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Mental and behavioural symptoms

Drug treatment of psychiatric symptoms in the context of other conditions CHAPTER 10 Mental and behavioural symptoms A wide variety of mental and behavioural symptoms occur in HD, including anxiety, depression, suicidality, preservation, disinhibition, irritability, apathy and, rarely, psychosis.13 Mental and behavioural symptoms can emerge before motor disturbances and reduce quality of life substantially.13 In comparison with other HD features, psychiatric symptoms are perhaps the most amenable to pharmacotherapy.6 In general, psychiatric treatment choices are selected as they would be in other conditions5 although patients are relatively more sensitive to adverse effects.5 The most commonly prescribed psychotropics are summarised in Tables 10.10 and 10.11 (mostly based on low-quality evidence).13 Table 10.9 Evidence and experience regarding the pharmacological treatment of motor symptoms in Huntington's disease (HD). Symptoms Treatment Chorea Tetrabenazine: unlike antipsychotics, tetrabenazine's effectiveness is well established.2,3,8 However, adverse effects including sedation, depression and parkinsonism may limit its clinical benefit. In clinical practice, many prefer to use tetrabenazine first line in patients without depressive symptoms and suicidal behaviour.8 Compliance with a multiple daily dosing regimen (e.g. three times a day) is needed. Other VMAT2 inhibitors: deutetrabenazine and valbenazine are licensed in the USA for the treatment of chorea in HD.2,4,9 Where available, they may be preferred over tetrabenazine owing to an improved pharmacokinetic and adverse effect profile,2,9 although direct comparisons are lacking.4 Antipsychotics: considered first-line treatment in clinical practice, particularly in the presence of depression, aggression, psychosis or when poor drug compliance is suspected5,8,10 despite a lack of data from RCTs.2 SGAs such as aripiprazole, risperidone or olanzapine are used most commonly.8,11 Potentially limiting adverse effects include dyskinesia, parkinsonism and metabolic syndrome.5 FGAs have been used successfully but are less popular in clinical practice because of the risk of EPSEs.10 LAI antipsychotics have been used in some published case reports, in cases of non- compliance or motor fluctuations with oral antipsychotics.12 For severe chorea, antipsychotics and VMAT2 inhibitors have been used in combination.8 Note that VMAT2 inhibitors have the potential for QT prolongation, as do most antipsychotics. Hypokinetic rigidity Levodopa may provide partial and temporary relief of symptoms.8 Note the potential for such drugs to exacerbate behavioural disturbances. Rigidity

may be caused/worsened by antipsychotics or tetrabenazine; dose reduction or discontinuation should be considered in the first instance, after weighing any derived benefits against symptom severity.8 Positive case reports exist for amantadine and dopamine agonists (although guidelines do not make recommendations on their use).8 Myoclonus Valproate or clonazepam has been suggested, used alone or combination.8 Levetiracetam is a therapeutic alternative.8 Dystonia Low-dose tetrabenazine has been suggested11 and a 2022 review concluded that deutetrabenazine is likely also to be effective.2 Botulinum toxin injections have been suggested for focal dystonia;8 clonazepam or baclofen has been suggested for non-focal dystonia.5 EPSEs, extrapyramidal side effects; LAI, long-acting injectable; VMAT2, vesicular monoamine transporter 2.

832 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 10 Table 10.10 Pharmacological treatment of mental and behavioural symptoms in Huntington's disease (HD). Symptoms Treatment Anxiety Reported 16.7–24% lifetime prevalence in HD.13 There are no RCTs to guide choice; however, olanzapine 5mg/day substantially improved anxiety symptoms in one small open-label pilot study.13 SSRIs and SNRIs have been suggested as first-line treatment.5,8 Some guidelines have recommended considering SGAs (quetiapine8, risperidone or olanzapine) for anxiety associated with personality or behavioural disturbances14 or when other treatments fail.8 Anxiolytics such as benzodiazepines or buspirone may also be useful.11,14 Depression Reported 30–70% prevalence in HD.15 Treatment is typically required because depression is linked to a lower quality of life in HD and increases the risk of suicide.13,15 There are almost no RCTs to guide choice.11,16 However, most experts agree that depression in HD responds well to antidepressants. SSRIs are the preferred first-line treatment5,8 but this is based on a less than perfect literature base.17 SSRIs: two controlled trials examined the effects of fluoxetine and citalopram in non--depressed patients with HD. Despite excluding depressed patients, both showed near significant improvements in depressive symptoms.16 Note that VMAT2 inhibitors are metabolised by CYP2D6; so inhibitors of this enzyme (e.g. fluoxetine, paroxetine) are predicted to increase exposure to active metabolites. SNRIs: venlafaxine was effective in an uncontrolled study;16 however, one in five developed adverse effects such as nausea and irritability.13 TCAs: beneficial effects reported in some cases18 but generally their use should be avoided or limited. Anticholinergic properties of TCAs may worsen hyperkinesias and cognition.11,18 Toxicity in overdose may also make them less suitable choices (suicidality is increased in HD13). Others: Mirtazapine was used successfully in one case report of severe depression.5 In a case registry study it was one of the most frequently prescribed treatments for depression in HD.13 Bupropion and SSRIs were found to be superior to SNRIs in one analysis of an observational study.19 Lithium produced improvements in suicidality in a small case series16 but experience is very limited, and tolerability may be poor. MAOIs have been used in earlier case studies;18 a lack of recent experience and important interactions with VMAT2 inhibitors make these less suitable. ECT can be used safely and effectively and may be considered in life-threatening cases.8,20 Obsessive compulsive behaviours or perseveration There are no RCTs.21 International consensus supports the use of SSRIs first line;8 use of clomipramine is also supported13 but tolerability may be poor. Case studies document the successful use of fluoxetine, paroxetine and sertraline.5 One study of two patients with perseveration and aggression reported beneficial effects with buspirone.13 For ideational perseveration, consensus also supports the use of olanzapine or risperidone (particularly if associated with irritability).8 Irritability or agitation22 Reported prevalence of 38–73% in HD. Initial management is non--pharmacological (e.g. by addressing possible triggers such as pain or akathisia and using behavioural/psychological approaches). No medications are approved specifically, but expert

consensus supports the use of SSRIs as preferred first-line agents, with antipsychotics being the next most favoured alternative monotherapy. Clinical features influence treatment choice. For example, SGAs (e.g. olanzapine, risperidone, quetiapine) may be preferred in the presence of chorea, acute irritability, aggression or impulsivity. Benzodiazepines are a widely used adjunctive therapy. Guidelines have also recommended mirtazapine or mianserin in patients not benefitting from maximum doses of SSRIs, especially in those with a comorbid sleep disorder. In cases non--responsive to antidepressants and/or antipsychotics, adjunctive mood stabilisers have also been recommended.8 The effect of dextromethorphan/quinidine for irritability in HD is, at the time of writing, being studied in a phase III RCT.4 Aggressive behaviours: a wide variety of psychotropics have been used with reported beneficial effects (e.g. antipsychotics, lithium, valproate, propranolol, medroxyprogesterone, SSRIs, buspirone).18,23 Antipsychotics have been used most commonly. The evidence base is too limited to make specific treatment recommendations23 but low-dose antipsychotics can be considered.5 ECT was helpful in a few case reports of agitation refractory to pharmacotherapy.20

Drug treatment of psychiatric symptoms in the context of other conditions CHAPTER 10 Symptoms Treatment Apathy Common in HD and appears to worsen with disease progression.13 Some sedative medications (e.g. antipsychotics, benzodiazepines, tetrabenazine) may contribute, so dose reduction or withdrawal should be considered.8 In one small open study of 16 participants, cariprazine was associated with improvements in apathy, depressive symptoms and cognitive test scores.11 Bupropion was studied in one multicentre RCT and found to be ineffective.11 Other agents, including methylphenidate, atomoxetine, modafinil, amantadine and bromocriptine, have been trialled with little success.13 Psychosis One of the least prevalent psychiatric manifestations of HD, perhaps because of the use of antidopaminergics for motor symptoms.13 There are no RCTs to guide choice11 – treatment is empirical. Note that antipsychotic drugs may exacerbate any underlying movement disorder. VMAT2 inhibitors may have antipsychotic activity24 but they are not drugs of choice for psychosis in HD. SGAs: olanzapine and risperidone are used most frequently.13 Low starting doses are recommended.5 Case reports support the efficacy of risperidone, quetiapine, aripiprazole and amisulpride.18 Clozapine may be considered in refractory cases6,18 or akinetic forms of HD with debilitating parkinsonian symptoms.8,11 FGAs: used less frequently due to the risk of dystonia and parkinsonism; however, haloperidol has been used when chorea is also problematic to the patient.18 MAOIs, monoamine oxidase inhibitors; TCAs, tricyclic antidepressants; VMAT2, vesicular monoamine transporter 2. Table 10.10 (Continued) Table 10.11 Summary of treatments for mental state and behavioural changes in Huntington’s disease.6,8,13 Symptoms Most commonly prescribed pharmacological treatments Alternatives Anxiety SSRIs, mirtazapine, pregabalin, venlafaxine Olanzapine, risperidone, quetiapine, benzodiazepines, propranolol, buspirone Depression or suicidality SSRIs, bupropion, mirtazapine, venlafaxine TCAs; ECT in refractory cases Obsessive compulsive behaviours SSRIs Clomipramine Irritability or agitation SSRIs, SGAs (olanzapine, risperidone, sulpiride), tiapride, benzodiazepines Anticonvulsants (lamotrigine, carbamazepine, valproate), TCAs, buspirone, propranolol; consider trial of an analgesic Apathy None None Psychosis Olanzapine, risperidone, haloperidol, sulpiride, tiapride, LAI antipsychotics Clozapine, quetiapine LAI, long-acting injectable; TCAs, tricyclic antidepressants.

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