.

OBSESSIVE-COMPULSIVE DISORDER

Definition, Classification, and Presentation

Obsessive thoughts may be difficult to ascertain in persons with cognitive impairment and limited speech. Repetitive, compulsive acts, by their very nature, are easier to appreciate in persons with DS [O'Dwyer, 1992; Prasher and Day, 1995]. In persons with DS + OCD, ordering and tidiness compulsions are common, especially rearranging personal belongings or opening/closing doors, cabinets, blinds, and light switches. If the compulsion to perform a certain action is so strong that anxiety or agitation ensues when the person is interrupted or prohibited from carrying it out, then criteria for obsessive-compulsive disorder (OCD) may be met. Caretakers sometimes report the sudden appearance or intensification of pre-existing OCD symptomatology, accompanied by notable changes in affect and sociability [O'Dwyer, 1992; Stavrakaki and Antochi, 2004]. Sudden, unplanned changes at school or workplace, the loss of a friend or family member, and physical or emotional trauma are commonly cited occurrences.

Associated Behaviors and Symptoms

Hording of seemingly worthless objects (clips, pens, or papers), and repetitive list-making may be seen. Perseveration on past relationships or events, and the need to frequently ask about scheduled activities may be annoying to caretakers. If some degree of physical or emotional trauma can be substantiated a diagnosis of post-traumatic stress disorder (PTSD) should be considered. Mood disturbance is often present, which may be mild without neurovegetative signs, or severe enough that a diagnosis of major depression is warranted. Self-care routines typically take progressively more time to complete and require excessive prompting or supervision by caretakers. Resting tremor, cogwheel rigidity and motor slowing suggesting a Parkinsonian-like condition is sometimes noted on examination. Occasionally, extreme motor slowing may take the form of "obsessional slowness" [Charlot, 2002].

Associated Medical Factors

In the general population, motor or vocal tics, adventitial movements, complex-mannerisms, or bizarre motor behaviors may be seen in OCD [Yaryura-Tobias et al., 2003]. These symptoms, when present in pre-pubertal children with an abrupt symptom onset, should raise suspicion of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection or (PANDAS), [Snider and Swedo, 2004; Van Toorn et al., 2004].

PSYCHOTIC-LIKE DISORDER

Definition, Classification, and Presentation

Psychotic disorder usually occurs within the setting of major depression in persons with DS, but sometimes occurs as the primary syndrome without neurovegetative signs of depression. Though uncommon in persons with DS, delusions or psychosis may represent the manic-phase of bipolar disorder [Pary et al., 1999]. Positive symptoms such as paranoia, delusions, and hallucinations often exist in the setting of low mood, apathy, motor slowing, and sleep disturbance [Myers and Pueschel, 1994, 1995; Khan et al., 2002]. It is important not to mistake increased self-talk, or talk to imaginary friends, which may occur during times of stress or isolation, as *prima facia* evidence of psychosis [Hurley, 1996]. Occasionally, the presentation is characterized predominantly by "negative symptoms" in the absence of delusions or hallucinations. Negative symptoms such as cognitive and behavioral disorganization, social withdrawal, apathy, psychomotor slowing, reduced speech, and affective blunting may be striking. Except in cases where neurovegetative signs are absent, pure negative symptoms can be difficult to distinguish from depression. As in depression, self-care skills may be lost or greatly impaired in persons with DS + Psychotic-like disorder. A history of daytime somnolence, frequent yawning, and fatigability especially in conjunction with negative symptoms alone, should raise a suspicion of sleep apnea.

Associated Behaviors and Symptoms

Anxiety, motor slowing, and perseveration may be prominent. In our experience, many subjects have subtle extrapyramidal symptoms, tremor, cogwheel rigidity, or adventitial movements.

Associated Medical Factors

In the general population disturbance of sleep architecture related to frequent microarousals, or severe sleep apnea with hypoxemia or hypercarbia, has a significant impact on frontal executive function, attention, and cognition organization [Jones and Harrison, 2001; Beebe and Gozal, 2002]. In persons with DS, it may be necessary to manage positive symptoms with medication in

order to obtain the level of cooperation needed for an overnight sleep study. Basal ganglia calcifications are common in persons with DS [Wisniewski et al., 1982], and have been associated with mood disturbance and psychotic symptoms [Jakab, 1978; Thase, 1984].

ADOLESCENTS AND ADULTS WITH MOOD DISORDERS: REISS SCALE

The DS Clinic at Kennedy Krieger Institute has evaluated over 100 adolescents and young adults (13–30 years) with DS and co-morbid psychiatric disorders since 1999. The Reiss Scale is used to characterize their behavioral profile for clinical and research purposes. Parents provide informed consent and typically complete the 60-item Reiss at the time of initial evaluation. A comprehensive medical, developmental, behavioral, and psychiatric history and assessment is performed by a neurodevelopmental pediatrician (gc) after which a diagnosis is made. Our findings from 68 adolescents and young adults with DS suggest that mood disorders have a profile on the Reiss, which permits them to be distinguished from control DS subjects without behavioral co-morbidity. Subjects diagnosed with major depression scored significantly higher (>3 points average, $P < 0.0001$) on the Withdrawal, Depression, Attention, Anxiety subscales compared to typical subjects with DS and no behavioral concerns. Those with major depression also demonstrated moderate but significantly increased (1–3 points average, $P < 0.001$) scores on the Psychosis, Conduct and Anger subscales. In comparison, subjects diagnosed with a minor mood disorder had moderately increased scores on Withdrawal, Depression, Attention, Anxiety, Conduct, and Psychosis subscales which were also significant (1–3 points average, $P < 0.001$) when compared to DS controls (Capone, unpublished).

PHARMACOLOGIC STRATEGIES

A summary of medications often used to treat specific target symptoms in adolescents and young adults with DS and dual diagnosis is provided in Table VII.

CONSIDERATIONS FOR STARTING PSYCHOTROPIC MEDICATIONS

Many parents prefer to utilize low-risk, developmentally based interventions or other techniques in young children before considering medications. Some of these interventions may be unfamiliar to physicians [Lilienfeld, 2005]. If developmental progress becomes stifled and chronic behavioral problems ensue, parents may avail themselves to try

Prompt management of physiologic, emotional, and neurocognitive symptoms would permit educational and behavioral strategies to be more successful early on.

TABLE VII. Medication Guidelines for Adolescents and Adults With Down Syndrome

Psychiatric syndrome	Common target behavior	Initial consideration	Other considerations
Depressive illness	Depressed mood	SSRI	Second SSRI, dual re-uptake inhibitor, Bupropion
	Anxiety, OCD	SSRI	
	Insomnia	Trazadone (HS)	Second SSRI, Alprazolam Melatonin
	Atypical mood or cycling	Mood stabilizer	Atypical neuroleptic, low-dose SSRI (cautiously)
	Pre-menstrual dysphoria and anxiety (females)	SSRI	Oral contraceptives
	Fatigue, somnolence	Dual re-uptake inhibitor	Bupropion, Modafinil
	Catatonia	Benzodiazepine	ECT
	Poor responder	Dual re-uptake inhibitor, SSRI + Bupropion	Augmentation, ECT CPAP?
Obsessive-compulsive disorder	Obsessions-compulsions perseveration	SSRI, TCA	Second SSRI, atypical neuroleptic
	Anxiety, agitation, disruptiveness	Alprazolam, atypical neuroleptic	SSRI, mood stabilizer
	Tics, mannerisms	Typical/atypical neuroleptic	Guanfacine/clonidine
Psychotic-like disorder	Delusions-Hallucinations	Atypical neuroleptic	Second atypical neuroleptic
	Negative symptoms	Atomoxetine, Bupropion	Atypical neuroleptic?
	EPS, tremor, cogwheel rigidity	Lower dose of neuroleptic	Benzotropine, Amantadine
	Catatonia	Benzodiazepine	Lower neuroleptic dosage, ECT

TABLE VIII. Considerations for Use of Psychotropic Medications in Persons With Down Syndrome

Medications are unlikely to be helpful	Medications may be helpful
Only mild or occasional behavior problems exist	Behaviors are rapidly becoming worse in an otherwise stable environment, in the absence of acute medical illness
The child is young <3–4 years	A major psychiatric disorder is present: autism-spectrum disorder, bipolar disorder, obsessive-compulsive disorder, depression or mood disorder, psychosis
Behaviors are limited to a specific environment (aggressive at home, but not at school); or only in the presence of a specific person, (hits mother but not father) or situation, (becomes agitated-disruptive when exposed to loud noise or chaos)	A psychiatric disorder or syndrome is present: ADHD, anxiety, oppositional-defiant disorder, disruptive behavior disorder, with complex co-morbidity and/or significant impairment
A medical condition exists which is triggering or maintaining the behavior, such as: pain or physical discomfort (ENT, dental, GI, musculoskeletal, menstrual)	Physiologic, emotional or neurocognitive changes are VERY prominent
Physiologic, emotional or neurocognitive changes are NOT present	Person did well on medications previously, but they were stopped
There has NOT been an adequate trial of behavior management and/or functional communication	There has been an adequate trial of behavioral management and/or functional communication

"anything that works" including medications. It is unfortunate that so many families choose this entry into medications, as a last resort, for it is likely that prompt management of physiologic, emotional, and neurocognitive symptoms would permit educational and behavioral strategies to be more successful early on. In Table VIII we have specified circumstances which can inform clinicians about when to consider use of medication as part of their treatment plan.

Improvement in physiologic regulation, emotional stability, and neurocognitive processing is one of the most elusive but fundamental goals of pharmacotherapy. Enhanced behavioral self-regulation with concomitant reduction in the intensity, severity, or duration of maladaptive behaviors often occurs once impulse control, activity level, sleep quality, anxiety-mood state, and attention-cognitive dysorganization have improved. In many individuals, successful management of these impairing physiologic and behavioral symptoms will allow play-leisure activities, learning-academics, and social function to progress.

RECOMMENDED READING

There are many timely reviews in the pediatric and psychiatric literature addressing medication management for childhood and adolescent psychiatric disorders. Recommended reading for childhood disorders include: general overview and guidelines [Reiss and Aman, 1998]; ADHD [Hunt et al., 2001]; ODD-DBD [Althoff et al., 2003; Ruths and Steiner, 2004]; anxiety disorders [Rosenberg et al., 2003]; ASD-SMD [King et al., 2004; Findling, 2005]; treatment of sleep apnea [Goldstein et al., 2000; Pakyurek et al., 2002]. Recommended reading for adolescent and adult disorders include: general overview and guidelines [Reiss and Aman, 1998; Mikkelsen and McKenna, 1999; Antochi and Stavrakaki, 2004]; depression [Shoaf et al., 2001; Cheung et al., 2005; Ryan, 2005; Thase, 2005; Zajecka and Goldstein, 2005]; psychotic disorders [Birmaher, 2003]; obsessive-compulsive disorder [Grados and Riddle, 2001; Rosenberg et al., 2003]; treatment of sleep apnea [Means et al., 2003].

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