

Behavioral and Psychiatric Disorders in Children and Adolescents With Down Syndrome

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Not all children and adolescents with Down syndrome are happy and sociable. Some have behavioral problems, such as aggression or self-injury. Others may suffer with major depression or obsessive-compulsive disorder. There are few epidemiologic studies of psychiatric disorders in Down syndrome. Consequently, clinicians often have limited guidance from peer-reviewed literature, in selecting treatment options. This paper will review the behavioral disorders of aggression and self-injurious behavior as well as depression, bipolar disorder, psychosis, and obsessive-compulsive disorder. Although more research is needed in almost all areas, there are a few observations. Before using a psychotropic for aggression, attempt to rule out communication, social, environmental or medical etiologies. Similar to the general population, the first-line treatment for major depression is a SSRI (with the exception of paroxetine).

Keywords: bipolar disorder, developmental disability, Down syndrome, intellectual disability, mental retardation, mood disorder, obsessive-compulsive disorder, psychiatric disorder, psychosis, self-injurious behavior

Roizen and Patterson⁴⁸ stress that children with intellectual disability (ID) have more behavioral and psychiatric problems than children without a developmental disability. The public often has a mythical image of children with Down syndrome (DS). Articles in peer-reviewed journals typically describe children with DS as “cheerful, happy, and sociable.”⁵⁴ Some children with DS, however, do suffer from psychopathology, though the rates are less than their counterparts with other developmental disabilities.²² This paper will cover the behavioral disorders of aggression and self-injurious behavior (SIB) and the psychiatric disorders of depression, bipolar disorder, psychosis, and obsessive-compulsive disorder (OCD). In addition, attention-deficit/hyperactivity disorder (ADHD) and autism will be briefly discussed in the aggression section.

AGGRESSION

Children with certain genetic disorders such as Prader-Willi syndrome, are likely to be aggressive.²³ While aggressiveness is not a prominent part of the behavioral phenotype for children and adolescents with DS, some children are aggressive.⁴⁸ Gath and Gumley²⁶ found that children with DS were as likely to have aggressive gestures, as were children in the control group (ID without DS). Interestingly, they noted that children with DS, however, were significantly less likely to scream or shout. In contrast to Gath and Gumley’s study, Walz and Benson⁵⁴ concluded

that the 91 children and adolescents with DS demonstrated good social skills and few behavior problems compared to children with Prader-Willi syndrome or Angelman syndrome.

Myers and Pueschel³⁴ surveyed their large outpatient clinical practice (over 250 children and adolescents with DS). Slightly more than six per cent (6.5%) were aggressive. Dykens, *et al.*²² found 6% of the children and adolescents with DS fought and 12% were physically aggressive. The peak age appeared to be 10-13 years. Older teenagers had the least aggressive behavior.

EVALUATION AND TREATMENT OF AGGRESSION IN CHILDREN AND ADOLESCENTS WITH DS

Perhaps, the best rule is that there is no single etiology or medication for aggression. One needs to approach aggression as a symptom that may be based on communication, social, medical, or psychiatric concerns/disorders. (see Table 1) Before treating aggressive behavior with psychotropic medications, the child should have a comprehensive evaluation.³⁷

COMMUNICATION

Impaired verbal skills are often implicated as a contributing factor to childhood aggression.²⁷ Children with DS frequently have articulation problems and delayed speech. Fortunately, parents of children with DS are generally aware of the delayed language development and the

TABLE 1. DIFFERENTIAL DIAGNOSIS AND TREATMENT OF AGGRESSION

ETIOLOGY	SUGGESTED EVALUATION	TREATMENT
Impaired communication skills leading to frustration and aggression	<ul style="list-style-type: none"> •Speech and language assessment •Functional analysis •Consider augmented communication strategies 	Per evaluation
Social	<ul style="list-style-type: none"> •Functional analysis and plan •Sexuality education 	Plan stresses proactive strategies to promote positive behavior
Environmental	<ul style="list-style-type: none"> •Functional analysis and plan 	Plan based on functional analysis
Medical	<ul style="list-style-type: none"> •Assessment may include hearing and vision, thyroid, sleep apnea, joints, celiac disease 	Directed towards correcting health concern
Psychiatric	<ul style="list-style-type: none"> •Reiss Screen⁴⁶ •Aberrant Behavior Checklist² 	<ul style="list-style-type: none"> •ADHD – stimulants •Autism – caregiver education, support positive behavior, if minimal improvement in above, consider atypical neuroleptics •Major Depression - SSRI's except paroxetine •OCD - SSRI's except paroxetine •Psychosis – Atypical neuroleptics
Non-specific	Reassess the above items	If communication, social, environmental, medical and psychiatric do not yield a treatment strategy – consider: SSRI's except paroxetine, mood stabilizers or atypical neuroleptics

need for speech therapy.²⁴ Nevertheless, clinicians should not assume that a potential link between aggression and impaired communication has been properly investigated. One clue to a impaired language and aggression link is exploring the context of aggressive episodes through a functional analysis.⁶ If impaired communication leads to aggression in a specific setting (e.g., only school), then treatment can be aimed not only at the child, but also at the communication of those adults who interact with the child with DS.

SOCIAL

The social context of aggression should not be ignored. If aggression occurs largely with siblings, especially sisters, one might explore the contribution of the sisters to the aggression. A provocative study from Australia¹⁹ found that though children with DS had more problem

behaviors than their non-DS siblings, their sisters had significantly more conduct disorder. Another study also found more conduct disorder among sisters of children with DS than in siblings of children without DS.²⁰

MEDICAL

Clinicians are encouraged to utilize one of the health care guidelines for persons with DS.^{10,18,47} Several medical conditions, common in DS, can be associated with aggression. Sleep apnea is more common in DS.⁴⁸ Aggression improved following treatment for sleep apnea in two children.³⁶

Up to 7% of persons with DS have coeliac disease.⁴⁸ Furthermore, it may take years for the correct diagnosis after the onset of symptoms. “Explosive anger” and “obsessive aggressive” were

descriptors in two teenagers with untreated celiac disease.⁴⁵ Following a gluten-free diet, the behavioral symptoms diminished.

Hypothyroidism is another common illness in DS. The risk of hypothyroidism increases throughout life and may be 15%.⁴⁸ In children and adolescents with DS, the risk is 5%.¹⁸ To date, there are no studies associating hypothyroidism with aggression in DS. Nevertheless, the sluggishness of hypothyroidism could be mistaken for “non-compliance.” Misguided attempts at “correcting” the non-compliance could deteriorate into verbal, and potentially, physical aggression.

Sensory losses are common DS. Up to 75% of persons with DS are at risk for hearing loss and 50% of DS for refractive errors.¹⁸ Sensory losses, per se, do not cause aggression. They may increase the likelihood, however, that other factors (e.g., social, environmental, pain, etc.) could result in aggression.

PSYCHIATRIC

ADHD occurs in about 6% of children with DS.³⁴ Children with DS appear to have more inattention than children in the control group.²² In a study of 28 children aged 6 to 11 years, the children with DS showed a “hyperactive profile.”⁴⁴ Concentration improved, however, in older teenagers with DS.²² If aggression occurs in the context of ADHD, stimulants can have a significant effect on aggression, apart from the core ADHD symptoms.¹³ Overt aggression (physical assault or temper tantrums), coupled with conduct disorder, responded less well to stimulants.¹³ Interestingly, there is a lack of published information about use of stimulants in DS.

Aggression can occur in autism.³³ Autism and DS can occur together. Seven percent of 33 children with DS (out of 58 identified) in South Birmingham, UK were diagnosed with autism.²⁹ Estimates of autism and DS have ranged from 1% of a large clinic population of persons with DS³⁴ to 11.3%.³² Risperidone may be helpful in some children with autism.³³ Risperidone helped severe tantrums, aggression and SIB to placebo. In response to the study, Valiquette⁵² was concerned about risperidone use because risperidone induces hyperprolactinemia. Hyperprolactinemia can lead to osteoporosis. Furthermore, persons with DS are at risk for reduced bone mineral density.⁴

Aggression can also be associated with mood disorders, OCD, or psychosis. These topics will be discussed separately.

NON-SPECIFIC TREATMENT OF AGGRESSION

Applied behavior analysis utilizing positive behavioral supports can be effective in many behavioral problems. Being proactive and consistently reinforcing positive behavior is often more effective long-term in reducing aggression than trying to react to each incident.²⁵ Psychosocial interventions, without psychotropic medication, can manage some children with aggression.⁴³ Perhaps the most extensively studied psychologic treatment for aggression in children is Parent Management Training (PMT).²⁸ PMT focuses on maladaptive parent-child interactions. For example, some aggressive behavior is actually “rewarded” and reinforced by parental responses.

Schur, *et al.*⁴⁹ discuss several psychotropic treatments for aggression. These include: stimulants (mentioned above), beta-blockers, mood stabilizers, selective serotonin reuptake inhibitors (SSRI's), alpha2-agonists and atypical antipsychotics.

Beta-blockers, such as nadolol, have been studied in aggressive adolescents with developmental delay.¹⁴ There were significant declines in systolic blood pressure, diastolic blood pressure, and pulse rates. These cardiovascular effects occurred earlier than the behavioral effects. Only one of 12 subjects, however, were prevented from having the dose raised. None of individuals had DS. The blood pressure effects, however, suggest that nadolol may not be an ideal choice for aggression in children with DS. If nadolol (or another beta-blocker) is used, then blood pressure and pulse rate should be closely monitored.

Divalproex was used in 20 children and adolescents with explosive temper and mood lability.²¹ Unfortunately, ID was an exclusion criterion. Of the 15 subjects who completed the study, 12 had a better response to divalproex. Carbamazepine, however, was not more effective than placebo in 22 children.¹⁷ Twelve of 13 receiving carbamazepine had side effects. Leukopenia, headache, rash, dizziness, and diplopia were seen.

SSRI's have been tried in aggressive youth. Armenteros and Lewis⁵ studied citalopram (dose range 20-40) mg/d in 12 children and teens (7-15 years). These subjects had impulsive aggression in contrast to planned or purposeful aggression. One

subject was dropped because of the need for stimulants to treat ADHD. Citalopram was effective in the remaining 11. Four of the 11 had daytime somnolence that disappeared when the dose was changed to evening. Headaches and nightmares occurred, but did not require discontinuation.

The Medicines and Healthcare Products Regulatory Agency (MHRA)⁵³ recently recommended that paroxetine not be used in children and adolescents because of higher rates of suicidal thoughts and behavior (25/738 3.4%) on paroxetine versus (8/647 1.2%) placebo. There were no cases of actual suicide. Though suicidal ideation is significantly less in DS than in other persons with ID,⁴² it is clinically prudent to avoid paroxetine in children or adolescents with DS.

The alpha2-agonist, clonidine, reduces aggressive symptoms.¹² Cantwell *et al.*,⁷ however, reported four cases of adverse cardiovascular effects to clonidine, including one death. Furthermore, they note there were four other children who died suddenly while taking clonidine. The authors stress that the deaths had other complicating factors. As noted with beta-blockers, alpha2-agonists require monitoring of blood pressure and pulse rate. There are no case reports to guide the use of beta-blockers or alpha2-agonists in DS and aggression, so they are definitely not first-line treatment at this stage.

Risperidone was effective in a study of aggression and children with sub-average IQ's.⁵⁰ Unfortunately, it was not stated whether the study included children with DS. Extrapyramidal reactions were the most common side effects (13.2% vs. 5.3% in control). Given that neuroleptics are being used for aggression in children and adolescents, a task force developed recommendations.³⁷

Pappadopulos *et al.*³⁷ synthesized expert consensus focus group with evidenced-based literature to provide clinicians with recommendations for using antipsychotics for aggression in children. The recommendations pertain to evaluation, acute treatment, stabilization, and maintenance. The authors conclude that no generally accepted measure of aggression exists. They emphasize that psychosocial and educational interventions should be the first line. If a psychiatric disorder is present, then treatment should be focused on that (i.e., SSRI's for aggression in a child with major depression). Pappadopulos *et al.*³⁷ stressed that atypical antipsychotics may be effective for

aggressive children and adolescents. No data exists comparing the atypical neuroleptics relative superiority of one versus for aggression in children and adolescents. Furthermore, the usual daily dose for aggression is known only for clozapine and risperidone. Interestingly, the usual daily dose for clozapine is the same for aggression as it is for psychosis (150-300 mg/d for children and 200-600 mg/d for adolescents). However, the risperidone dose for aggression is less than for psychosis (1.5-2 mg/d vs. 3-4 mg/d in children; 2-4 mg/d vs. 3-6 mg/d in adolescents). Other recommendations reflect good clinical practice: systematic monitoring of side effects, decrease medications if child is not responding to a multiple medication regimen, and taper if aggression is in remission for six months.

At this time, there is not a clear first choice among atypical neuroleptics. As noted above, Valiquette⁵² is concerned about hyperprolactinemia from risperidone and the risk of osteoporosis. Olanzapine is associated with weight gain, a problem for many children with DS. (see Table 2) There is a paucity of literature on the use of aripiprazole, quetiapine, or ziprasidone in DS.

SELF-INJURIOUS BEHAVIOR

Self-injury does occur in DS, though it is infrequent. Myers and Pueschel³⁴ listed two persons under 20 years old with DS (0.8%) who had SIB. Sometimes, the SIB in DS can be severe, such as the report of traumatic blindness from SIB.³⁰ In general, the approach to an individual with severe SIB is the same as one with aggression. One does a thorough evaluation to determine if there is a psychosocial explanation for the self-abuse (as means to communicate displeasure or avoidance of a task), medical (ear infections, dental problems, visual abnormalities, etc) or associated psychiatric condition (e.g., depression).

DEPRESSION

Few epidemiologic studies of depression in DS exist. Furthermore, the findings are inconsistent.

TABLE 2. ATYPICAL NEUROLEPTIC SIDE EFFECTS¹

- **Agranulocytosis:** clozapine
- **Akathisia:** olanzapine and risperidone
- **Anxiety:** aripiprazole
- **Constipation:** aripiprazole, risperidone and quetiapine
- **Diabetes, weight gain, and hyperlipidemia:** olanzapine and clozapine
- **Dizziness or lightheadedness:** aripiprazole, olanzapine, quetiapine, risperidone
- **Extrapyramidal symptoms (higher doses):** olanzapine, risperidone and ziprasidone (5%)
- **Headache:** aripiprazole
- **Hyperglycemia:** risperidone and quetiapine (also see diabetes above)
- **Hyperprolactinemia:** risperidone
- **Insomnia:** risperidone
- **Myocarditis:** clozapine
- **Nausea:** aripiprazole
- **Neuroleptic malignant syndrome:** probably all (case reports for all but aripiprazole as of 7/03)
- **Postural hypotension:** olanzapine, quetiapine and risperidone (initially)
- **QT changes on electrocardiograph:** risperidone and ziprasidone
- **Seizures (increased risk):** clozapine
- **Somnolence:** clozapine, olanzapine, quetiapine, and ziprasidone
- **Weight gain:** clozapine, olanzapine, risperidone; **limited weight gain:** quetiapine

Cooper and Colacott¹⁵ surveyed the health district in Leicestershire, United Kingdom. They found 378 adults with DS and 11% had depression (though only half of the episodes met DSM criteria for major depression). They did not report on children, though the age range for depressive episodes included an 11 year old. Collacott and Cooper¹¹ found 42/371 (11%) with depression compared to 16/371 (4.3%) controls. In contrast, a survey of 11,277 persons with DS (including children, teens, adults and elderly) in California determined that major depression was significantly less than controls (2.3% vs. 7.1%).⁴¹

Myers and Pueschel³⁴ did not list any affective disorders in persons under 20 years old. In adults, 6.1% of the clinic had major depression.³⁴ Clues to the diagnosis of depression include: depressed affect, irritability, social withdrawal, anhedonia, tearfulness, poor energy, psychomotor agitation or retardation, change in weight and/or appetite, change in speech (reduced and or softer), tantrums, decline in personal hygiene and daily living skills, increased somatic complaints without physical etiology, and increased clinginess.⁴⁰

TREATMENT

Persons with DS have serotonin abnormalities.⁵⁵ This perhaps explains why antidepressants, with their primary action on serotonin, are more effective.³¹ Primarily the

noradrenergic drug, desipramine, may have a poorer response in DS.³⁵ As noted above, however, paroxetine should be avoided.

BIPOLAR DISORDER

Bipolar disorder is much less common in DS.^{39,41} Significantly fewer cases of DS and bipolar disorder appear in the literature than would be predicted from a normal distribution.¹⁶ In the individuals who do have both DS and bipolar disorder, treatment with mood stabilizers (e.g., Tegretol or valproic acid) is effective.

PSYCHOTIC DISORDERS

Psychosis in DS has some controversies. Using a Reiss Screen in 60 children with DS, Clark and Wilson⁹ noted that psychosis was the third highest aggregate score. Hallucinations are frequently described in persons with DS and mood disorders.⁴⁰ Gath and Gumley²⁶ noted "psychotic" behavior in children with DS. The "psychotic" behavior, however, included "stereotypies, use of objects as twiddles or unresponsiveness." With the possible exception of unresponsiveness (if it is catatonia), none of the descriptions of "psychotic behavior" would be a neuroleptics-responsive condition. Sovner and Hurley⁵¹ emphasize that psychosis is often overdiagnosed in persons with DS. For example, talking to oneself and acting out "mini dramas" are common in DS and often has no clinical

significance. They also believe that bizarre behavior (e.g., smearing feces), preoccupation with specific objects, posttraumatic flashbacks, or severe ritualistic behaviors inaccurately may be assumed to be "psychotic" behavior equivalents.

Sovner and Hurley⁵¹ worried about the overuse of neuroleptics in DS. Their concern arose during the era of irreversible tardive dyskinesia (TD) as a common neuroleptic side effect. The atypical neuroleptics appear to have a lower risk of TD. There is greater acceptance for a role of neuroleptics in non-psychotic conditions (such as impulsive aggression). This does not mean, however, that atypical neuroleptics are free of risks. (See Table 2) Certain risks, such as agranulocytosis with clozapine can be fatal. Atypical neuroleptics can still cause neuroleptic malignant syndrome. Weight gain associated with olanzapine, clozapine and to some extent risperidone, can be problematic in DS because of sleep apnea.

OBSESSIVE-COMPULSIVE DISORDER

Most children and adolescents with DS are stubborn. Almost 80% of parents rated their offspring with DS as stubborn.²² Stubbornness, however, is not related to patterns of obsessions and compulsions seen in OCD.³ A particular type of OCD, however, that persons with DS may show is obsessional slowness.^{8,38} Obsessional slowness is characterized by taking hours to get bathed, dressed, or eat a meal. This can interfere with getting children to school or day activities and can be a burden on caretakers. Three of the 11 persons with DS described by Charlot *et al.*³⁸ had onset as a teenager. Almost all were treated with SSRI's (one family refused medications). Two improved, and the rest showed partial improvement. One of the two that improved, received fluoxetine 20 mg/d. The other took sertraline 50 mg/d.

SUMMARY

Children and adolescents with DS are at some risk of behavioral challenges and psychiatric disorders. Behavioral challenges, such as aggression or SIB, require a thorough assessment to rule out communication, social, environmental, medical or psychiatric etiology. For psychiatric disorders, a few generalities can be made. For depression or OCD, SSRI's, except for paroxetine, should be considered. Atypical neuroleptics are preferred over typical neuroleptics for psychosis,

but more research is needed before recommending a specific atypical.

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