Disruptive behavior and aggressive disorders

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Children and adolescents with behavioral disturbances commonly come to the attention of primary care physicians. Although disruptive behaviors can be associated with any number of psychiatric disorders, this chapter will focus on three diagnoses wherein behavioral symptoms are key diagnostic criteria: oppositional defiant disorder (ODD), conduct disorder (CD), and intermittent explosive disorder (IED). A fourth diagnosis, attention-deficit/hyperactivity disorder (ADHD), is usually included in the disruptive behavior disorder (DBD) category, but will not be included in this chapter (see Chapter 4 for details about the treatment of ADHD).

Definition

The disorders covered in this chapter are considered *disruptive*, in that individuals diagnosed with them evidence behaviors that have a negative effect on their immediate environment and elicit negative responses from others. A common element of the negative behavior is *aggression*, which can be verbal or physical. Verbal aggression includes loud, profane, or threatening speech that intimidates others. Physical aggression includes damage to property or person, the latter also known as *violence*. Violent behavior exists in two basic forms: *proactive* aggression, which is premeditated and fairly dispassionate; *reactive* aggression is impulsive and affectively driven. The distinction between proactive and reactive aggression is an important one, since it is the reactive type that tends to respond to pharmacotherapy.

The disruptive aspect of ODD comes from the conflict that the individual has with rules and authority figures. Legal problems associated with ODD are relatively minor, e.g. truancy and running away. The symptoms of CD exist at another level of disruption, with major violations of societal norms and major disregard for boundaries of property and person. Legal problems associated with CD are more serious, e.g. robbery or rape, and often lead to involvement in the legal system, including incarceration. Individuals with IED have problems that are episodic and associated with intense anger outbursts ("rage"); their legal problems are usually limited to destruction of property and assault.

■ Epidemiology

The lifetime prevalence of ODD in the USA is about 8.5% in the general population, with symptoms usually obvious before the age of 8 years. The lifetime prevalence of CD is about 9.5% (12% among males and about 7% among females), and the median age of onset is around 11.5 years. Lifetime prevalence estimates of IED in the general population are about 7% versus about 5%, depending on whether broad or narrow diagnostic criteria, respectively, are used. The mean age of onset of the first major anger attack is somewhere between 14 and 15 years, although much younger ages are not uncommon in clinical settings.

■ Differential diagnosis/comorbidity

Angry and irritable moods, as well as disruptive, aggressive, or violent behaviors are often not diagnoses in their own right, but signs and symptoms of underlying medical, substance-related, or psychiatric disorders. Table 7.1 lists the diagnoses to consider when evaluating patients with disruptive and aggressive behaviors; references are also given to other chapters in this book for more details.

■ Psychopharmacology

Table 7.2 lists the pharmacologic classes and agents which may be used to treat disruptive and aggressive behavior disorders. Recommendations for use in specific problem areas will be described in the section "How to use the medications."

Table 7.1 Disorders associated with disruptive behaviors and aggression.

Medical
Seizure disorders
Traumatic brain injury
Encephalitis/meningitis
Sensory impairments
Huntington's disease
Wilson's disease
Lafora's disease
Acute intermittent porphyria
Hartnup's disease
Neuroacanthocytosis
Developmental disorders (see Chapter 10)
Substance-related (see Chapter 13)
Alcohol abuse/dependence: Intoxication or withdrawal
Anxiolytic abuse/dependence: Intoxication or withdrawal
Cannabis abuse/dependence: Withdrawal
Stimulant abuse/dependence: Intoxication
Psychiatric
Attention-deficit/hyperactivity disorder (see Chapter 5)
Oppositional defiant disorder
Conduct disorder
Intermittent explosive disorder
Mental retardation (see Chapter 10)
Autistic spectrum disorders (see Chapter 9)
Language disorders
Mood disorders (see Chapter 4):
Major depressive disorder
Bipolar disorder
Anxiety disorders (see Chapter 3):
Post-traumatic stress disorder
Social anxiety disorder
Separation anxiety disorder
Psychotic disorders (see Chapter 8)
Tic disorders (see Chapter 12)
Personality disorders
Borderline personality disorder (mostly females)
Antisocial personality disorder (mostly males)
Paranoid personality disorder (mostly males)

Table 7.2 Medications used to treat disruptive and aggressive behavior disorders, and ages at which use may be appropriate.[a]

Class	Agent	Doses[a]	Ages[b]
Psychostimulants: See Chapter 5 for details			
Antidepressants: See Chapter 6 for details			
Anxiolytics: See Chapter 4 for details			
Alpha-agonists	Clonidine	0.05–0.20, 2–3×/d	≥12
Antipsychotics			
First-generation			
Phenothiazines	Chlorpromazine	50–400 mg/d	≥1[b]
	Thioridazine	50–400 mg/d	≥2[b]
Butyrophenones	Haloperidol	2–10 mg/d	≥3[b]
Second-generation	Risperidone	1–4 mg/d	≥18
	Olanzapine	5–20 mg/d	≥18
	Quetiapine	200–600 mg/d	≥18
	Ziprasidone	80–120 mg/d	≥18
Mood stabilizers			
Lithium salts	Lithium carbonate	25–35 mg/kg/d, div. 2–3x/d (adj. to level)	≥12
Anticonvulsants	Carbamazepine	7 mg/kg/d, 2–3×/d (adj. to level)	Any (?)
	Valproic acid	20 mg/kg/d, 2–3×/d (adj. to level)	≥10
	Oxcarbazepine	**20–29 kg**: 900 mg/d **30–39 kg**: 1200 mg/d **>39 kg**: 1800 mg/d	≥18
Beta-blockers	Propranolol	**<35 kg**: 10–20 mg; **>35 kg**: 20–40 mg, both at 2×/d dosing	
	Metoprolol	12.5–25 mg, 2×/d	≥18 (all)
	Pindolol	6.25–12.5 mg, 2×/d	
	Nadolol	5–10 mg, 1×/d	

[a] Dosing is clinically based, unless stated otherwise.

[b] Ages (years) are for FDA-approved indications; use for other indications and/or at other ages is based on clinical judgement.

Medication classification and mechanism of action

Psychostimulants

The amphetamines are non-catecholamine, sympathomimetic amines that act as powerful CNS stimulants. Their putative mechanism of action involves reuptake blockade of neurotransmitters (dopamine and norepinephrine) into presynaptic neurons, as well as an increased release of those neurotransmitters into the synaptic cleft. Methylphenidate, a non-amphetamine sympathomimetic, acts as a mild CNS stimulant; its mechanism of action is believed to be mediated through activation of brain stem and cortical arousal systems. Atomoxetine, a nonstimulant used to treat ADHD, is discussed with the antidepressants.

Antidepressants

Although the precise mechanisms through which these agents exert their clinical effects are unknown, their efficacy is hypothesized to be related to an increase of available catecholamine neurotransmitters in the CNS. Therapeutic changes occur via downregulation of postsynaptic neurons. The MAO inhibitors (MAOI) prevent the breakdown of the monoamine neurotransmitters present in presynaptic neurons. The tricyclic antidepressants (TCAs) block reuptake of all the catecholamine neurotransmitters into presynaptic neurons. The selective serotonin reuptake inhibitors (SSRIs) selectively block the reuptake of serotonin into presynaptic neurons. Atomoxetine, although used to treat ADHD, is essentially an antidepressant, in that its mechanism of action relies on selective inhibition of norepinephrine reuptake. Antidepressants in other classes exert their effects through reuptake inhibition, pre- and/or postsynaptic antagonism, or a combination.

Anxiolytics

Benzodiazepines bind to specific receptors in the CNS, especially in the limbic system and other deep-brain structures, producing the calming effect that these medications are known for. Buspirone, a nonbenzodiazepine anxiolytic, may produce its calming effects through $5HT_{1A}$ receptor binding.

Alpha-agonists

These agents stimulate brainstem $alpha_2$-adrenoreceptors, effectively reducing CNS sympathetic outflow. As the sympathetic nervous system is

involved in the "fight or flight" response, the alpha-agonists may serve to blunt anxiety or aggression in some individuals.

Antipsychotics

The hypothesized mechanism of action for these medications is related to their ability to antagonize dopamine receptors. Regarding the "atypical" or second-generation antipsychotics (SGAs), an additional action may be derived via serotonin receptor antagonism.

Mood stabilizers

Lithium affects neuronal sodium transport, which may affect how nerve cells process catecholamines; how this contributes to its anti-manic or anti-aggressive effects is unclear. The numerous available anticonvulsants likely have different mechanisms by which they exert their effects. Proposed theories include neuronal membrane stabilization, the inhibition of excitatory amino acids (e.g. glutamate and aspartate), and the increase of gamma amino-butyric acid (GABA), a known inhibitory neurotransmitter.

Beta-blockers

These agents block beta-adrenergic receptors, effectively reducing sympathetic nervous system activity. It is not known how they exert their effects in the CNS, as agents vary by degree of selectivity for $beta_1$ (mostly cardiac) and $beta_2$ (noncardiac) receptors, and also vary in degree of lipophilia (propranolol, pindolol, and metoprolol are quite lipid-soluble; nadolol is more water-soluble).

Side-effects (adverse effects)

Psychostimulants

Observed adverse reactions include bland facial expression, decreased social interactions, and impaired cognition. The stimulants can provoke or increase irritability, psychomotor activity (including tics), and anxiety. Insomnia may be produced or exacerbated by stimulant use. These medications commonly reduce appetite and can also lead to loss of body weight, and in some patients may prevent them from achieving their full height potential.

Antidepressants

The SSRIs can cause agitation, akathisia, and hypomania (especially in those at risk for bipolar disorder). Another concern with the SSRIs is the serotonin syndrome, especially when they are used concomitantly with other serotonergic agents. Bupropion can lower the seizure threshold. With the exception of bupropion and mirtazapine, all of the commonly used antidepressants can cause hyponatremia and/or SIADH. Atomoxetine commonly causes headache and stomach upset, may increase blood pressure and heart rate, and can cause irritability and mood instability.

Anxiolytics

The benzodiazepines can cause sedation, behavioral disinhibition (similar to that seen with alcohol intoxication), worsening of cognitive functioning, and withdrawal seizures. They also have the potential for being abused or causing dependence. The use of buspirone avoids the abuse and dependence issues, but not the side effects.

Alpha-agonists

Common side effects include dry mouth, drowsiness, dizziness, constipation, and sedation. Children generally experience orthostatic hypotension less than adults do; however, children may be more susceptible to rebound hypertension if these agents are discontinued abruptly.

Antipsychotics

Adverse effects from these agents include hyperglycemia, hyperlipidemia, hyperprolactinemia, extrapyramidal symptoms (EPS), and weight gain. As treatment with antipsychotics may need to be long term in some cases, the possible development of tardive dyskinesia is a serious concern.

Mood stabilizers

Common lithium side effects include increased thirst, polyuria, fine resting hand tremors, mild gastrointestinal upset, and leukocytosis. More serious associated conditions include hypothyroidism, renal insufficiency, cardiac arrhythmias, diarrhea with electrolyte disturbances, and lithium toxicity (with significant neurologic signs and symptoms).

All of the anticonvulsants used as mood stabilizers can elevate liver function tests values. They have also been associated with Stevens–Johnson

syndrome and toxic epidermal necrolyis. Hepatic failure has been reported with valproic acid and carbamazepine. Valproic acid can cause life-threatening pancreatitis; it can also cause thrombocytopenia. Aplastic anemia and agranulocytosis have been reported with carbamazepine. Carbamazepine and oxcarbazepine may reduce the efficacy of oral contraceptives. Anticonvulsants increase the risk of suicidal thoughts and depression (FDA, 2008).

Beta-blockers

Common side effects include dizziness, fatigue, bradycardia, mental status changes, gastrointestinal upset, and various skin rashes. Less common – but more serious – adverse events can be bronchospasm and heart failure, both of which may occur more readily in children.

Contraindications

Psychostimulants

These medications are contraindicated in patients who are already experiencing significant levels of anxiety, inner tension, or psychomotor agitation. They should not be used if glaucoma is present. They should also not be used if patients are on MAOIs, inhibitors, or if those medications have been discontinued within the last 2 weeks. Their use in the presence of motor tic disorder or Tourette's disorder is relatively contraindicated (see Chapter 12). Another relative contraindication is a seizure disorder. The use of the mixed amphetamines is also contraindicated if the patient has symptomatic cardiovascular disease, hypertension, or hyperthyroidism.

Antidepressants

All of the non-MAOI antidepressants (and atomoxetine) are contraindicated for concurrent use with MAOIs, or if an MAOI has been discontinued within the previous 2 weeks. Before starting an MAOI, most other antidepressants should be stopped at least 2 weeks beforehand (venlafaxine requires at least 1 week; fluoxetine requires at least 5 weeks). All antidepressants with serotonergic activity (except mirtazapine and venlafaxine) are contraindicated for use with pimozide, the combination of which can greatly prolong the QT_c interval (fluoxetine and paroxetine should not be used concurrently with thioridazine, and nefazodone with carbamazepine, for similar reasons).

Bupropion is contraindicated in patients with a seizure disorder or an eating disorder (which, in combination with bupropion, increases the risk of a seizure).

The MAOI antidepressants should not be used in patients with pheochromocytoma, heart failure or other cardiovascular disease, cerebrovascular disease, or liver disease. There are also several medications which should not be used in combination with the MAOIs, especially dextromethorphan, meperidine, and any with sympathomimetic actions.

Atomoxetine should not be used in patients with narrow angle glaucoma.

Anxiolytics

The benzodiazepines should not be used if patients have acute narrow angle glaucoma. Abuse or dependence potential may exclude use in certain individuals. The use of buspirone is contraindicated in combination with an MAOI.

Alpha-agonists

There are no known specific contraindications to their use, although hypotension may preclude their use in certain individuals.

Antipsychotics

The older, first-generation antipsychotics (FGA) are contraindicated in patients with blood dyscrasias, hepatic damage, subcortical brain damage, and obtundation. The use of thioridazine is also contraindicated in patients with congenital long QT_c syndrome, who are taking other medications that can prolong the QT_c interval, or who already have cardiac arrhythmias.

The SGAs, as a group, do not carry any specific contraindications, with some exceptions. The cautions about potential cardiac arrhythmias during the use of ziprasidone are similar to those associated with thioridazine.

Mood stabilizers

Lithium should not be used in patients with severe cardiovascular disease, renal disease (unless already on dialysis), dehydration, or sodium depletion (or medications that cause it). Persons with brain damage may be more sensitive to lithium's neurotoxic potential.

Given that carbamazepine has a tricyclic structure, its use with MAOI needs to follow the same guidelines as noted previously for the

antidepressants. It should be avoided in persons with prior bone marrow suppression, as well as in individuals with acute intermittent porphyria. Although oxcarbazepine is very closely related to carbamazepine, it does not have specific restrictions to its use (other than known hypersensitivity to the drug itself).

Valproic acid should not be used in the presence of significant hepatic dysfunction or a urea cycle disorder.

Beta-blockers

These medications should not be used in patients with sinus bradycardia and greater than first-degree heart block, asthma, sick sinus syndrome, significant peripheral arterial disease, pheochromocytoma, and right ventricular failure associated with pulmonary hypertension.

How to use the medications

If a patient's disruptive/aggressive behavior is felt to be secondary to a specific psychiatric disorder, treatment for that disorder should proceed in a manner that will have the best chance of relieving all symptoms, including the behavioral ones. Recommendations for medications are listed in Table 7.3, and are discussed below. For the treatment of any disorder, if none of the interventions are effective or tolerated, a re-evaluation of the patient should be undertaken, looking for previously missed comorbid diagnoses or even a misdiagnosis. The clinician has the option of referring the patient to a psychiatrist at any point during the treatment process.

Psychostimulants

The disruptive behaviors in a child with ADHD may often improve, or even resolve, if the ADHD itself is properly treated. The stimulant medications should be used cautiously, however, as they may provoke irritability and aggression in some individuals. If a trial of a stimulant – methylphenidate or mixed-amphetamine salts – is ineffective or worsens the behavior, a second trial with the stimulant not previously used is indicated. If neither stimulant is effective, or if they especially exacerbate the behavioral symptoms, then a trial of either clonidine or a beta-blocker (preferably the former) should be tried (see their respective sections below). How the medications are dosed is important. The longer-acting stimulants are preferred, as the wearing

Table 7.3 Disorders associated with aggressive or violent behaviors, and recommended pharmacotherapeutic strategies.

	Medications		
Disorder	First-line	Second-line	Third-line
ADHD	Stimulant	2nd stimulant	Alpha-agonist or beta-blocker
Anxiety	SSRI	2nd SSRI or alpha-agonist	Buspirone
ASD ± MR	Risperidone	2nd SGA	AED
Bipolar disorder	Lithium	VPA or CBZ	2nd AED or an SGA
Conduct disorder	Lithium	SGA	Chlorpromazine
Depression	Fluoxetine	2nd SSRI	Non-SSRI AD or lithium
IED	Lithium	AED	SGA
Psychosis	SGA	2nd SGA	3rd SGA or an FGA
TBI	Alpha-agonist or beta-blocker	AED	SSRI

ADHD, attention-deficit/hyperactivity disorder; ASD, autistic-spectrum disorder; MR, mental retardation; IED, intermittent explosive disorder; TBI, traumatic brain injury; AD, antidepressant; AED, antiepileptic drug; CBZ, carbamazepine; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; SSRI, selective serotonin reuptake inhibitor; VPA, valproic acid.

off of the shorter-acting stimulants is more likely to produce agitation and irritability.

Antidepressants

For depression, fluoxetine is the clear choice for first agent to use. As noted previously, the patient's lack of, or adverse, reaction to fluoxetine would dictate a second medication trial with another SSRI. If that agent also is ineffective or exacerbates the behavioral symptoms, then a third trial, this time with a non-SSRI antidepressant (except for bupropion) or with lithium, should be initiated.

For anxiety, treatment can start with any SSRI, followed by a second SSRI (if the first was ineffective or poorly tolerated) or an alpha-agonist. If neither of the second-line medications are effective, an anxiolytic should be considered (see below).

Anxiolytics

The recommended agent for the combination of anxiety and aggression (not responsive to other agents – see above) is buspirone. Dosing needs to be on a 3 times a day schedule, to compensate for the higher metabolic activity in younger people, and to prevent rebound anxiety and agitation.

Alpha-agonists

Clonidine is a versatile agent. As discussed above, it is a third-line agent for use in patients with ADHD-associated aggression, and a second-line agent for aggression associated with anxiety. Along with the beta-blockers (see the discussion below), clonidine is a first-choice treatment for the aggression associated with traumatic brain injury. Dosing should be at least twice-daily to avoid rebound symptomatology (clonidine is short-acting).

Antipsychotics

The use of these agents for aggression associated with psychosis essentially follows the standard protocol for treatment of schizophrenia (see Chapter 8). Risperidone is the drug of choice for the agitation and aggression associated with autistic spectrum disorders (the other second-generation antipsychotics (SGAs) can be used as second-line agents). Any of the SGAs can be used as third-line agents for the aggression associated with conduct disorder or bipolar disorder. The first-generation antipsychotic (FGA) chlorpromazine can be used as a third-line agent to treat the disruptive behaviors associated with conduct disorder.

Mood stabilizers

Lithium is the treatment of choice for the aggression seen in patients with bipolar disorder, conduct disorder, and intermittent explosive disorder. As mentioned previously, lithium is also a third-line agent for depression-associated aggression. The anticonvulsants valproic acid and carbamazepine are second-line agents for bipolar disorder with marked behavioral disturbances. The anticonvulsant mood stabilizers are second-line agents for treating the aggression in intermittent explosive disorder and the disruptive behavior in patients with traumatic brain injury. They

are also used as third-line agents in autistic spectrum disorders and bipolar disorder.

Beta-blockers

These agents can be used, instead of alpha-agonists, as first-line agents to treat the aggression associated with traumatic brain injury, or as third-line agents to control disruptive behaviors associated with ADHD.

How to monitor the medications

Psychostimulants

In cases of chronic treatment, periodic complete blood count (CBC), with differential and platelet count, are recommended. Blood pressure and pulse should be checked at each medication visit, as both values can increase with stimulant treatment. Height and weight should be measured per routine schedule, and any significant slowing, stoppage, or loss should prompt discontinuation and medical evaluation.

Antidepressants

No routine laboratory tests are required for any of these medications. However, venlafaxine may raise serum cholesterol, such that checking levels should be considered during prolonged treatment. The selegiline patch infrequently elevates liver function test values; routine testing is not recommended. For patients on atomoxetine pulse and blood pressure should be measured at baseline, following dose increases, and periodically during treatment.

Anxiolytics

For patients on long-term therapy with a benzodiazepine, periodic blood testing of the WBC (to check for neutropenia) and liver function tests (to check for elevated bilirubin or LDH) are advised.

Alpha-agonists

Blood pressure should be monitored for hypotension and rebound hypertension. No laboratory studies are required.

Antipsychotics

It is important that the patient's height, weight, body-mass index, blood pressure, pulse, and fasting glucose and lipids be measured before starting treatment with these agents. A baseline examination for extrapyramidal signs is suggested. The only atypical antipsychotic that requires baseline and follow-up ECGs is ziprasidone. All of these parameters, as well as a serum prolactin level (especially in females), should be rechecked during the course of treatment.

Mood stabilizers

Before starting lithium obtain baseline electrolytes, BUN, creatinine, thyroid function tests, WBC, and urine specific gravity; repeat 1 or 2 times/year, once the patient is stabilized. A serum lithium trough level (10–12 hours after last dose) should be measured 4–5 days after starting the medication, 4–5 days after any dosage increase, and every 3–6 months during the maintenance phase.

In patients on valproic acid, baseline and follow-up (every 6–12 months) AST, ALT, LDH, and CBC should be measured. The drug level should be checked 1–2 weeks after initiation or after each dosage increase, and also every 3–6 months during maintenance.

The monitoring for carbamazepine is essentially the same as for valproic acid.

Beta-blockers

Blood pressure and pulse should be routinely monitored. There is rarely a need for laboratory testing for these medications. Propranolol can sometimes cause elevations in serum potassium, AST, ALT, and alkaline phosphatase in hypertensive patients. Pindolol can also occasionally elevate AST, ALT, and alkaline phosphatase, as well as LDH and uric acid.

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