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Treatment of Irritability in Huntington's Disease

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Opinion statement

Irritability is a common neuropsychiatric feature of Huntington's disease (HD), with prevalences varying from 38% to 73%. Similar prevalences of irritability are reported in other neurodegenerative disorders and traumatic brain injury, especially when the frontal lobe is involved. Before therapeutic interventions are initiated, the clinician should analyze the severity and frequency of the irritable behavior. By examining irritability in a broader spectrum, a tailor-made treatment can be provided.

In general, I recommend as a first step a selective serotonin reuptake inhibitor (SSRI), such as sertraline, or the mood stabilizer valproate; they both have a mild side effect profile. Next, if the result is insufficient, I advise a switch between these two medications. As an alternative, I recommend a switch to a low dose of an atypical antipsychotic, preferably twice daily. Buspirone may be another alternative. Both antipsychotics and buspirone are also used as an add-on. Other mood stabilizers and beta-adrenergic receptor antagonists should only be used when earlier treatments are ineffective. The use of acetylcholinesterase inhibitors for the treatment of irritability is discouraged, as results are unclear. Synthetic cannabinoids are an interesting new therapeutic option, though their "illicit" compound and side effect profile make them not a first-line option.

It is important to identify possible comorbid psychiatric disorders, because irritability may be secondary to a psychiatric condition, and the choice of medication partly depends on the co-occurrence of a specific psychiatric disorder. For example, antipsychotic medication would be the treatment of choice in delusional HD patients with excessive irritability, instead of an SSRI or valproate.

Besides psychiatric comorbidity, the choice of medication also depends on the general medical condition, the side effect profile, and drug-drug interactions with other medications in concomitant use. Patients with advanced disease are particularly likely to be using various other types of medications.

In addition to pharmacotherapy, behavioral therapy or other psychotherapeutic interventions may be helpful to reduce levels of stress and should be considered.

Introduction

Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by motor symptoms, cognitive decline, and psychiatric disorders [1]. HD is caused by a trinucleotide expansion in the *IT15* gene, coding for the mutant protein huntingtin, and has an autosomal dominant hereditary pattern. Neurodegeneration occurs primarily in the striatum and cerebral cortex. The onset of HD most commonly occurs between 30 and 50 years of age, and the average disease duration is 16 years.

Although motor symptoms remain at the forefront of the clinical diagnosis, neuropsychiatric symptoms often precede the onset of motor symptoms. Next to depression, obsessive-compulsive disorder, and anxiety, irritability and aggression are frequent neuropsychiatric symptoms in HD [2,3,4]. Irritable patients are frequently hard to get along with, have emotional lability and eruptions, and demonstrate outbursts in response to minor provocations. The burden of this neuropsychiatric symptom is highly associated with functional disability.

The term *irritability* is often poorly defined and is used as synonym for agitation, hostility, aggressive behavior, and violent outbursts. *Irritability* is best defined as a temporary mood state characterized by impatience, intolerance, and reduced control over temper, which usually results in verbal or behavioral outbursts. It includes elements of anger, aggression, and reduced impulse control and can occur independently of other neuropsychiatric conditions [5,6].

A variety of psychotropic medications are used to treat irritability in HD, although no medication is officially approved for this indication. In this review of the literature, we aimed to investigate all reported treatments for irritability in HD.

The present level of evidence is based on small studies, with different definitions of irritability and measurement tools, and many patients used concomitant medications that may have affected the clinical outcome. In addition to these methodologic shortcomings, the choice of the medications in the studies examined seems to be rather arbitrary. For example, only one publication is available on the use of a selective serotonin reuptake inhibitor (SSRI) [7, Class IV], whereas in clinical practice, SSRIs are often prescribed as a first-choice treatment for irritability.

Most of the studies discuss the use of antipsychotics, in particular olanzapine [8,9,10,11, Class IV]. Relatively large case series show an improvement of irritability after initiating treatment with olanzapine, indicating that olanzapine may be an effective treatment for irritability. However, olanzapine has not been compared with other medications, so the results are inconclusive.

So far, only one study comparing the effect of two different medications (lithium carbonate and haloperidol, in a crossover study), and their combination, has been published [12, Class III]. Recently, a placebo-controlled study measuring the effect of nabilone was published, showing an overall improvement in behavior [13•, Class III].

In conclusion, there is a low level of evidence for current treatments of irritability, and systematic research with randomized controlled trials is warranted to measure the effect of medication.

Treatment

Pharmacologic treatment

Selective serotonin reuptake inhibitors (SSRIs)

Sertraline

	A hospitalized patient showed a "dramatic improvement" in irritability shortly after starting sertraline (100 mg), in combination with an ongoing treatment of haloperidol, whereas earlier treatment with carbamazepine was not effective [7, Class IV]. Another patient improved with sertraline after treatments with several other psychotropic medications had been ineffective [7, Class IV].
Contraindications	No strict contraindications.

Main drug interactions	Sertraline should not be used in combination with monoamine oxidase inhibitors or with the antipsychotic drug pimozide. Sertraline may displace warfarin from plasma proteins and increase the prothrombin time. Because sertraline is metabolized by the hepatic CYP2D6 enzyme, sertraline may interfere with the metabolism of other drugs that are metabolized by CYP2D6, especially in so-called poor metabolizers [14].
Main side effects	Most adverse effects appear within the first 1 to 2 weeks, and they generally subside or resolve spontaneously. Sexual dysfunction, gastrointestinal problems (nausea, diarrhea, anorexia, vomiting, and dyspepsia), weight gain or loss, and headache are common adverse effects of SSRIs. Less frequent adverse effects are anxiety, suicidal tendencies, insomnia, sedation, and vivid dreams or nightmares.
Special points	SSRIs require several weeks to produce a beneficial effect on behavioral problems, whereas a fast response is usually needed. SSRIs may be especially effective for irritability associated with depression.

Azapirones

Buspirone

	Episodic aggression that was due to a subjective sense of anger and irritability in a patient with juvenile-onset HD was effectively treated with 60 mg of buspirone per day [15, Class IV]. Agitation and aggressive behavior also abated in a 74-year-old patient treated with buspirone (10 mg three times per day) [16, Class IV]. Dramatic responses on buspirone at a dosage of 20 mg daily were described after initial treatments with haloperidol and carbamazepine [17, Class IV].
Contraindications	Buspirone should be used with caution by persons with hepatic or renal impairment.
Main drug interactions	If buspirone is used in combination with serotonergic agents, there is an increased risk for the occurrence of a serotonin syndrome. Buspirone may increase the plasma concentration of haloperidol [14]. Agents with an inhibitory effect on CYP3A4 (eg, diltiazem, verapamil, itraconazole, erythromycin) increase the buspirone plasma concentration.
Main side effects	The most common adverse effects of buspirone are headache, nausea, dizziness, and sometimes feelings of restlessness. Buspirone has no sedative or hypnotic effects.
Special points	The short half-life (2 to 11 hours) necessitates dosing three times daily.

Atypical neuroleptics

Olanzapine

	In an open-label study, 11 HD patients were treated with olanzapine for several indications, including disruptive behavior and "psychomotor agitation" [11, Class IV]. After 6 and 12 months, the behavioral score of the Unified Huntington's Disease Rating Scale (UHDRS) [18] was significantly reduced, whereas the UHDRS motor score was unchanged.

	Olanzapine (5 mg) was a useful antipsychotic drug in an open-label study with 10 patients, with significant changes in behavior, including irritability [8, Class IV]. Reported dosages of olanzapine as a treatment for agitation vary between 5 mg and 10 mg daily in combination with valproate [9, Class IV]. Impulsivity and aggressive behavior diminished with 5 mg of olanzapine. Chorea movements and functioning in activities of daily life improved when the dose was increased to 10 mg per day [10, Class IV].
Contraindications	Risk for narrow-angle glaucoma.
Main drug interactions	Concentrations of olanzapine are increased by coadministration of the CYP1A2 inhibitor fluvoxamine and decreased by coadministration of the CYP1A2 inducer carbamazepine.
Main side effects	Somnolence, orthostatic hypotension, hyperglycemia, dry mouth, constipation, dyspepsia, increased appetite, prolonged QT interval, and tremor are associated with olanzapine use. Olanzapine is more likely than the other neuroleptics to cause weight gain.
Special points	The dopamine D_2 antagonist properties of olanzapine may explain its possible benefits in the improvement of chorea.

Risperidone

	In a patient with anger, anxiety, and impulsive behavior, risperidone was initiated after a treatment with haloperidol. The dosage was titrated gradually up to 1 mg twice daily, giving a moderate improvement in movement and overall psychiatric symptoms [19, Class IV]. Another case report described a late-onset HD patient who showed behavioral changes with temper outbursts and psychotic symptoms, which disappeared after starting risperidone at a dosage of 1 mg twice daily [20, Class IV]. A retrospective review of a group of HD patients treated with risperidone (average dose, 2.5 mg) for an average of 15 months showed improved psychiatric functioning measured with the UHDRS behavioral score, but the effect on irritability was not specified [21•, Class III].
Contraindications	No strict contraindications.
Main drug interactions	Concurrent use of risperidone and phenytoin or SSRIs may produce extrapyramidal symptoms [14]. Carbamazepine has been shown to decrease the plasma concentration of risperidone. Otherwise, risperidone has little effect on other drugs.
Main side effects	The most frequent adverse effects observed with risperidone are insomnia, agitation, anxiety, headache, weight gain, nausea and vomiting, and extrapyramidal effects. Less frequent effects are prolonged QT interval, postural hypotension, dizziness, fatigue, sexual dysfunction, and hyperglycemia.

Quetiapine

	With dosages varying from 150 mg to 300 mg daily, improvement of behavioral symptoms, including irritability, was noted in five HD patients without worsening of motor functioning [22, Class IV]. However, all patients had multiple psychiatric symptoms and were treated with several types of medications. In a case report concerning an elderly HD patient with hypersexuality, the addition of quetiapine (25 mg at bedtime) to cyproterone for his deviant sexual behavior was effective in reducing agitation [23, Class IV].

Contraindications	No strict contraindications.
Main drug interactions	Coadministration of the CYP3A4 inducers carbamazepine and phenytoin increases the clearance of quetiapine. Inhibitors of CYP3A4, such as cimetidine, ketoconazole, and protease inhibitors, reduce quetiapine clearance [14].
Main side effects	The most common adverse effects of quetiapine are somnolence, headache, orthostatic hypotension, and dizziness, which are usually transient. Quetiapine is also associated with weight gain, constipation, increase of heart rate, prolonged QT interval, and rise in liver transaminases.

Aripiprazole

	In a patient with irritability and delusions, aripiprazole (20 mg per day) gave an improvement of his psychotic symptoms and his personal hygiene, though the effect on irritability remained unclear [24, Class IV]. One advanced symptomatic patient with agitation showed an improvement of agitation with aripiprazole (15 mg per day), with good control of motor symptoms and without adverse effects [25, Class IV]. However, precise assessment of behavioral functioning in this patient was not possible because of severe cognitive dysfunction.
Contraindications	No strict contraindications.
Main drug interactions	Coadministration of the CYP3A4 inducers carbamazepine and phenytoin increases the clearance of aripiprazole. Inhibitors of CYP3A4, such as cimetidine, ketoconazole, and protease inhibitors, reduce aripiprazole clearance. CYP2D6 inhibitors (eg, quinidine) increase aripiprazole plasma concentrations [14].
Main side effects	Orthostatic hypotension, nausea, and vomiting are the most frequent adverse effects. Aripiprazole rarely induces extrapyramidal and metabolic adverse effects.

Mood stabilizers

Valproate

	One study reported an effective treatment of agitation with valproate, 1500 mg daily, with a plasma concentration range from 60 to 80 μg/mL, in combination with olanzapine [19, Class IV].
Contraindications	Preexisting hepatic or renal failure, hepatitis, pancreatitis, bone marrow depression, and hematologic coagulation disorders are contraindications.
Main drug interactions	Coadministration with lithium may result in a drug-induced tremor. Valproate also interacts with carbamazepine. Valproate decreases the clearance of amitriptyline and nortriptyline [14].
Main side effects	Nausea, vomiting, dyspepsia, and diarrhea are the most common adverse effects in the first month of treatment. Other possible effects are sedation, ataxia, dysarthria, tremor, hair loss, and weight gain.

Carbamazepine

	Carbamazepine (500 mg/d) was effectively used in combination with haloperidol, clonazepam, and a strict behavior modification plan in a patient with aggressive and disinhibited behavior [26, Class IV].
Contraindications	Atrioventricular block, a history of bone marrow depression, acute porphyria, and hepatic or renal failure are relative contraindications.

Main drug interactions Because carbamazepine induces several hepatic enzymes, it may interact with many drugs. For the most part, adding carbamazepine lowers the plasma concentration of affected drugs, including oral contraceptives and warfarin. Carbamazepine may increase plasma concentrations of clomipramine and phenytoin. Carbamazepine should not be used in combination with monoamine oxidase inhibitors.

Main side effects Adverse effects particularly occur in the initial stages of therapy. These effects include drowsiness, sedation, headache, ataxia, nystagmus, diplopia, cardiac conduction disorder, dermatologic problems, and hepatitis. Blood dyscrasia is a severe, but rare adverse effect of carbamazepine.

Lamotrigine

Only one study describes an effective treatment with lamotrigine (300 mg/d), together with clonazepam (4 mg/d) in a patient with irritability, mood swings, and depression [27, Class IV].

Contraindications No strict contraindications.

Main drug interactions The lamotrigine concentration is increased with concurrent administration of valproate, and to a lesser extent with sertraline. Lamotrigine plasma concentrations are decreased with concomitant administration of carbamazepine, phenytoin, or phenobarbital [14].

Main side effects Common adverse effects are dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and dermatologic side effects. These dermatologic problems vary from self-limiting skin rashes to severe Stevens-Johnson syndrome.

Lithium carbonate

In a small, double-blind, crossover trial with six female patients, a combination of lithium and haloperidol during 3 weeks resulted in a decrease of irritability and angry outbursts, but this effect did not occur when either drug was administered separately [12, Class III].

Contraindications Renal failure, cardiac conduction disorder, and Addison's disease are contraindications. Lithium should be used with caution in patients with diabetes mellitus and hypothyroidism.

Main drug interactions Coadministration of lithium with anticonvulsants or antipsychotics may increase lithium concentrations and aggravate adverse effects. Most diuretics decrease renal lithium clearance and increase lithium concentrations. Nonsteroidal anti-inflammatory drugs can decrease lithium clearance, thereby increasing lithium concentrations. Combining lithium with methyldopa, verapamil, or diltiazem may cause neurotoxicity [14].

Main side effects The most common adverse effects of lithium are increased thirst, polyuria, edema, tremor, thyroid dysfunction, weight gain, fatigue, diarrhea, nausea, vomiting, cardiac effects, dermatologic problems, and mild cognitive impairment.

Acetylcholinesterase inhibitors

Donepezil

No clinical or statistical improvement in behavioral, cognitive, or functional assessment was measured in an open-label study with 10 mg per

	day of donepezil in eight symptomatic HD patients [28, Class IV]. However, a high dropout rate of 50% was noted after 6 weeks of treatment.
Contraindications	No strict contraindications.
Main drug interactions	Metabolism of donepezil may be increased by phenytoin, carbamazepine, rifampicin, or phenobarbital.
Main side effects	Nausea, diarrhea, anxiety, sedation, fatigue, vomiting, and weight loss due to anorexia are possible adverse effects of donepezil. Donepezil has been related to bradyarrhythmias.
Special points	Donepezil may have a positive effect on memory and concentration impairments.

Rivastigmine

	Data on the effect of rivastigmine (3 mg twice daily) show a tendency to improvement of the total score of the UHDRS behavioral scale [29, Class IV].
Contraindications	Severe hepatic failure.
Main drug interactions	Rivastigmine has no significant known drug interactions.
Main side effects	The most common adverse effects are nausea, vomiting, dizziness, headache, diarrhea, fatigue, somnolence, and anorexia.
Special points	Rivastigmine may have a positive effect on memory and concentration impairments.

Beta-adrenergic receptor antagonists (beta-blockers)

Propranolol

	With dosage varying from 30 to 240 mg daily, propranolol was an effective treatment for aggression in three patients [30, Class IV], but propranolol also precipitated paradoxic aggression in a patient with HD [31, Class IV].
Contraindications	Beta-adrenergic receptor antagonists are contraindicated in people with asthma, insulin-dependent diabetes, congestive heart failure, significant vascular disease, atrioventricular conduction defect, persistent angina, or hypothyroidism.
Main drug interactions	Concomitant administration of propranolol results in increased plasma concentrations of antipsychotics, anticonvulsants, theophylline, and levothyroxine [14].
Main side effects	Hypotension and bradycardia are adverse effects of beta-blockers.
Special points	The dosage of beta-blockers must be individually titrated, with regular measurement of pulse and blood pressure.

Cannabinoids

Nabilone

	One HD patient had an improvement of mood, was calmer and more relaxed after she started smoking of cannabis [32, Class IV]. Nabilone, a synthetic 9-keto cannabinoid, was given in a larger study, resulting in an

	overall improvement of UHDRS behavioral and the Neuropsychiatric Inventory scores [13•, Class III].
Contraindications	Allergy to cannabinoids, history of psychosis, and liver dysfunction are contraindications for the use of nabilone.
Main drug interactions	Concomitant use of benzodiazepines may potentiate the central nervous system effects of nabilone.
Main side effects	Sedation, drowsiness, dizziness, forgetfulness, headache, mood changes, hallucinations, dry mouth, blurred vision, and loss of appetite are possible adverse effects of nabilone.
Special points	Nabilone is available in a few countries and is indicated for treatment of nausea and vomiting associated with cancer. Theoretically, nabilone has a high potential for abuse.

Other interventions

Behavioral therapy

Both classical and operant conditioning are useful in managing irritability. Operant conditioning involves the reinforcement of more appropriate behaviors and discouragement of inappropriate behaviors [33]. Furthermore, limits and consequences of deviant behavior need to be clearly defined to the patient [34]. Especially for patients in an advanced disease stage, a behavior modification plan may include a structured daily schedule and reinforcement of desired behaviors [26].

Nursing interventions

Stressful psychosocial factors may result in irritability. After identification of stressors, the patient should be helped to look for ways to avoid these stressors and to develop concrete ways of coping, in order to decrease the level of stress within the nursing home or day care setting. Patients may be advised to break tasks down into simpler components.

Adaptive devices and specialized equipment are valuable in maintaining comfort, thereby decreasing the expression of problematic behaviors [33].

Disclosure

No potential conflicts of interest relevant to this article were reported.

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