

# Expert Opinion

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## A systematic review of the treatment studies in Huntington's disease since 1990

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Huntington's disease (HD) is an autosomal dominant, inherited, neuropsychiatric disease that gives rise to progressive motor, cognitive and behavioural symptoms. Current drug therapy has no effect on the progression of disability, and the need for any pharmacological treatment should be carefully considered. Hyperkinesias and psychiatric symptoms may respond well to pharmacotherapy, but neuropsychological deficits and dementia remain untreatable. Pharmacological intervention in the treatment of the movement disorder of HD is aimed at restoring the balance of neurotransmitters in the basal ganglia. A surprising amount of current drug therapy of HD in clinical practice is based on studies published before 1990. The authors conducted a systematic review of pharmacological therapy in HD using the available papers that were published between 1990 and 2006.

**Keywords:** chorea, Huntington's disease, neuroleptics, neuroprotection

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### 1. Introduction

Current drug therapy for Huntington's disease (HD) has no effect on the progression of disability, and the need for any pharmacological treatment should be carefully considered. Hyperkinesias and psychiatric symptoms may respond well to pharmacotherapy, but neuropsychological deficits and dementia remain untreatable. Pharmacological intervention in the treatment of the movement disorder of HD is aimed at restoring the balance of neurotransmitters in the basal ganglia. Neuroprotective or neurorestorative (i.e., neurotransplantation) treatment is still experimental. A surprising amount of drug therapy of HD in clinical practice is based on studies published before 1990 [1,2]. This article is a review of the literature on pharmacological therapy in HD that has been published between 1990 and 2006.

Literature searches were done using electronic databases including Medline (1990 – 2006), the central database in the Cochrane Library (1990 –2006), and systematic searches of reference lists published in review articles and other clinical reports. All of these studies are systematically analysed in this review, and the publications are grouped based on a hierarchical organisation of evidence. Analogous to most evidence-based reviews, randomised controlled trials represent level I studies in this review if the following additional criteria are fulfilled: i) a minimum of 2-weeks treatment period on the active drug, ii) a minimum of 10 HD patients on the active drug who complete the study, iii) full paper citation. Controlled trials that did not fulfill these criteria were assigned to level II. In addition, non-randomised or observational controlled trials were classified as level II. Level III was assigned to uncontrolled case series (i.e., open-label trials and retrospective reports). Finally, case reports were considered the lowest level of evidence. Papers were accepted regardless of their language and rating scales, provided the latter were operationally defined.

## 2. Treatment of chorea

Conventional antipsychotic drugs are still used to treat chorea in clinical practice. They are widely accepted to have significant anti-choreic effects, although complications such as aggravated Parkinsonism, impaired balance, difficulties in swallowing, apathy and dysphoria limit their utility [3]. Practically no data are available from the last 15 years, with the exception of a case report on sulpiride [4]. Low doses of conventional dopamine-blocking antipsychotics are often well tolerated, and may ameliorate the severity of choreatic hyperkinesias, whereas high doses are rarely helpful and may impair oculomotor [5], orolingual [6], motor control and cognitive function. Moreover, these neuroleptics may accelerate functional decline [7] and may induce tardive dystonia [8]. Indeed, the severity of dystonia in HD has been associated with the use of an anti-dopaminergic agent [9], although this point needs further study. It is noteworthy that neuroleptic malignant syndrome, albeit being a known adverse effect of conventional antipsychotics, has never been reported in HD patients for this substance class (Table 1).

Tetrabenazine selectively depletes central monoamines by reversibly binding to the type 2 vesicular monoamine transporter. Level II and III reports indicated that tetrabenazine is effective in treating chorea [10,11]. To examine the safety, efficacy and dose tolerability of the substance for treating chorea in HD, the Huntington Study Group recently randomised 84 ambulatory patients with HD to receive tetrabenazine ( $n = 54$ ) or placebo ( $n = 30$ ) for 12 weeks [12]. Tetrabenazine was increased over 7 weeks up to a maximum of 100 mg/day, or until the desired anticholinergic effect occurred or intolerable adverse effects supervened. This resulted in a reduction of 5.0 Unified HD Rating Scale (UHDRS) units in chorea severity compared with a reduction of 1.5 UHDRS units for patients on placebo treatment. There was also a significant benefit on ratings of clinical global improvement. Unfortunately, adverse reactions are frequent and limit the usefulness of tetrabenazine. In a recent study, there were five withdrawals in the tetrabenazine group and five serious adverse events in four subjects (drowning suicide, complicated fall, restlessness/suicidal ideation and breast cancer) compared with one withdrawal and no serious adverse event in the placebo group. Generally, side effects include sedation, insomnia, depression, anxiety, Parkinsonism, dysphagia, akathisia and, rarely, neuroleptic malignant syndrome [13-15]. In contrast to traditional neuroleptics, neuroleptic malignant syndrome has been reported in HD patients due to the use of tetrabenazine [14,15]. For these reasons, the substance is still controversial [16] (Table 2).

Atypical antipsychotic drugs have not been evaluated in level I or II trials (with the exception of clozapine), however, they represent novel agents for treating movement disorders associated with HD. Clozapine showed poor

symptomatic effects in a level I trial with 33 patients [17]; moreover, adverse reactions (drowsiness, fatigue, anticholinergic symptoms and walking difficulties) forced trial termination in six patients and dose reduction in another eight. A level III study [18] revealed similar results. However, another level III study [19] and a case report [20] found positive effects on chorea. The serious adverse effect of leukopenia makes clozapine less feasible for HD patients, especially those who are prone to noncompliance due to behavioural symptoms. Other atypicals are more promising, although not as well documented. Behavioural subscores (primary outcome measure) improved with low doses (5 mg/day) in two level III studies of olanzapine [21,22], and higher doses (up to 30 mg/day) significantly ameliorated not only chorea, but also orolingual dysfunction, finger dexterity and gait, in a level III study [23]. A series of case reports confirm the latter results [24-31]. However, unfortunately, a case of seizure [32] and tardive dyskinesia [33] in HD have been described. Risperidone is even less documented, but seems to be helpful for the treatment of HD associated psychosis [34-36] and chorea [34,37,38] in a series of case reports. Motor function of the UHDRS has been shown to significantly improve with quetiapine [39], zotepine [40] and ziprasidone [41] in further case reports. Interestingly, a recent case report suggests drug holidays in atypical antipsychotics when the antichoreatic effect wanes [42] (Table 3).

In the 1990s, the excitotoxin theory has suggested that neurodegeneration in HD is caused by a relative excess of excitatory neurotransmitters such as glutamate [43]. For this reason, several NMDA-receptor antagonists were tested for a symptomatic or even neuroprotective effect. However, ketamine [44] and milacemide [45] did not show any symptomatic effect in level II studies. Moreover, ketamine caused a decline in memory and verbal fluency in the ten patients tested [44]. In a level I paper, Verhagen-Metman *et al.* [46] showed that amantadine (400 mg/day) lowered chorea scores, with a median reduction in extremity chorea (at rest) of 36% for all 22 evaluable patients. Parkinsonian rating scores did not worsen in this study, there was no consistent change in cognitive measures, and the adverse-event profile was benign. These data were confirmed by a level II study of a 2-h intravenous infusion of amantadine or placebo to nine patients with HD on two different days [47] and a level III paper by the same authors [48]. However, in contrast, in a high-quality, level I randomised placebo-controlled crossover trial with 2 weeks of treatment, O'Suilleabhain and Dewey [49] did not observe any effect of amantadine 300 mg/day on chorea of HD patients, and this is confirmed by a level II study [50]. Remacemide was shown to be a safe drug in a tolerability study [51]. Thereafter, the Huntington Study Group examined its benefits [52]. Unfortunately, it did not significantly alter the decline in total functional capacity of the UHDRS (i.e., no neuroprotective effect), although it tended to have a beneficial effect on the chorea subscale of the UHDRS (i.e., some

Table 1. Level I studies since 1990.

Active drug	Versus	Ref.	HD diagnosis	Effect	n	Study design	Study duration	HD score
<b>Antidopaminergics</b>								
Clozapine	Placebo	van Vugt (1997) [17]	CAG	Poor effect	26	Crossover	4 weeks	AIMS, UHDRS
Tetrabenazine	Placebo	HSG (2006) [12]	CAG	Positive	49	Crossover	7 weeks	UHDRS
<b>NMDA-antagonists</b>								
Amantadine	Placebo	O'Suilleabhain (2003) [49]	CAG	No effect	24	Crossover	2 weeks	Video, self
Amantadine	Placebo	Verhagen (2002) [46]	CAG	Positive	24	Crossover	2 weeks	UHDRS
Riluzole	Placebo	HSG (2003) [53]	CAG	Poor effect	41	Parallel	8 weeks	UHDRS
Fluoxetine	Placebo	Como (1997) [59]	NS	No effect	12	Parallel	4 months	TFC
Cannabidiol	Placebo	Consroe (1991) [60]	History	No effect	15	Crossover	6 weeks	Self
Coenzyme q10	Remacemide, placebo	HSG (2001) [52]	History or CAG	Trend	76	Parallel	30 months	UHDRS
Remacemide	Coq10, placebo	HSG (2001) [52]	History or CAG	No effect	66	Parallel	30 months	UHDRS
Remacemide	Placebo	Kieburts (1996) [51]	History	Safe	18	Parallel	6 weeks	HDMRS
Lamotrigine	Placebo	Kremer (1999) [136]	CAG	No effect	28	Parallel	30 months	TFC, QNE
Opc-14117	Placebo	HSG (1998) [133]	History	Safe	23	Parallel	3 months	UHDRS
Idebenone	Placebo	Ranen (1996) [135]	History	No effect	48	Parallel	12 months	QNE
$\alpha$ -tocopherol	Placebo	Peyser (1995) [134]	History	No effect	40	Parallel	12 months	QNE
Minocycline	Placebo	HSG (2004) [131]	History or CAG	Safe	37	Parallel	8 weeks	UHDRS
Unsaturated fatty acids	Placebo	Puri (2005) [126]	History or CAG	No effect	39	Parallel	12 months	UHDRS
Creatine	Placebo	Hersch (2006) [124]	CAG	Safe	29	Parallel	4 months	UHDRS

AIMS: Abnormal Involuntary Movement Scale; CAG: Genetically proven; Clinic: Clinical impression alone; HD: Huntington's Disease; HDMRS: HD Motor Rating Scale; History: Clinic and positive family history; HSG: Huntington study group; NS: Not staed; QNE: Quantified neurological examination; TFC: Total functional capacity; UHDRS: Unified HD Rating Scale.

symptomatic effect). Baclofen and lamotrigine are discussed in Section 5.

Riluzole is the most promising substance in the NMDA-receptor antagonist group. It was tested in an 8-week, double-blind, dose-ranging, level I, multi-centre study [53]. The authors could show that, whereas riluzole 100 mg/day did not change chorea, a 200 mg/day dose somewhat ameliorated chorea without improving functional capacity or other motor, cognitive, behavioural or functional components of the UHDRS. In fact, the mean reduction of the UHDRS chorea score (range 0 – 28 units) was 2.2 units – a clinically irrelevant difference. Unfortunately, only a few of the dopamine antagonist studies use the UHDRS and therefore, only these few are comparable. Olanzapine reduced the same chorea score for 6.5 units in an open-label study [23]. Riluzole probably fails to be sufficiently potent to treat moderate and severe chorea. Moreover, treatment was accompanied by liver transaminase abnormalities that would require monitoring in long-term studies [53]. Level III

studies have found transient antichoreatic effects (i.e., not significant after 1 year of treatment) and more sustained effects on psychomotor speed and behaviour with riluzole treatment [54,55]. Another three case reports with positive effects on chorea have been published [26,56,57]. A European level I trial seems to have negative results (Table 4).

Interestingly, apomorphine proved to be effective in a level II study [58]. Low-dose apomorphine may result in dopaminergic autoreceptor stimulation with consequent inhibition of dopamine release. Negative results for the treatment of chorea were found in level I treatment trials with fluoxetine [59] and cannabidiol – a constituent of cannabis [60]. Piracetam even worsened chorea in a 1-day, level II trial [61]. Other investigated substances [62-66] are listed in the tables. A remarkable case report on (-)-OSU6162, which belongs to a novel class of functional modulators of dopaminergic systems, with long-lasting improvement in a patient with HD should be mentioned in this section [67].

**Table 2. Level II studies since 1990**

Active drug	Control substance	Ref.	HD diagnosis	Effect	n	Randomized	Blinded	Study design	Study duration	HD score
<b>Dopamine-depleting agents</b>										
Tetrabenazine	–	Ondo (2002) [10]	CAG	Positive	18	No	Single	–	2 – 11 months	AIMS, video
<b>NMDA-antagonists</b>										
Amantadine, IV	Placebo	Lucetti (2003) [47]	CAG	Positive	9	Yes	Double	Crossover	1 day	AIMS, UHDRS
Amantadine	Placebo	Heckmann (2004) [50]	CAG	No effect	7	Yes	Double	Crossover	6 weeks	UHDRS
Ketamine	Placebo	Murman (1997) [44]	History	No effect	10	Yes	Double	Crossover	1 day	UHDRS
Milacemide	Placebo	Giuffra (1992) [45]	History	No effect	7	No	Double	Crossover	3 days	AIMS
<b>GABA agonists</b>										
L-acetyl-carnitine	Placebo	Goetz (1990) [139]	History	No effect	10	Yes	Double	Crossover	1 week	AIMS
<b>Dopa-agonists</b>										
apomorphine	Placebo	Albanese (1995) [58]	History	Positive	9	No	Double	Crossover	1 day	DCRS-HD
<b>Others</b>										
Piracetam	Placebo	Mateo (1996) [61]	NS	Worsen	11	No	Double	Crossover	1 day	Self
Creatine	Placebo	Verbessem (2003) [123]	CAG	No effect	26	No	Double	Parallel	12 months	UHDRS
<b>Neuroprotection</b>										
Unsaturated fatty acids	Placebo	Puri (2002) [107]	NS	Positive	3	yes	Double	Parallel	6 months	UHDRS
Unsaturated fatty acids	Placebo	Vaddadi (2002) [106]	CAG	Positive	9	yes	Double	Parallel	6 months	UHDRS

AIMS: Abnormal Involuntary Movement Scale; DCRS-HD: David Clinical Rating Scale for HD; HD: Huntington's Disease; NS: Not stated; Self: Subjective chorea quantification by the authors; UHDRS: Unified HD Rating Scale; Video: Video-rating.

### 3. Treatment of other neurological features

As functional capacity worsens, chorea lessens and dystonia intensifies [9,68]. The prevalence of dystonia in HD of any severity is > 80% [9]; ~ 12% of HD patients suffer from dystonia-predominant HD [69]. Although the dystonia is not bothersome to most HD patients, it may cause functional impairment in others, and then require therapeutic intervention in such cases. Generally, treatment of dystonia is difficult and largely ignored in HD research. Astonishingly, HD dystonia has never been the primary end point of any pharmacological intervention. Some trials evaluating amantadine [46], riluzole [54,55] or olanzapine [23] in HD have

employed the UHDRS as an outcome measure. These studies were unable to show significant improvement of dystonia subscores. Gait disorder in HD significantly decreases the quality of life and level of independence of a patient. The clinical characteristics of this disorder include a wide-based gait, lateral sway, spontaneous knee flexion, variable cadence and Parkinsonian features [70,71]. Pharmacological intervention in HD gait disorders has rarely been studied. A small and short level III study with high-dose olanzapine achieved significant (35%) amelioration of UHDRS-defined gait dysfunction (gait, tandem walking and retropulsion pull test) in nine HD patients [23]. Other drugs have not yet been studied (Table 5).

Table 3. Level III studies since 1990.

Substance	Ref.	HD diagnosis	Effect	n	Study design	Study duration	HD score
<b>Antidopaminergics</b>							
Clozapine	Colosimo (1995) [18]	NS	Poor effect	8	Retrospective	Mean 18 months	No rating
Clozapine	Bonuccelli (1994) [19]	NS	Positive	5	Open label	3 weeks	AIMS
Olanzapine	Paleacu (2002) [22]	CAG or clinic	Poor effect	9	Open label	6 months	UHDRS
Olanzapine	Bonelli (2002) [23]	CAG	Positive	9	Open label	2 weeks	UHDRS
Olanzapine	Squitieri (2001) [21]	CAG	Poor effect	11	Open label	6 months	UHDRS
<b>NMDA-antagonists</b>							
Amantadine	Lucetti (2002) [48]	CAG	Positive	8	Open label	12 months	AIMS, UHDRS
<b>Others</b>							
Donepezil	Fernandez (2000) [103]	CAG	Poor effect	8	Open label	2 – 6 weeks	UHDRS
Rivastigmine	de Tommaso (2004) [104]	CAG	Poor effect	11	Open label	8 months	MMSE
Dextromethasone	Nuti (1991) [65]; Bonuccelli (1992) [66]	History	Positive	6	Open label	20 days	AIMS
Levetiracetam	Zesiewicz (2006) [140]	CAG	Poor effect	9	Open label	48 days	UHDRS
<b>Neuroprotection</b>							
Riluzole	Rosas (1999) [55]	NS	Positive	8	Open label	6 weeks	UHDRS
Riluzole	Seppi (2001) [54]	CAG	Positive	9	Open label	12 months	UHDRS
Minocycline	Bonelli (2003) [108]	CAG	Positive	14	Open label	6 months	UHDRS
Minocycline	Bonelli (2004) [129]	CAG	Positive	11	Open label	24 months	UHDRS
Minocycline	Thomas (2004) [130]	CAG	No effect	30	Open label	6 months	UHDRS
Coenzyme Q10	Feigin (1996) [137]	NS	No effect	10	Open label	6 months	HDRS
Coenzyme Q10	Koroshetz (1997) [138]	NS	No effect	18	Open label	> 2 months	MRS
Creatine	Tabrizi (2003) [120]	CAG	No effect	13	Open label	12 months	UHDRS
Creatine	Tabrizi (2005) [121]	CAG	Possible effect	9	Open label	24 months	UHDRS
Creatine	Bender (2005) [122]	CAG	No effect	20	Open label	8 weeks	UHDRS

AIMS: Abnormal Involuntary Movement Scale; HD: Huntington's disease; MMSE: Mini Mental State Examination; MRS: Magnetic Resonance Spectroscopy; NS: Not stated; UHDRS: Unified HD Rating Scale.

Rigidity and akinesia are a major source of motor disability in the akinetic-rigid Westphal variant of HD [72]. Anti-Parkinsonian benefits were induced by levodopa (up to 1000 mg/day) [73,74], pramipexole [75] and cabergoline [76] in open-label case reports or case series. Amantadine was helpful in a recent case report [77]. Although bradykinesia is a major feature of adult HD [78], it has never been a target for therapeutic intervention. Epilepsy is especially frequent in the Westphal-variant, and it may also occur in adults with HD [79]. Two HD patients with epilepsy and myoclonus responded to treatment with valproate [80]. Urinary incontinency is a major, widely ignored problem of late-stage HD [81] and is usually caused by a detrusor hyperreflexia. It was reported to respond to carbamazepine 200 mg/day in three HD patients [82]. Bruxism was treated successfully with botulinum toxin in one patient [83].

## 4. Treatment of psychiatric symptoms

The behavioural assessment of the UHDRS comprises mood, low self-esteem/guilt, anxiety, suicidal thoughts, disruptive or aggressive behaviour, irritable behaviour, obsessions, compulsions, delusions and hallucinations [84]. These are the main psychiatric challenges in clinical practice. No single level I or level II study has been carried out in this field.

### 4.1 Depression

The most frequent psychiatric onset symptom in HD is depression that often starts as an isolated symptom [85]. There is evidence for postulating an 'organic depression' in HD: a significantly lower metabolic activity in the basal ganglia and cingulate cortex is found in depressed (compared with

non-depressed) HD patients [86]. Despite the prevalence of depression among HD patients, only case reports are available on the use of antidepressants in this disorder. Positive results were reported for single cases with fluoxetine [87] and mirtazapine [88]. A case of psychotic depression has also successfully been treated with clozapine [89]. Controlled trials on antidepressants in HD are urgently required.

#### 4.2 Psychotic symptoms

Psychotic symptoms seem to be quite common in HD patients [90,91]. A review of 11 studies of HD patients found psychosis to be present in 3 – 12% of patients, ranging from nonspecific paranoia to presentations that are similar to schizophrenia [92]. However, only two case studies on risperidone in psychotic symptoms are available, and both report clinical improvement [34,36]. Moreover, amisulpride ameliorated psychosis in four patients with HD, two of whom developed extrapyramidal side effects [93].

#### 4.3 Frontal lobe, behavioural and sexual dysfunction

Increased irritability, lack of control and aggression are probably all related to frontal lobe dysfunction. Irritability and emotional dyscontrol are common in patients with HD and can cause great disturbance in their families or living situation. In male HD patients, crime rates are significantly increased when compared with first degree relatives and controls [94]. Two small level III studies on olanzapine showed a significant improvement in the UHDRS psychiatric subscores depression, anxiety, irritability and obsessions [21,22]. None of the patients reported side effects. Recently, quetiapine improved behavioural symptoms (i.e., psychotic symptoms, agitation, irritability and insomnia) without worsening of motor functioning in five consecutive patients with HD in a long-term facility [95]. Other case reports deal with sertraline [96], fluoxetine [62], olanzapine combined with valproate [28] and buspirone [97-99]. However, severe behavioural disturbance needs a multimodality treatment schedule [100]. Of all HD patients, 82% have one or more sexual disorders as per the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria [101]. Most commonly, this is in the form of sexual hypoactivity, although some patients may exhibit hypersexuality. The only data available on the treatment of hypersexuality in HD are from case reports. A patient with HD and exhibitionism was successfully treated with leuprolide (a gonadotropin-releasing hormone agonist) [102]. In another group, medroxyprogesterone was used to reduce hypersexuality [100].

#### 4.4 Dementia

Dementia is one of the three cardinal clinical features in HD and its prevalence depends on the clinical stage of the disease. Even asymptomatic gene carriers may reveal mild neuropsychological deficits. There is no level I dementia treatment available for HD patients. Cholinesterase inhibitors proved ineffective in level III trials [103,104] and a case report [105].

However, unsaturated fatty acids [106,107], riluzole [54] and minocycline [108] have shown to provide mild cognitive benefits (secondary end points) in open-label trials.

#### 4.5 Other psychiatric symptoms

HD patients with obsessive or compulsive symptoms show significantly greater impairment on neuropsychological tests measuring executive function than those without such symptoms [109]. In two case reports, the efficacy of sertraline [110] and paroxetine [111] for ameliorating obsessive behaviour in HD have been shown. level III evidence on olanzapine for obsessions in HD has been mentioned [21,22]. Propranolol was helpful in an HD patient with hypomania [112].

### 5. Neuroprotective treatment strategies

Evidence has accumulated that therapies aimed at transcriptional modulation might target early events in HD pathogenesis [113]. Similarly, agents disrupting pathological interactions of mutant huntingtin (either in a soluble form, or within aggregates) might also target early pathogenic steps [114]. The proximal events caused directly by mutant huntingtin or its fragments, in turn, trigger cascades of both damaging and compensatory molecular processes and genetic programmes, ultimately leading to increasingly fragile, atrophic and dysfunctional neurons that are susceptible to more generic stresses, such as oxidative injury, excitotoxic stress, disordered neurophysiology, expression of potentiating inflammatory signals, pro-apoptotic signals, malfunctioning proteolysis and energy depletion. All of these stresses might play roles in neuronal death in HD and also provide more distal therapeutic targets [113].

The discovery of the HD gene and its product, huntingtin, has improved understanding of the disease process and opened new approaches to interventional treatments [115,116]. Recent studies using transgenic mouse and *Drosophila* models have helped resolve some of these issues, and raise hopes for the development of therapeutic targets [117-119]. Most neuroprotective studies have employed interventions that attenuate or modulate glutamatergic neurotransmission, enhance bioenergetic mechanisms or exert antioxidative properties [3].

Based on the evidence that, similar to coenzyme Q10, creatine enhanced mitochondrial oxidative functions defective in HD, and motivated by positive results in the transgenic mouse model, Tabrizi *et al.* undertook an open-label study of nine HD patients on creatine [120,121]. After 24 months of creatine treatment, there was no significant deterioration in the UHDRS (in terms of TMS, functional capacity scores or neuropsychological testing), which actually should be expected after 2 years. In a second short-term level III study, Bender *et al.* did not find any motor effect, but noted a change in brain metabolite levels (measured by proton magnetic resonance spectroscopy) after 8 weeks of treatment [122]. Unfortunately, a level II, non-randomised, 1-year, double-blind, pla-

**Table 4. Therapeutic case reports on HD since 1990.**

Active drug	Ref.	Therapeutic area	n	Effect
<b>Typical antipsychotics</b>				
Sulpiride	Knowling (1991) [4]	Chorea	1	Effective
<b>Atypical antipsychotics</b>				
Clozapine	Valette (2001) [20]	Chorea	1	Effective
Clozapine	Sajatovic (1991) [89]	Chorea, psy. depression	1	Effective
Olanzapine	Laks (2004) [31]	Chorea, behaviour	1	Effective
Olanzapine	Jimenez (2002) [24]	Chorea	2	Effective
Olanzapine	Bonelli (2002) [25]	Chorea	1	Effective
Olanzapine and riluzole	Bonelli (2002) [26]	Chorea	2	Effective
Olanzapine	Bogelman (2001) [27]	Chorea	1	Effective
Olanzapine, valproate	Grove (2000) [28]	Chorea, aggression	2	Effective
Olanzapine	Dipple (1999) [30]	Chorea	1	Effective
Olanzapine	Etchebehere (1999) [29]	Chorea	1	Effective
Risperidone	Erdemoglu (2002) [34]	Psychosis, chorea	1	Effective
Risperidone	Madhusoodanan (1998) [35,36]	Psychosis	1	Effective
Risperidone	Parsa (1997) [38]	Chorea	1	Effective
Risperidone	Dalocchio (1999) [37]	Chorea	4	Effective
Ziprasidone	Bonelli (2003) [41]	Chorea	3	Effective
Quetiapine	Bonelli (2002) [39]	Chorea	1	Effective
Quetiapine	Alpay (2006) [95]	Behaviour	5	Effective
Zotepine	Bonelli (2003) [40]	Chorea	1	Effective
Amisulpride	Saft (2005) [93]	Psychosis	4	Effective
<b>Dopa-agonists and glutamate-antagonists</b>				
Pramipexole	Bonelli (2002) [75]	Rigidity	1	Effective
Amantadine	Magnet (2004) [77]	Rigidity	1	Effective
L-dopa	Racette (1998) [74]	Rigidity	1	Effective
L-dopa	Reuter (2000) [73]	Rigidity	4	Effective
Bromocriptine	Tsuneizumi (1994) [141]	Chorea	1	Effective
Riluzole and olanzapine	Bonelli (2002) [26]	Chorea	2	Effective
Riluzole and olanzapine	Bonelli (2002) [57]	Chorea	1	Effective
Riluzole	Bodner (2001) [56]	Chorea	1	Effective
Cabergoline	Magnet (2006) [76]	Rigidity	1	Effective
<b>Antidepressives</b>				
Mirtazapine	Bonelli (2003) [88]	Depression	1	Effective
Sertraline	Ranen (1996) [96]	Aggression	2	Effective
Sertraline	Patzold (2002) [110]	Obsessive disorder	1	Effective
Paroxetine	Royuela Rico (2003) [111]	Obsessive disorder	1	Effective
Fluoxetine, L-deprenyl	Patel (1996) [87]	Depression	1	Effective
Fluoxetine	De Marchi (2001) [62]	Agitation	2	Effective
Fluoxetine	De Marchi (2001) [62]	Chorea	2	Effective
Fluoxetine	Chari (2003) [63]	Chorea	1	Worsen
<b>Others</b>				
Propranolol	Stewart (1993) [112]	Hypomania	1	Effective

**Table 4. Therapeutic case reports on HD since 1990.**

Active drug	Ref.	Therapeutic area	n	Effect
Medroxyprogesterone acetate	Blass (2001) [100]	Sexual dishibition	1	Effective
Carbamazepine	Cochan (2000) [82]	Dysuria	3	Effective
Nabilone	Müller-Vahl (1999) [64]	Chorea	1	Worsen
Leuprolide	Rich (1994) [102]	Exhibitionism	1	Effective
(-)-Osu6162	Tedroff (1999) [67]	Chorea	1	Effective
Rivastigmine	Rot (2002) [105]	Dementia	3	No effect
Minocycline	Denovan-Wright (2002) [132]	Chorea, psychiatry	1	Effective
Buspiron	Bhandary (1997) [97]	Aggression	1	Effective
Buspiron	Byrne (1994) [98]	Aggression	1	Effective
Buspiron	Findling (1993) [99]	Aggression	2	Effective
Valproate	Vogel (1991) [80]	Myoclonus	2	Effective
Botulinum toxine	Nash (2004) [83]	Bruxism	1	Effective
Levetiracetam	Zesiewicz (2005) [142]	Chorea	1	Effective

**Table 5. Case reports on adverse effects in HD patients since 1990.**

Active drug	Ref	n	Therapeutic area
Tetrabenazine	Ossemann (1996) [15]	1	Neurol. malignant syndrome
Tetrabenazine	Mateo (1992) [14]	1	Neurol. malignant syndrome
Olanzapine	Bonelli (2003) [32]	1	Seizure
Olanzapine	Benazzi (2002) [33]	1	Tardive dyskinesia
Levetiracetam	Zesiewicz (2005) [142]	1	Parkinsonism, lethargy

cebo-controlled trial of creatine in 41 patients with HD (stages I – III) came to other conclusions [123]. Scores on the functional checklist of the UHDRS, maximal static torque and peak oxygen uptake decreased from the start to the end of the study in both groups, independent of the treatment received. In a recent randomised, double-blind, placebo-controlled study in 64 subjects with HD, creatine 8 g/day administered for 16 weeks was well tolerated and safe. Serum and brain creatine concentrations increased in the creatine-treated group and returned to baseline after washout. Serum 8-hydroxy-2'-deoxyguanosine levels, an indicator of oxidative injury to DNA, were markedly elevated in HD, and were reduced by creatine treatment [124].

Highly unsaturated fatty acids were found to be effective in two small, short, double-blind, placebo-controlled studies [106,107]. The rationale was based on the role of highly unsaturated fatty acids in cell membrane function, which may affect the likelihood of a cell to undergo apoptosis, and so may be effective in slowing the rate of

neuronal cell death, both within and outside the striatum in HD [125]. However, as the number of treated patients was small (three and nine, respectively), these results must be treated with caution. Unfortunately, a recently published level I trial in 61 HD patients is inconsistent with these prior findings [126]. The authors did not find a significant difference between unsaturated fatty acids and placebo for the motor score. However, some subanalysis provide reason to hope, and even larger level I studies are underway in the US and Europe.

Minocycline, an inhibitor of caspase and neuronal apoptosis, has been demonstrated to delay disease progression and extend survival by 14% in the R6/2 transgenic mouse model of HD [127,128]. The first open-label pilot study on minocycline in HD showed a significant amelioration in several motor capacities as well as cognitive parameters after 6 months [108]. After 2 years, patients exhibited stabilisation in general motor and neuropsychological function at end point, unlike the expected natural course of HD [129]. Moreover, a significant amelioration of psychiatric symptoms was present after 24 months. In contrast, a similarly designed level III study failed to find any effect after 6 months [130]. A safety and tolerability study found minocycline to be well tolerated and safe in HD patients [131], and a level I clinical study on minocycline is underway in the US. An interesting case report is available showing persistent beneficial effects of minocycline for > 1 year in 1 HD patient. Cessation of minocycline for 3 weeks resulted in an exacerbation of symptoms [132].

The lipophilic free-radical scavenger OPC-14117 was shown to be safe in a 3-month, level I trial (n = 23 on active drug), although no benefit on motor or cognitive function was observed [133]. Elevations of hepatic transaminase in sev-

eral subjects treated with OPC-14117 emphasised the need for adequate safety and tolerability studies before embarking on long-term neuroprotective trials. Two more level I clinical trials on free-radical scavengers have been carried out. A placebo-controlled trial of  $\alpha$ -tocopherol for 1 year in 73 HD patients (n = 40 on the active drug) did not show benefits [134]. A level I trial on the antioxidant idebenone in 91 HD patients (n = 48 on the active drug) over 1 year also failed to show any beneficial effect on the progression of HD [135].

Three level I studies pursued antiglutaminergic strategies. Baclofen and lamotrigine are thought to diminish glutamate neurotransmission by inhibiting corticostriatal glutamate release. However, a placebo-controlled trial of lamotrigine in 64 patients, followed for 30 months, failed to show any benefit to the progression of functional decline in HD [136]. The Huntington Study Group examined the effect of the glutamate antagonist remacemide and the enhancer of bioenergetics, coenzyme Q10 [52] after remacemide was reported to be safe in a safety level I trial [51] and coenzyme Q10 was tested in two level III open-label trials [137,138]. The authors conducted a multi-centre, parallel-group, double-blind, 2 × 2 factorial, randomised clinical trial. In total, 347 HD patients were randomised to receive coenzyme Q10 300 mg b.i.d., remacemide hydrochloride 200 mg t.i.d., both or neither treatment. The patients on each assigned treatment regimen were evaluated every 4–5 months for a total of 30 months. None of the interventions significantly altered the decline in total functional capacity of the UHDRS, although patients treated with coenzyme Q10 showed a trend toward slowing in total functional capacity decline over 30 months.

## 6. Expert opinion

There is poor evidence in the management of HD today. The analysis of the available level I studies fails to result in any treatment recommendation of clinical relevance. Studies with most substances have defined motor function (mostly chorea) as their primary outcome measure. Surprisingly, no single

dopamine antagonist has good data for the treatment of chorea. This is easily explained by the fact that they all lack level I trials. Due to the very methodology of a systematic review, substances that would be considered the strongest antichoreatic agents by the vast majority of clinicians today, have to be classified to have insufficient evidence with regard to their efficacy. For daily practice, there is some evidence for treating chorea with haloperidol or fluphenazine, and less evidence for olanzapine.

There is very poor evidence today for the treatment of psychiatric disturbances or dementia, which are the other two aspects of clinical trials on HD. Possibly useful drugs for clinical practice would be L-dopa and pramipexole for rigidity; amitriptyline and mirtazapine for depression; risperidone for psychosis; and olanzapine, haloperidol and buspirone for behavioural symptoms in HD.

For the neuroprotective agents, it is even harder to make an appropriate judgment, possibly due to the complex methodology (how does one prove neuroprotection?). The coenzyme Q10 data and the data on unsaturated fatty acids could be interpreted somewhat differently as we have done in this paper. There still is hope that these two substances are demonstrated to be effective with highly-powered studies. In total, three substances are investigational as possible neuroprotective agents in this paper: coenzyme Q10, minocycline and unsaturated fatty acids.

In fact, systematic reviews emphasise efficacy studies. Sometimes there is a discrepancy between information provided by studies focused on efficacy and the simple clinical reality (effectiveness). The level I paper on riluzole makes the dilemma somewhat visible [53]. In some illnesses, actual treatment and evidence-based information are slowly converging. In other illnesses, such as HD, patents are treated with medications that have very limited evidence to support their use. For many of the problems arising in HD, the recommended treatment may have limited evidence-based support, due to our limited knowledge in the area. Treatment for HD may still rely more on common sense of physicians than on the information provided by the literature.

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