Table 3.

Pharmacologic Interventions for Rage

Medication/relevant FDA indication	Mechanism of action	Typical dose	Indication/evidence	Common side effects	Serious reactions	Caution/other information
Antidepressants						
Fluoxetine MDD, OCD, bipolar depression	SSRI	20 mg daily; typically, 20–80 mg daily, max 120 mg/d in OCD	Aggression associated with mood disorders Would try first line if patient has mild-moderate aggressive behaviors Off-label: primary impulsive aggression, PTSD	Insomnia, headache, nausea, sexual side effects, weight gain	Bleeding (especially GI bleeding), hyponatremia/SIADH, serotonin syndrome, fractures	2D6 inhibitor; black box warning for suicidality <24 y old; long half-life
Atomoxetine ADHD	SNRI	Children: -<70 kg: 0.5 mg/kg/d in 2 divided doses; max 100 mg/d ->70 kg: follow adult dosing Adult: 40 mg/d, max 100 mg/d	Off-label: impulsivity due to ADHD, binge eating disorder	Sedation, fatigue, nausea, increase in blood pressure, insomnia, dizziness, anxiety, agitation, anticholinergic side effects, sexual dysfunction, dysmenorrhea	Hyper/hypotension, increased heart rate and risk of cardiac adverse events, orthostasis, suicidality, chemical hepatitis	Minimum trial 6–8 wk though improvement can continue for 8–12 wk; can be combined with stimulants
Antiepileptic drugs/anticonvulsants						
Carbamazepine (CBZ) BPAD, focal seizures, and generalized onset seizures	Blocks voltage-gated sodium channels, inhibits glutamate release	Adults: 100–400 mg/d, max 1,600 mg/d For primary impulsive aggression, 450 mg/d is initial target dose with low-subtherapeutic drug levels	Off-label: primary impulsive aggression, IED	Dizziness, sedation, nausea, headache, rash	Myelosuppression, hepatitis, jaundice, SJS/TEN, angioedema, SIADH	Monitor drug level (mean 4.3 µg/mL; therapeutic 4–12 µg/mL), CBC count with differential, sodium, LFTs, HLA-B1502 in people of Asian descent; teratogenic; self-inducer; enzyme inducer and inhibitor of many common medications (OCPs, antibiotics, psychotropics)
Oxcarbazepine Focal seizures	Unknown; thought to be blocking voltage-gated sodium channels, stabilizing neuronal membranes, decreasing propagation of synaptic impulses; modulates activity of calcium channels	300 mg bid; max 2,400 mg/d	Off-label: BPAD, primary impulsive aggression, IED	Headache, ataxia, dizziness, nausea, vomiting, drowsiness	SJS/TEN, anaphylaxis, angioedema, hyponatremia	Better tolerated than CBZ and is not teratogenic; reduce efficacy of OCPs by up to 50%; moderate enzyme inducer; check HLA-B1502 in people of Asian descent before starting
Valproic acid BPAD, focal seizures, and generalized onset seizures	Inhibits voltage-gated sodium channels, increases GABA activity, inhibits GABA transaminase, modulates calcium channels	Adults: 250 mg tid; increase by 250–500 mg to target serum level 20–30 mg/kg in 1–4 divided doses for rapid symptom control Geriatric patients: 125–250 mg tid; increase by 125–250 mg to target serum level	Off-label: primary impulsive aggression, bipolar depression, IED, aggression in brain injury and dementia	Thrombocytopenia, PCOS, weight gain, somnolence, tremor, hair loss, nausea, fatigue, dizziness	Hepatotoxicity, pancreatitis, teratogenic	Effective for aggression at mean level 39.2 µg/mL (therapeutic 50–120 µg/mL); teratogenic: need baseline pregnancy test; monitor: CBC, weight, PT/PTT, LFTs, glucose, lipids, check drug level 3 d after dose change; check level, CBC, LFTs q 6 mo
Phenytoin Focal onset seizures and generalized onset seizures	Voltage-gated sodium channel blocker, prolongs neuronal refractory period, stabilizes inactive state of the sodium channel	Adults: 100 mg tid or 200 mg q AM, 100 mg q PM; max 400 mg/d in 2–3 divided doses Treat for 6–12 weeks before deciding if the medication is helpful	Does not have an approved psychiatric use Off-label: primary impulsive aggression	Headache, nausea, vomiting, constipation, dizziness, ataxia, swollen gums, tremors, rash, nystagmus, drowsiness, coarse facies, hirsutism	Hypotension, severe cardiac arrhythmias, hepatotoxicity and acute liver failure, blood dyscrasias, SJS, DRESS, suicidality	Effective at serum levels of 3.3 µ/mL (therapeutic 10–20 µg/mL); check 12-hour serum trough 2 weeks after first dose and 1 week after dose change; impairs vitamin D absorption causing hypocalcemia; interferes with folate metabolism causing megaloblastic anemia; fetal malformations; enzyme-inducing
Antimanic agents						
Lithium BPAD	Unknown; alters cation transport across cell membranes, influences the reuptake of serotonin and norepinephrine, inhibits second messenger systems, has neuroprotective effects	Children: 600–900 mg in 2–3 divided doses; max dose 600–1,200 mg/d based on level Adults: 600–900 mg/d in 2–3 divided doses based on chosen formulation; max 900–1800 mg/d based on level Geriatric patients: adult dosing but start low and go slow	Off-label: MDD, postpartum psychosis, primary impulsive aggression	GI upset, tremor, thirst/polydipsia, hypothyroidism, acne, leukocytosis	Nephrogenic DI, dysrhythmia, bradycardia	Monitor: lithium level, TSH, BMP at initiation, then 1–2 months, then every 6–12 months; check level after every dose change and when adding a medication that alters metabolism such as NSAIDs, ACEi, HCTZ; levels altered by dietary sodium intake

(continued)

Table 3 (continued).

Medication/relevant FDA indication	Mechanism of action	Typical dose	Indication/evidence	Common side effects	Serious reactions	Caution/other information
Beta-blockers						
Propranolol	Nonselective β-adrenergic blocker; blocks β_1 and β_2 adrenergic stimulation	Adults and geriatric patients: -IR: 10 mg bid, max 120 mg/d; may go higher in some cases of aggression -ER: 20 mg/d; max 80 mg/d Performance anxiety: 10–20 mg 30–60 min prior to activity; max 40 mg tid	Off-label: anxiety, agitation due to primary psychotic disorder, autism, developmental delay, performance anxiety	Dizziness, fatigue, bradycardia, hypotension	May mask clinical signs of hypoglycemia and hyperthyroidism	May exacerbate asthma, COPD, CHF; requires taper
Antipsychotics						
Clozapine Treatment-resistant schizophrenia, suicidal behavior in schizophrenia or schizoaffective disorder	$D_{1\text{-}4}$, 5-HT_{2A}, 5-HT_{2C} antagonist	Adults: 12.5–25 mg daily; 300 mg by the end of 2 wk; max 900 mg/d Geriatric patients: 6.25 mg/d, max 50 mg/d	Off-label: dementia, Parkinson psychosis, treatment-resistant BPAD, autism, developmental disability	Orthostasis, weight gain, sedation, sialorrhea, tachycardia	Agranulocytosis, myocarditis, gastrointestinal hypomotility, NMS, QTc prolongation	Dose requirements higher in smokers; if a patient stops smoking, reduce the dose by 60–70%; must be tapered; requires frequent blood draws; can lower seizure threshold
Aripiprazole BPAD, MDD, schizophrenia, irritability in autism	Partial D_2 agonist, partial 5-HT_{1A} agonist, 5-HT_{2A} antagonist	Children: 1–2.5 mg/d; up to 15 mg/d Adults: 10–15 mg/d; max 30 mg/d Geriatric patients: 2–5 mg once daily, up to 15 mg/d	Off-label: dementia, OCD, Tourette syndrome, conduct disorder, aggression in autism	Akathisia, anxiety, insomnia, tremors, somnolence, weight gain, headache	Pathologic gambling and impulse control disorders, NMS	Minimal risk of hyperprolactinemia, can be combined with clozapine for rational polypharmacy; black box warning with dementia; requires metabolic monitoring
Risperidone Schizophrenia, BPAD, irritability in autism	D_2, 5-HT_{2A}, α_1, α_2, H_1 antagonist	Children: 0.25–0.5 mg/d depending on weight; max 2–3 mg daily Adults: 2 mg/d in 1–2 divided doses; max 6 mg/d Geriatric patients: 0.5 mg bid; max 6 mg daily	Off-label: Tourette syndrome, ODD, conduct disorder, dementia, aggression in autism	Somnolence, orthostatic hypotension, weight gain	Hyperprolactinemia, EPS (typically at > 4 mg daily)	Requires metabolic monitoring; black box warning for increased mortality in older adults
Olanzapine Schizophrenia, agitation, bipolar mania, bipolar depression, treatment-resistant depression	5-HT_{2A}, D_2, H_1, M_1, α_1, 5-HT_{2C} antagonist	Children: 1.25–5 mg; max 20 mg/d Adults: 2.5–10 mg daily; max 20 mg/d Geriatric patients: 2.5 mg/d; max 10 mg	Off-label: Tourette syndrome, OCD, reduces self-injurious behaviors in borderline personality disorder, aggressive behaviors in dementia	Significant weight gain, hyperglycemia, dyslipidemia, somnolence, dry mouth, constipation	DRESS	Cigarette smoking may increase clearance by 40%; black box warning for increased mortality in older adults
Quetiapine Schizophrenia, bipolar mania, bipolar depression	5-HT_{2A}, D_2, H_1, α_1 antagonist, 5-HT_{1A} agonist	Children: -IR: 25 mg bid; max 800 mg/d -XR: 50 mg/d; max 800 mg/d Adults: -IR: 100–200 mg d; max 800–1,200 mg/d -XR: 300 mg/d; max 800–1,200 mg/d Geriatric patients: 25 mg at bedtime; max 300 mg/d	Off-label: Parkinson psychosis	Dizziness, sedation, weight gain, constipation, hypotension	Orthostatic hypotension, possibly cataract formation	Requires metabolic monitoring; black box warning for increased mortality in older adults
Alpha-2 agonists						
Clonidine ADHD	Stimulates α_2 adrenoreceptors and supports neuronal inhibition by hyperpolarizing nerves, resulting in reduced sympathetic outflow from the CNS	Children: 0.05–0.1 mg nightly, max 0.2–0.4 mg/d depending on weight Adults and geriatric patients: 0.1 mg daily, increase by 0.1 mg and divided doses; max 0.4 mg/d	Off-label: ICU sedation, opioid withdrawal, agitation in autism, ADHD, Tourette syndrome	Sedation, dizziness, dry mouth, depression, anxiety, nausea, hypotension	Sinus bradycardia, AV block, hypertensive encephalopathy during withdrawal	Requires taper; comes in transdermal formulation
Guanfacine ADHD	Selective α_{2A} adrenergic receptor agonist, which reduces sympathetic activity on the heart and circulatory system	Child: 1 mg nightly; max 3–7 mg/d depending on formulation Adult: 1 mg nightly; max 4 mg/d	Off-label: OCD, ADHD	Sedation, weakness, dizziness, dry mouth, constipation	Hypotension, syncope, sinus bradycardia	Less likely to cause hypotension than clonidine

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Table 3 (continued).

Medication/relevant FDA indication	Mechanism of action	Typical dose	Indication/evidence	Common side effects	Serious reactions	Caution/other information
Anxiolytics						
Lorazepam Anxiety, procedural anxiety/sedation	Short-to-intermediate acting benzodiazepine	Children: 0.25–2 mg 2–3 times/d; max 2 mg/dose Adults and geriatric patients: 0.5–1 mg bid; max 6–10 mg/d Agitation: 1–4 mg IV every 3–10 min until symptom control achieved	Often given parenterally with an antipsychotic in acute agitation Off-label: agitation, stimulant intoxication, GABAergic withdrawal, NMS, serotonin syndrome	Somnolence, ataxia	Anterograde amnesia, paradoxical reaction, increased fall risk, respiratory depression	Risk of dependence; risk when used with opioids; avoid in geriatric; withdrawal syndrome; propylene glycol toxicity when used >10 mg/d IV
Alprazolam GAD, short-term anxiety, panic disorder	Short-acting benzodiazepine	Children: 0.005–0.02 mg/kg tid; max 4 mg/d Adults: 0.25 mg 3–.4 times/d; max 8 mg/d Geriatric patients: 0.25 mg 2–3 times/d and titrate slowly	Off-label: GABAergic withdrawal	Somnolence	Anterograde amnesia, paradoxical reaction	Risk of dependence; risk when used with opioids; avoid in geriatric; withdrawal syndrome
Buspirone GAD	Serotonin 5-HT_{1A} receptor partial agonist	Children: 5 mg/d, range 7.5–30 mg bid Adults and geriatric patients: 10 mg/d in 2–3 divided doses; max 60 mg/d	Off-label: depression augmentation	Dizziness, lightheadedness, drowsiness, nausea, headache, jitteriness	None	Absorption doubles with food, so be consistent if taking with or without food
Stimulants						
Methylphenidate ADHD	Blocks the reuptake of norepinephrine and dopamine into presynaptic neurons	Dosing varies based on formulation and brand Children: -IR: 2.5–5 mg bid; max 60 mg/d -XR: 18 mg/d; max 72 mg/d Adults and geriatric patients: -IR: 10–20 mg/d in 2 doses; max 60 mg/d -Intermediate acting: 10 mg bid; max 60 mg/d -XR: 18–36 mg/d; max 72 mg/d	May reduce aggression in patients with ADHD, as impulsivity and acting out are known symptoms	Hypertension, decreased appetite, anxiety, irritability	Acute MI, sudden cardiac death, growth suppression, priapism, new-onset psychosis or exacerbation of psychotic or manic symptoms	May increase aggression and anger in patients without ADHD
Amphetamine salts ADHD	Sympathomimetic amines that promote the release of catecholamines (dopamine and norepinephrine) from their storage sites in the presynaptic nerve terminals	Children: -IR: 2.5–5 mg 1–2x/d; max 40 mg/d -XR: 5–10 mg/d; max 60 mg/d Adults and geriatric patients: -IR: 5 mg 1–2 times/d; max 40 mg/d -ER: 10–20 mg/d; max 60 mg/d	May reduce aggression in patients with ADHD, as impulsivity and acting out are known symptoms	Hypertension, decreased appetite, anxiety, irritability	Acute MI, sudden cardiac death, growth suppression, priapism, new-onset psychosis or exacerbation of psychotic or manic symptoms	May increase aggression and anger in patients without ADHD

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor, ADHD = attention-deficit/hyperactivity disorder, AV = atrioventricular, bid = twice daily, BMP = basic metabolic panel, BPAD = bipolar affective disorder, CBC = complete blood count, CHF = congestive heart failure, CNS = central nervous system, COPD = chronic obstructive pulmonary disorder, CPZ = carbamazepine, DI = diabetes insipidus, DRESS = drug reaction with eosinophilic and systemic symptoms, EPS = extrapyramidal symptoms, ER = extended release, FDA = US Food and Drug Administration, GABA = γ-aminobutyric acid, GAD = generalized anxiety disorder, GI = gastrointestinal, HCTZ = hydrochlorothiazide, HLA = human leucocyte antigen, ICU = intensive care unit, IED = intermittent explosive disorder, IR = immediate release, IV = intravenous, LFTs = liver function tests, MBSR = mindfulness-based stress reduction, MDD = major depressive disorder, MI = myocardial infarction, NMS = neuroleptic malignant syndrome, NSAIDS = nonsteroidal anti-inflammatory drugs, OCD = obsessive-compulsive disorder, OCPs = oral contraceptive pills, ODD = oppositional defiant disorder, PCOS = polycystic ovary syndrome, PT = prothrombin time, PTSD = posttraumatic stress disorder, PTT = partial thromboplastin time, q AM = every morning, q PM = every evening, SIADH = syndrome of inappropriate antidiuretic hormone secretion, SJS = Stevens-Johnson syndrome, SNRIs = serotonin-norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, SUDs = substance use disorders, TEN = toxic epidermal necrolysis, tid = 3 times daily, TSH = thyroid-stimulating hormone, XR = extended release.