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PHARMACOLOGICAL INTERVENTION AT HUNTINGTON'S DISEASE: A REVIEW STUDY

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ABSTRACT

Huntington's chorea, also recognized as Huntington's disease (HGD), is a poisonous neurological illnesswhich affects three to seven persons per 100,000 of Eastern European heritage. HGD is thought to be one of the maximum frequent genetic abnormalities in the developed world. The condition often manifests itself between the ages of 30 and 50, is autosomal dominantly inherited, and is marked by chronic motor, cognitive, and mental symptoms. It causes gradual nerve cell destruction in the brain. As a result, the person's physical and mental capabilities might diminish normally within their prime active age, and symptomatic therapy is available. It is a hereditary condition that causes brain cell death.A Huntington gene mutation occurs in either of the two copies of a person's Huntington gene. The HGD gene was discovered in 1993. It is made up of a trinucleotide repeat, which is a repeating sequence of three base pairs. An excess of repeated CAG triplets in the gene leads in a protein with an unusually high amount of glutamine amino acids. On chromosome 4, a CAG triplet increases in the Huntington's gene.(4p 16.3), leading in an extensive polyglutamine stretch near the protein's N-terminus. Because it is a hereditary condition, there is a 50% risk that it will be passed down to the children.Currently, there is no cure for HGD, however clinical studies of powerful drugs are underway, and there are other promising prospective therapies in research. The estimation of important biomarkers for therapy assessment is currently under progress. Researchers prioritise therapeutic effectiveness over anything else. The current study's goal was to examine previous studies on

pharmacological therapeutic intervention in HGD. A comprehensive literature search was conducted using Medline, The Cochrane Library's core database, and references lists in review papers as well as many different clinical reports.In this research, randomised controlled trials (RCTs)were categorised as Type I studies. Non-randomized, controlled clinical trials were used in type II investigations. Case reports were not included in type III studies, which instead assessed effectiveness, safety, and tolerability. HGD is a hereditary autosomal dominant condition with several subtypes based on its genetic background, diagnosis, symptoms, and therapy. The disorder is hereditary and can be discovered by testing for the HGD gene. Chorea symptoms include uncontrollable jerking and writhing motions. Although there is no cure for the abrupt development of chorea and behavioural problems, research is ongoing. Recent technological advances, on the other hand, have enabled scientists to discover and comprehend the gene responsible for this disease, providing tremendous promise for subsequent effective treatment.

KEYWORDS: Huntington’s chorea, gene, mutant Huntington,toxicity.

INTRODUCTION

It is possible to understand Huntington's Disease in terms of its genetic foundation, symptoms, diagnosis, and therapy. HGD is aadvanced neurological condition which exhibits autosomal dominant inheritance. When George Huntington conducted rounds with his father as a young child in 1872 on Long Island, New York, and then later as a doctor himself, he saw it for the first time in patients spanning several generations. Motor, cognitive, and behavioural symptoms of HGD are present, and prevalence studies using genetic and clinical diagnostic criteria indicate that 10.6–13 out of 100,000 people, or 1 in 7,300, have HGD. HGD is brought on by the help of mutations in one of the 2 copies of this gene (HTT). Ten years after the 1983 finding of the gene locus towards the end of chromosome 4, or in 1993, the HGD gene was discovered. It has a triplet repeat, also called a trinucleotide repeat, which is a repeating sequence of three base pairs. Axon 1 contains too many CAG repeats, which causes the protein to have too many glutamine amino acids. ssHGD (4p 16.3) results from recurrent CAG triplet expansions on chromosome 4. A protein with an extremelyextended polyglutamine stretch at its N-terminus is the outcome of this.[1] When the CAG repeats exceed 36, the prevalence of HD peaks, and when the repeats exceed 40, penetrance is complete.[2] Age at which symptoms first develop is negatively correlated with the amount of CAG repeats.[3] Though they can happen at any age, the typical age at which symptoms first

appear is 40. Rigidity and bradykinesia are the most typical motor symptoms of juvenile HGD, which is characterised as an early start of symptoms, i.e. before age 20.[4] The patient can anticipate living for around 20 years after diagnosis, during which time they are completely reliant.[1] There is a high risk of suicide as well as secondary reasons of death, such as pneumonia.[4] The chorea (random, dance-like motions) that HGD is defined by.[4,5] Other motor symptoms include tics, myoclonus, dysarthria, ataxia, bruxism, dystonia, ataxia, tourette's, trouble beginning voluntary movements, dystonia, and saccadic eye movements.[4,5] Psychosis, depression, dementia, decreased executive function, apathy, irritability, violence, personality changesapathy, anxiety, hallucinations, or cognitive deterioration are additional major cognitive as well as behavioural symptoms.[6] Dysphagia, weight loss, dysarthria, as well as sleep difficulties are further signs that the total impairment is present.[7] Sometimes, these indicationsseemearlier the start of motor symptoms.[1] There is currently no recognised treatment for HGD that is either neuroprotective, disease-modifying, or curative.[8] Pharmacological treatment seems to concentrate on providing systemic comfort.[9] The majority of pharmacological treatments are used to treat cognitive or behavioural symptoms, such as antidepressants, neuroleptics, SSRIs, as well as neuroleptics for both psychotic and motor symptoms. Acetylcholinesterase inhibitors can also be used to treat memory loss.[7] Dopamine, glutamate, as well as GABA are the neurotransmitters implicated in the pathophysiology of HGD, and pharmacotherapy seeks to restore their balance.[10] Tetrabenzine (TBZ), a DA depleting agent, DA D2 receptor antagonists (typical and atypical neuroleptics), anti-glutamatergic medicines, as well as GABA-agonists are a few of the medications involved. Levodopa is a dopaminergic medication used to treat juvenile HGD.[4] HGD is a debilitating, progressive neurodegenerative condition. There is currently no known neuroprotective or current modifying therapy for HGD-related neurodegeneration, despite a plethora of research devoted to the genetics and molecular processes of this condition. It is essential that individuals with HGD receive the appropriate treatment, whether it be symptomatic or pathophysiological, in order to enhance their quality of life in terms of their health.The reader is directed to recent research for considerations of genetics, pathology, imaging, as well as additional aspects of the illness, that are not the topic of this review article.[4] We hope to present the key EBR on the efficacy of symptomatic pharmaceutical therapy for motor, behavioural, as well as cognitive HGD in this publication. The most suitable symptomatic therapy will be determined by the most noticeable or bothersome symptoms.[11] We eliminated non-pharmacological techniques from the current EBR, which will be examined separately.

METHODS

The authors used the available papers that were published since 1990 to conduct this systematic review. The following databases were used for computerised literature searches: MEDLINE, PubMed, Embase, Thomson Web of Science, systematic reference searches of review papers and other clinical reports' reference lists, as well as the main database in the Cochrane library. Additional searches were undertaken using Google Scholar and Sci-Hub. All research are thoroughly analysed, and the papers are organised in a hierarchical order of evidence. Because the vocabulary used to describe the symptoms of HGD is so diverse, each database is searched twice. The phrases 'Huntington,"medication,' 'drug,' and 'pharmaco' were used in both searches.To include trials exploring medication for motor symptoms, the following phrases were added to the first search: "chorea," "motor," "dystoni," "movement," and "tic"; the following search phrases were added to the second search:: The terms 'behavior,"mood,' 'affect,' 'delusion,' 'depression,' 'anxi*,' and 'psycho' were used to refer to studies on the treatment of psychiatric and neuropsychological disorders. The following databases were accessed for the purpose of indexing papers and finding alternative search terms: pubmed, scihub, google scholar, EMBRASE, and the medical subject headings **(**MeSH**)** database. Furthermore, articles published in journals that were relevant to this and not found in initial searches were reviewed. Among them are Neurology, Clinical Neuropharmacology, Neurosurgery, and Psychiatry; Movement disorder; and Neurology. Finally, HGD specialists were interviewed to confirm that no HGD-related papers were overlooked. Case reports, case series, editorials, comments, and letters to the editors of scientific publications were also excluded. Over 150 results remained acceptable for inclusion after deleting duplicate or irrelevant studies. As a result, open-label and retrospective investigations were ruled out. The preliminary search yielded over 2500 items, which were then restricted to English language studies published between 1980 and the present. The literature searches include evidence-based reviews (EBR) on randomised controlled trials (RCTs), as well as double-blind trials with 20 or more patients and research on RCTs with high quality evidence. All of these research are methodically examined and presented in a table in this review. Studies on purported neuroprotective remedies were only included if the primary method of evaluation was how the drugs affected the most common and troublesome symptoms..Randomised controlled trials are divided into three categories of investigations. Type 1 studies should meet the following criteria in this review.

1. A minimum of two weeks of therapy with the active medication.

2. A minimum of ten HGD patients using the active medication and completing the research term.
3. Citation for the entire paper.

Controlled trials that did not meet these requirements were classified as type 2 studies. Type 2 also included non-randomized or observational controlled trials. Uncontrolled case series, which comprised open-level and retrospective reporting, were classified as Type 3 studies. Case reports were therefore considered to be the weakest kind of evidence. As long as each of these factors were operationally established, papers were accepted independent of language or grading scheme. HGD intelligences were characteristicallyrecognized based simply on the clinical judgement, without the need for a genetic diagnosis. Twenty RCTs meet the requirements for type 1, 55 for type 2, and 54 for type 3 **(Table 1-3 and fig3)**.

Table 1: (Type I study) Randomised Pharmacological controlled trials in HD chorea Acetylcholine Alzheimer's condition (ADAS) The acronyms AIMS, UHDRS, and HDMRS stand for the Unified HD Rating Scale, Irregular Involuntary Movement Scale, and HD Motor Rating Scale, respectively. The authors' arbitrary chorea quantification is referenced by the terms "Chorea Severity Score," "Video-rating," and "Self-Report.". Quantified Neurological Examination is known as QNE. Total functional capacity is known as TFC. n is the total number of patients who finished the experiment while taking an active drug. the period of time that all patients participated in the study. History includes both the clinic and a positive family history; clinic refers to a single clinical impression. CAG stands for genetically validated HD diagnosis. The Huntington Study Group is known as HSG. Qb = study quality less than 75%; Qa = research quality better than.

Medication control Agent	Reference HD Diagnosis	Effect N*	Design and duration of the study	HD score tools Consequences of HD medicine		Quality of the study
Antidopaminergics						
Sulpride Placebo	Quinn and Marsden et a[31]	Clinic Poor	Cross -ove 4 Weeks	CCS Kept constan 74		Qb
Clozapine Placebo	van Vugt et al. 1997[25]	CAG poor	Cross- ove 4 Weeks	Kept constan 72 UHDRS,A		Qb
Tiapride Placebo	Roos et al. 1982[27]	History None	Cross- ove 2 Weeks	Self, Vid	Controlled on 63	Qb
Tiapride Placebo	Deroover et al. 1984[26]	History Good	Cross- ove 3 Weeks	Self	Anxiolytic, 61 Antidepressa allow	Qb

Dopa-agonists						
trans- Placebo Dihydrolis	Bassi et al. 1986[21]	Clinic Good	Cross- ove 2 Weeks	Self	Kept Constan 63	Qb
trans- Placebo Dihydrolis	Stocchi et al. 1989[30]	History None	Cross- ove 4 Weeks	AIMS	Kept Constan 58	Qb
NMDA-antagonists						
Riluzole Placebo	Landwehrmever et al. 20CAG[68]	None	Parallel 3 Years	UHDRS	Controlled on 96	Qa
Riluzole Placebo	HSG et al. 2003[69] CAG	Poor	Parallel 8 Weeks	UHDRS	Kept constan 100	Qa
AmantadinPlacebo	Lucetti et al. 2003[62] CAG	Good	Cross- ove 300 min (I UHDRS, Kept constan 81			Qa
AmantadinPlacebo	Heckmann et al. 2004 (6 CAG	None	Cross- ove 6 Weeks UHDRS Kept constan 85			Qa
AmantadinPlacebo	O' Suilleabhain and Dew CAG 2003[63]	None	Cross- ove 2 Weeks Chorea s,Video		Controlled on 89	Qa
AmantadinPlacebo	VerhagenMetman et al. CAG[61]	Good	Cross- ove 2 Weeks UHDRS		Controlled on 89	Qa
Others						
Cannabidi Placebo	Consro et al. 1991[22]	History None	Cross- ove 6 Weeks Self		Kept constan 73	Qb
Fluoxetine Placebo	Como et al. 1997[19]	N.s. None	Parallel	4 Months TFC	Kept constan 71	Qb
Neuroprotection						
Coenzyme Ramace, placebo	HSG et al. 2001	History Trend CAG	parallel	30 Month UHDRS	Not Controlle 98 other than ex if taken coen Q10 in precee months.	Qa
LamotriginPlacebo	Kremer et al. 1999	CAG None	parallel	30 Month TFC, QNEKeptconstan 95		Qa
OPC-1411 Placebo	HSG et al.1998	History Safe	parallel	3 Months UHDRS	Not allowed 95	Qa
IdebenonePlacebo	Ranen et al. 1996	History None	parallel	12 Month QNE	Not allowed 92	Qa
Alpha- Placebo tocophero	Peyser et al. 1995	History None	parallel	12 Month QNE	Controlled on 95	Qa
Baclofen Placebo	Shoulson et al. 1989	History None	parallel	30 Month TFC	Not allowed 91	Qa
MinocyclinPlacebo	HSG et al. 2004	History Safe CAG	parallel	8 Weeks UHDRS	Controlled on 95	Qa
Unsaturat Placebo fatty acids	Puri et al. 2005	History None CAG	parallel	12 Month UHDRS	Controlled on 95	Qa
Remacem CoQ10,	P HSG et al. 2001	History None CAG	parallel	30 Month UHDRS	Not Controlle 98 other than ex if taken coen Q10 in preced months	Qa
Remacem Placebo	Kieburtz et al. 1996	History Safe	parallel	6 Weeks HDMRS	Controlled an 95 constant	Qa

Table 2: (Type II study) Non Randomised or observational trials in pharmacological intervention in HGD chorea.

S No.	Medication	Control agent	References	HGD diagnosis	Effect	N*	Randomized	Blinded	Study design	Study duration	HGD score
Antipsychotic drugs											
1	haloperidol	-	Koller 1985	history	Positive	13	no	single	-	n.s.	video, self
2	haloperidol	lithium, placebo	Leonard 1974, 75	history	Noeffect	6	yes	double	crossover	3 weeks	self
3	haloperidol	tetrabenazine	Gimenez, 1989	clinic	Positive	11	no	single	crossover	114 days	Kartzinel, 1976
4	fluphenazine	placebo	Terrence, 1976	n.s.	Positive	5	n.s.	double	parallel	4 weeks	self
5	**Perphenazine**	**placebo**	**Fahn, 1972**	**clinic**	**Positive**	**8**	**n.s.**	**double**	**crossover**	**4 weeks**	**video, self**
6	tiapride	placebo	Chouza 1982	n.s.	Positive	2	no	double	crossover	2 weeks	self
7	thiopropazate	tetrabenazine, placebo	McLellan, 1974	clinic	Positive	9	yes	double	crossover	2 weeks	video, self
8	clozapine	placebo	Caine, 1979	n.s.	poor effect	3	yes	double	crossover	4 weeks	n.s.
Dopamin-depleting agents											
9	tetrabenazine	-	Ondo, 2002	CAG	Positive	18	no	single	-	2-11 months	AIMS, video
10	tetrabenazine	placebo	Jankowic 1982	clinic	Positive	1	yes	double	crossover	3 weeks	video, self
11	tetrabenazine	placebo	Asher, 1981	clinic	Positive	8	no	double	crossover	3 weeks	video, self
12	tetrabenazine	-	Swash, 1972a	clinic	Positive	2	no	single	-	30 weeks	video, self
13	tetrabenazine	amantadine	Swash, 1972b	clinic	Positive	7	no	double	crossover	2 weeks	video, self
7	tetrabenazine	thiopropazate, placebo	McLellan, 1974	clinic	Positive	9	yes	double	crossover	2 weeks	video, self
3	tetrabenazine	haloperidol	Gimenez, 1989	clinic	Positive	11	no	single	crossover	114 days	Kartzinel, 1976

14	**tetrabenazine**	**haloperidol**	**Gilligan, 1972**	**n.s.**	**poor effect**	**6**	**no**	**double**	**crossover**	**8 weeks**	**video, self**
NMDA-antagonists											
15	amantadine	tetrabenazine	Swash, 1972b	clinic	Noeffect	7	no	double	crossover	2 weeks	video, self
16	amantadine, IV	placebo	Lucetti, 2003	CAG	Positive	9	yes	double	crossover	1 day	AIMS, UHDRS
17	amantadine	placebo	Heckmann, 2004	CAG	Noeffect	7	yes	double	crossover	6 weeks	UHDRS
18	ketamine	placebo	Murman, 1997	history	Noeffect	10	yes	double	crossover	1 day	UHDRS
19	milacemide	placebo	Giuffra, 1992	history	Noeffect	7	no	double	crossover	3 days	AIMS
GABA agonists											
20	L-acetyl-carnitine	placebo	Goetz, 1990	history	Noeffect	10	yes	double	crossover	1 week	AIMS
21	isoniazid	placebo	Manyam1980, 81, 87, 90	history	Noeffect	6	yes	double	crossover	6 weeks	AIMS, video
22	isoniazid	placebo	Perry, 1982	history	Noeffect	9	no	double	crossover	4 months	video, self
23	isoniazid	placebo	McLean, 1982	clinic	Noeffect	8	yes	double	crossover	3 months	video, self
24	GABA	baclofen	Fisher, 1982	n.s.	Noeffect	22	n.s.	double	crossover	6 months	video, self
25	**gamma-vinyl GABA**	**placebo**	**Scigliano, 1984**	**n.s.**	**Noeffect**	**6**	**yes**	**double**	**crossover**	**2 weeks**	**self**
26	THIP	placebo	Foster, 1983	history	Noeffect	5	no	double	crossover	2 weeks	AIMS
27	aminooxyacetic acid	placebo	Perry, 1980	history	Noeffect	7	no	single	crossover	15 weeks	video, self
28	muscimol	placebo	Shoulson, 1978	clinic	Noeffect	10	no	double	crossover	1 week	video, self
29	imidazole-4-acetic acid	placebo	Shoulson, 1975	n.s.	Noeffect	3	n.s.	double	parallel	4 weeks	self
24	baclofen	GABA	Fisher, 1982	n.s.	Noeffect	22	no	double	crossover	6 months	video, self
Dopa-agonists											
30	apomorphine	placebo	Albanese, 1995	history	Positive	9	no	double	crossover	1 day	DCRS-HD
31	apomorphine	placebo	Corsini, 1978	n.s.	Positive	4	no	single	crossover	1 day	self
32	apomorphine	placebo	Tolosa, 1974	history	Positive	4	n.s.	double	crossover	1 day	AIMS
33	SKF 39393	placebo	Braun, 1989	history	Noeffect	5	no	double	crossover	1 day	AIMS
34	bromocriptine	placebo	Frattola, 1977	clinic	Positive	11	no	double	crossover	4 weeks	self
35	bromocriptine	placebo	Kartzinel, 1976	history	worsen	6	no	double	crossover	8 weeks	self

36	**lisuride**	**placebo**	**Frattola, 1983**	**history**	**Positive**	**11**	**no**	**single**	**crossover**	**1 day**	**ARS**
Others											
37	piracetam	placebo	Mateo, 1996	n.s.	worsen	11	no	double	crossover	1 day	self
38	piracetam	placebo	Destee, 1984	history	worsen	6	n.s.	double	crossover	1 day	AIMS
39	cysteamine	placebo	Shults, 1986	n.s.	Noeffect	5	yes	double	crossover	2 weeks	video, self
40	FK 33-824	placebo	Agid, 1983	n.s.	Noeffect	12	yes	double	crossover	1 day	self
41	lithium	placebo	Vestergaard, 1977	history	Noeffect	6	yes	double	crossover	6 weeks	self
42	lithium	placebo	Aminoff, 1974	clinic	Noeffect	9	no	double	crossover	7 weeks	video, self
43	lithium	placebo	Carman, 1974	n.s.	Noeffect	6	n.s.	double	crossover	3 weeks	self
44	lithium	haloperidol, placebo	Leonard 1974, 75	history	Noeffect	6	yes	double	crossover	3 weeks	self
45	dimethylamin oethanol	placebo	Tarsy, 1977	n.s.	Noeffect	3	no	double	crossover	2 weeks	self
46	dimethylamin oethanol	placebo	Caraceni, 1978	history	Noeffect	9	yes	double	crossover	40 days	video, self
47	pindolol	placebo	Greendyke, 1986	n.s.	Positive	1	yes	double	crossover	2 weeks	self
48	arecoline	placebo	Nutt, 1978a	clinic	worsen	6	yes	double	crossover	1 day	self
49	**scopolamine**	**benztropine**	**Nutt, 1983a,b**	**history**	**worsen**	**4**	**yes**	**double**	**crossover**	**1 day**	**self**
50	naltrexone	placebo	Nutt, 1978b	n.s.	Noeffect	6	no	double	crossover	1 day	self
51	vitamin E	placebo	Caro, 1978	history	Noeffect	10	n.s.	double	crossover	24 weeks	self
52	physiostigmin	placebo	Davis, 1978a,b	history	poor effect	6	no	single	crossover	1 day	video, self
53	Choline	placebo	Davis, 1976	clinic	poor effect	4	no	single	crossover	8 weeks	video, self
54	Creatine	placebo	Verbessem, 2003	CAG	Noeffect	26	no	double	parallel	12 months	UHDRS
Neuroprotection											
55	unsaturated fatty acids	placebo	Puri, 2002	n.s.	Positive	3	yes	double	parallel	6 months	UHDRS
56	unsaturated fatty acids	placebo	Vaddadi, 2002	CAG	Positive	9	yes	double	parallel	6 months	UHDRS

ARS is for Arbitrary Rating Scale, whereas UHDRS stands for Unified HD Rating Scale, CSS for Chorea Severity Score, AIMS for Abnormal Involuntary Movement Scale, HDMRS for HD Motor Rating Scale, DCRS-HD for David Clinical RS for HD, and AIMS for Abnormal Involuntary Movement Scale. Self = the authors' arbitrary chorea quantification; video = video-rating.

N stands for the quantity of trial participants who were taking an active drug.

For all patients, the study's length was the same; n.s. = not specified in the publication.

Table 3: (Type III study) open level and retrospective trials in Pharmacological intervention in HGD chorea.

Sno.	Substance	First author, year	HD diagnosis	Effect	n =	Study design	Study duration	HGD score
Antidopaminergics								
1	haloperidol	Barr, 1988	history	Positive	10	open label	2 weeks	AIMS
2	haloperidol (+others)	Girotti, 1984	history	Positive	9	open label	4 weeks	self
3	haloperidol (+others)	Caraceni, 1977	n.s.	Positive	16	open label	2 weeks	video, self
2	pimozide (+others)	Girotti, 1984	history	Positive	11	open label	4 weeks	self
4	Pimozide	Arena, 1980	n.s.	Positive	5	open label	4 months	self
5	Pimozide	Siegmund, 1982	history	Positive	11	retrospective	weeks – years	Norating
6	Pimozide	Bobon, 1968	n.s.	Noeffect	1	open label	6 months	Norating
7	fluphenazine	Whittier, 1968	history	Positive	65	retrospective	8 weeks	self
8	Tiapride	Quinn 1985	n.s.	Noeffect	7	prospective	n.s.	n.s.
2	tiapride (+others)	Girotti, 1984	history	Noeffect	12	open label	4 weeks	self
9	Melperon	Mattson, 1974	n.s.	Noeffect	7	open label	3 weeks	self

10	Clozapine	Colosimo, 1995	n.s.	poor effect	8	retrospective	av. 18 months	Norating
11	Clozapine	Bonuccelli, 1994	n.s.	Positive	5	open label	3 weeks	AIMS
12	olanzapine	Paleacu, 2002	CAG or clinic	poor effect	9	open label	6 months	UHDRS
13	olanzapine	Bonelli, 2002	CAG	Positive	9	open label	2 weeks	UHDRS
14	olanzapine	Squitieri, 2001	CAG	poor effect	11	open label	6 months	UHDRS
Dopamin-depleting agents								
15	tetrabenazine	Jankovic, 1997	n.s.	Positive	29	retrospective	av. 28 months	self
16	tetrabenazine	Jankovic, 1988	n.s.	poor effect	10	retrospective	1-80 months	self
17	tetrabenazine	Toglia, 1978	history	Positive	7	retrospective	2-10 months	video, self
18	tetrabenazine	Huang, 1976	n.s.	poor effect	6	open label	9-18 months	self
19	tetrabenazine	Astin, 1974	n.s.	Positive	26	retrospective	weeks – years	self
20	tetrabenazine	McLellan, 1972	n.s.	poor effect	11	retrospective	1-12 months	self
22	tetrabenazine	Pakkenberg, 1968	n.s.	poor effect	11	open label	> 2 months	self
GABA agonists								
29	Isoniazid	Stober, 1983	n.s.	poor effect	11	open label	3-17 months	TFC
30	Isoniazid	Perry, 1979	history	poor effect	6	open label	4-25 months	self
31	Isoniazid	Perry, 1977	n.s.	Positive	6	open label	2-16 months	self
3	GABA (+others)	Caraceni, 1977	n.s.	Noeffect	3	open label	2 weeks	video, self
32	L-glutamate	Barr 1978	n.s.	Noeffect	5	open label	3 years	self
33	Baclofen	Paulson, 1976	n.s.	poor effect	15	open label	> 4 weeks	video, self
Others								
38	donepezil	Fernandez, 2000	CAG	poor effect	8	open label	2x 6 weeks	UHDRS
39	rivastigmine	de Tommaso 2004	CAG	poor effect	11	open label	8 months	MMSE
35	lysuride (+others)	Caraceni, 1980	n.s.	Noeffect	4		3 weeks	video, self
34	diazepam (+others)	Caraceni, 1980	n.s.	Positive	3	open label	1 day	video, self

35	cyproheptadine (+others)	Caraceni, 1980	n.s.	Positive	3	open label	2 weeks	video, self
3	diprophylacetic acid (+others)	Caraceni, 1977	n.s.	Noeffect	4	open label	2 weeks	video, self
3	CB 154 (+others)	Caraceni, 1977	n.s.	worsen	5	open label	2 weeks	video, self
3	physiostigmin (+others)	Caraceni, 1977	n.s.	Noeffect	4	open label	1 day	video, self
40	dextromethorphan	Walker, 1989	history	Noeffect	11	open label	4-8 weeks	TFC
41	dextromethasone	Nuti, 1991; Bonuccelli, 1992	history	Positive	6	open label	20 days	AIMS
42	somatostatin	Dupont, 1978	n.s.	Noeffect	1	open label	1 day	self
43	Choline	Davis, 1976,77,78	n.s.	Positive	4	open label	1 day	video, self
44	Choline	Aquilonius 1977	n.s.	Noeffect	5	open label	1 day	video, self
45	Lithium	Mattsson, 1973b	history	Positive	4	open label	3 weeks	self
46	Disulfiram	Mattsson, 1974	n.s.	Noeffect	5	open label	4 weeks	video, self
Neuroprotection								
47	Riluzole	Rosas, 1999	n.s.	Positive	8	open label	6 weeks	UHDRS
48	Riluzole	Seppi, 2001	CAG	Positive	9	open label	12 months	UHDRS
49	minocycline	Bonelli, 2003	CAG	Positive	14	open label	6 months	UHDRS
49	minocycline	Bonelli, 2004	CAG	Positive	11	open label open label open label	24 months	UHDRS
50	minocycline	Thomas, 2004	CAG	Noeffect	30		6 months	UHDRS
51	coenzyme Q10	Feigin, 1996	n.s.	Noeffect	10		6 months	HDRS
522	coenzyme Q10	Koroshetz, 1997	n.s.	Noeffect	18	open label	> 2 months	MRS
53	Creatine	Tabrizi, 2003	CAG	Noeffect	13	open label open label open label	12 months	UHDRS
53	Creatine	Tabrizi, 2005	CAG	possible effect	9		24 months	UHDRS
54	Creatine	Bender, 2005	CAG	Noeffect	20		8 weeks	UHDRS

The type 1 studies were also evaluated in terms of excellence of the study. The quality of study score was gotafter a list of chief technical topics relevant for establishing the trial's methodological soundness, as determined by a published checklist.[12] The studies were evaluated based on their outcomes, selection standards, dimension, statistical analysis, as well as usefulness of the outcome. For each investigation, a % score was derived as well as utilised as a measure of the completevalue of the study. A study was measured high quality, or type Qa, if its study quality was 75% or higher; otherwise, it was categorised as type Qb. The categories of efficacy were as follows: effective, ineffective, somewhat effective, least effective, and no evidence.[12] A medication was considered to be successful when information from at least one good (score 75%, or type Qa) RCT with no contradicting type 1 informationpresented that it had a helpful effect on the specified outcomes (regardless of the quality). A medicine was deemed ineffective when sign showed that it had no beneficial effect on selected outcomes, as maintained by facts from at least one high-quality (score 75 percent) RCT with no opposing type 1 data (regardless of quality). When data reveals that a medicine has no beneficial effect on defined outcomes, it was deemed least effective. These conclusions must be supported by information from any RCT (regardless of quality) with no contradictory type 1 data. Lastly, a medicine was measured no evidence when there is insufficient indication for or in contradiction of efficacy in Pharmacological treatment of HD, taking into account all variables not addressed by the previous claims. Safety was classified as follows: unacceptable risk, satisfactory risk without specialist screening, satisfactory risk with specialised screening, and inadequate information to draw judgments about the intervention's safety. The particular implications for clinical research were classified as follows: clinically relevant, perhaps beneficial, not useful, exploratory, and evidence unlikely.[12]

The development and certification of many clinical rating scales ensure consistent results evaluation in clinical studies.

The UHDRS was created by the HSG and includes numerous subscales that measure motor, cognitive, behavioral, functional status, as well as determination.[13] The AIMS rates abnormal motions from 0 (no movement) to 4 (severe).[14] Individual scores are assigned for aberrant actions touching the muscles of facial expression, the perioral and lios region, the tongue, jaw, the upper and lower limbs, and the trunk.To evaluate the functional state of HGD patients, the Total Functional Capacity Scale (TFC) and the Independence Scale (IS),

both of which are included in the UHDRS, are often employed.. The existence of dentures or edentia, as well as the patient's knowledge of and any difficulty brought on by atypical motions, are also included on this scale as shown in Fig 1.

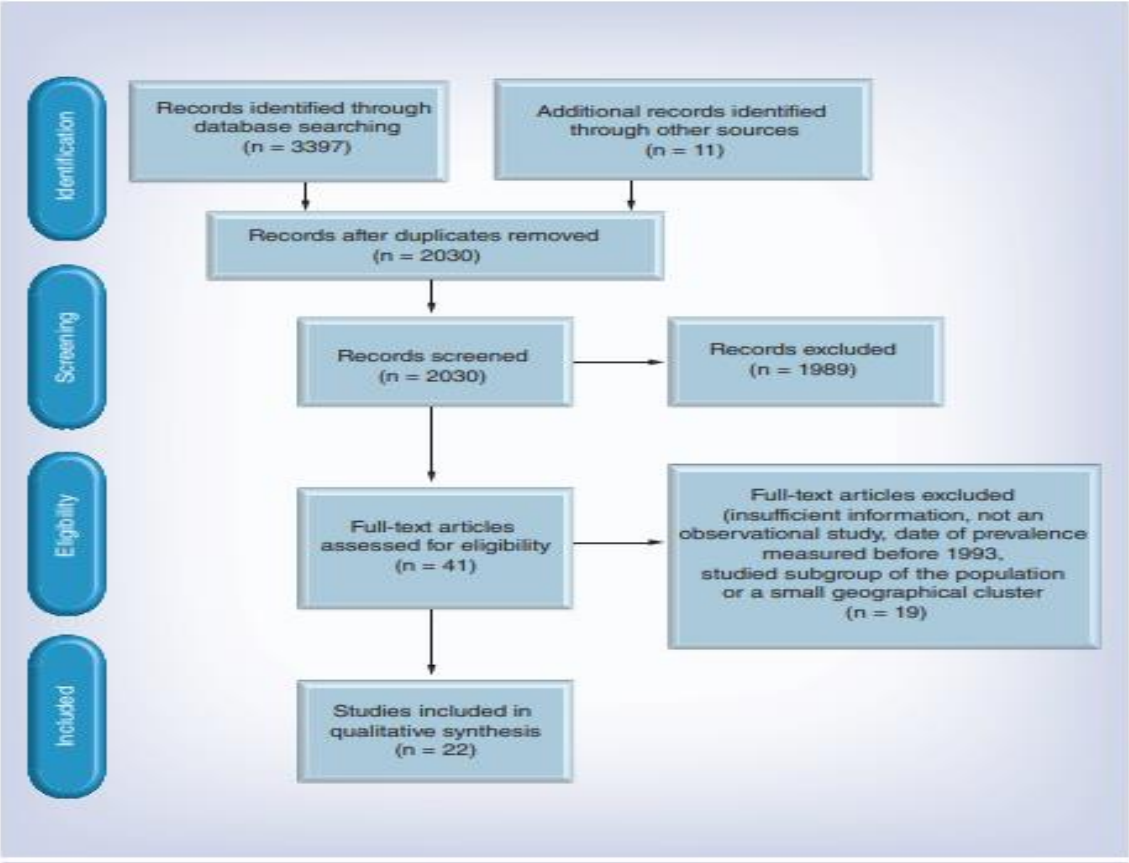

Figure 1: a flowchart showing the steps taken in a systematic review to find and select studies that report the prevalence of Huntington's disease in specific populations.

A clinical trial on HGD patients is a difficult endeavour; treatment will be difficult due to the disease's rarity, and protocol adherence must be closely watched to avoid a high dropout rate. Amazingly, just a few randomised clinical trials in HGD have been done.Small sample sizes (the majority of studies used less than 30 patients) and a variety of clinical measures that have not been validated, especially in early trials,) sometimes produce inconsistent results. The sections that follow discuss the limitations and strengths of clinical trials, as well as available data from less rigorously performed research and case reports in HGD.

This review is broken down into the following sections:

(1) Chorea therapy. (2) therapy of additional neurological symptoms, (3) treatment of mental symptoms, and (4) neuroprotective therapeutic options.

1. Treatment of chorea

1.1. Dopamine-Depleting Medications

Dopamine depleters were successful medications in the 1950s for treating hypokinetic movement disorders such as HGD chorea. The first medicine used as a dopamine depleter was reserpine, which was shown to be ineffective and has gone out of favour due to its poor tolerability, producing orthostatic hypotension, depression, and serious side effects.[15] Reserpine has mostly been replaced by the dopamine depleting drug tetrabenazine (TBZ).[16] In the 1960s, there were the first case reports of HGD patients who had improved after receiving TBZ medication.[17] Since then, seven of eight small type II double-blind studies[18], numerous clinical trials and case reports[19], mostly retrospective (a profusion of type III trials)[20], open-label, or employing a small number of subjects, have provided evidence and primarily support the antichoreatic efficacy of tetrabenazine in the treatment of HGD chorea or may be related to other causes.[21] One recent retrospective level III study had to be excluded from our analysis because to inaccurate data presentation (analysis of HGD inseparable in a pool with other chorea).[22] Unfortunately, unpleasant responses are common, limiting tetrabenazine's utility. Among these include sedation, sleeplessness, depression, anxiety, parkinsonism, dysphagia, akathisia, and, under extremely rare circumstances, neuroleptic malignant syndrome.[23]

Tetrabenazine selectively binds to the vesicular monoamine transporter VMAT-2 to decrease monoamine absorption into granular vesicles of presynaptic neurons. This inhibition accelerates the breakdown of monoamines including dopamine, norepinephrine, as well as serotonin in the cell, that causes monoamine depletion. However, reserpine inhibits VMAT2 irreversibly, which explains for certain peripheral side effects such orthostatic hypotension and diarrhoea. TBZ inhibits VMAT2 reversibly, which accounts for its short duration of action.[16] The effects of the TBZ are more likely to affect striatal dopamine.[24]

The most convincing proof of TBZ's efficacy in HD comes from clinical trials conducted by HSG on 84 HGD patients who participated in multicenter randomised, double-blind, placebo-controlled studies, known as TETRA-HGD.[25] The participants were randomised to receive either TBZ or a placebo for 12–13 weeks. To obtain the intended antichoreic effect or to prevent side effects, the dosage of the medication was increased. At 1, 3, 5, 7, 9, and 13 weeks, the patients were examined using the UHDRS chorea score. A score of 0 indicates no anomalies and a score of 4 indicates the most severe impairment. It is a standard test with 31

items rated on a scale of 0 to 4. The highest potential overall score is 124. The Clinical Global Impression Scale (CGI-1) is a seven-point scale that asks the doctor to determine whether the patient's condition has improved or deteriorated in comparison to a pre-intervention baseline, and the newly introduced .Functional Impact Scale is a case-based scale used to assess feeding, bathing, dressing, toileting, as well as social isolation. The prevalence of parkinsonism was assessed using the UPDRS, Barnes Akathisia Scale (BAS), Hamilton Depression Scale (HDS), and Epworth Sleepiness Scale (ESS).

The primary result of the placebo (adjusted, p0.0001) research indicates a substantial reduction in chorea severity of 23.5 percent from baseline to final evaluation. In addition, whereas 23 TBZ participants (45.1%) experienced more than moderate improvement, just 2 placebo patients (6.9 percent) did (p 0.0004), which was consistent with chorea improvement (p 0.0001).Barnes Akathisia Scale and parkinsonism (UPDRS) score demonstrate no meaningful response to TBZ; Epworth Tiredness Scale reports increased sleepiness in the TBZ group; as well as UHDRS functional checklist having Functional impact scale results point to a mildly worsening impact on the patient. After the one-week washout period ended (week 13), the chorea got worse; there was no difference between the TBZ and placebo groups compared to the starting point.

The study's adherence to the protocol was remarkably high (93 percent of patients finished it).Restlessness resulting in hospitalisation, intracerebral haemorrhage (after a fall), There were several reasons for stopping TBZ, including suicide (one instance; perhaps situational rather than directly connected to TBZ), breast cancer (the breast lump, existing before enrolment and hidden from the research investigators, was identified as breast cancer during the trial), and akathisia. Despite the fact that the group receiving 50 mg/day showed a statistically significant improvement in chorea, subjects who received less than 50 mg/day of TBZ showed a more significant improvement than those who received more than 50 mg/day. The most frequent dose-limiting side effects were sedation (27%) followed by akathisia (8%) Parkinsonism (4%) and depression (4%) all of which alleviated with a dosage reduction.

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The short duration of impact of TBZ was also confirmed in a double-blind experiment including 30 HGD patients who were randomly assigned to one of three groups. On day one, the first group of 12 patients (the withdrawal group) stopped taking TBZ and replaced it with a placebo; on day three, the second group did the same thing (the partial withdrawal group); and on day three, the third group (the non withdrawal group) remained taking TBZ.[26] With a difference in UHDRS change of 5.33 units at day 3 compared to 2.94 units in the nonwithdrawal group, the withdrawal group had re-emerged chorea (p0.077). Tetrabenazine's efficacy is demonstrated by the propensity for chorea to worsen after stopping the medicine.The tendency for chorea to intensify following medication cessation validates tetrabenazine's effectiveness.

To examine the clinical pharmacodynamics of TBZ on HD patients, an open-label observational study was conducted.[27] Ten HGD patients were evaluated by serial motor Between baseline and 12 hours after their last dose, UHDRS scores and the Beck Depression Inventory. Cholea was decreased by 42.4 percent on average, with the impact lasting bw3.2, 8.1 hours (Mean 5.4 1.3 hours), suggesting that a minimum dose of 3 times per day is enough to maintain an antichoreic action that does not wear out. For effective symptom management, the optimum tolerated dose of TBZ should vary widely between people, ranging from 12.5 mg/day to 400 mg/day. Although no blood levels or other pharmacokinetic information were obtained during this experiment, the findings support past research that suggested a brief half-life.

There was a dearth of information contrasting the efficacy and safety of TBZ versus conventional neuroleptics.In one trial including 11 HGD patients, TBZ was not shown to be better than haloperidol in terms of treating chorea.[28] Three patients in the TBZ group under type II study had significant depression (one of whom committed suicide), whereas three patients receiving haloperidol had tardive dyskinesia, which complicated therapy.[29] Three HGD patients died from aspiration pneumonia as a result of severe dysphagia, according to Snaith and Warren.[30] Tetrabenazine-induced neuroleptic malignant syndrome has been recorded three times in HGD patients, in contrast to normal neuroleptics.[18] (see Table 5).

There was a dearth of information contrasting the efficacy and safety of TBZ versus conventional neuroleptics. One study including 11 HGD patients found no evidence that TBZ was superior than haloperidol for the treatment of chorea.[28] Three patients in the TBZ group under type II study had significant depression (one of whom committed suicide), whereas three patients receiving haloperidol had tardive dyskinesia, which complicated therapy.[29] Three HGD patients died from aspiration pneumonia as a result of severe dysphagia, according to Snaith and Warren.[30] Tetrabenazine-induced neuroleptic malignant syndrome has been recorded three times in HGD patients, in contrast to normal neuroleptics.[18] (see Table 5). A diagnosis of pre-existing depression does not represent an absolute contraindication for starting medication if patients are otherwise acceptable candidates, but continuous monitoring is definitely important. Dysphagia has seldom been described as an adverse effect of TBZ. Similar to HGD, it can be challenging to tell symptoms apart from swallowing problems that are typically related to the underlying illness.[32] Rarely has TBZ been associated with neuroleptic malignant syndrome, particularly in HGD patients.[33] This drug has a notable advantage over other neuroleptics in that it has never been associated with tardive dyskinesia.

Since its discovery, it is clear that TBZ has been utilised by millions of individuals. Despite a sizable body of research demonstrating TBZ's tolerability and safety, it took until 1971 for the United Kingdom to grant it a licence for the treatment of choreaIt is also available in a number of European countries, Canada, and Australia. Although TBZ is not yet accessible in the United States, some doctors have obtained it by means of the Notice of Claim Investigational Exemption for a New Drug (IND). According to past studies and open trials demonstrating TBZ efficacy in chorea, "Tetrabenazine is the drug of first choice for the suppression of chorea in individuals with Huntington's disease".[34]

1.2. Conventional Dopamine-Blocking Medications

Since its discovery, it is clear that TBZ has been utilised by millions of individuals. In 1971, TBZ received a licence in the United Kingdom for the treatment of chorea., despite a considerable body of data proving its tolerance and safety. It is also accessible in Canada, Australia, and a number of European nations. Although TBZ is not yet accessible in the United States, some doctors have obtained it by means of the Notice of Claim Investigational Exemption for a New Drug (IND). "For people with Huntington's disease, tetrabenazine is the drug of choice for reducing chorea.," according to earlier findings and open trials proving

TBZ effectiveness in chorea.[34] Clinical trial studies on haloperidol were conducted on 13 patients with a dose of 2-80mg/d continued until chorea suppression showed effective results in single-blind trials[39], but it was found to be ineffective in a double-blind,crossover trial conducted on six patients with a dose of 15 mg/d for an unknown study duration when compared to lithium.[40]

In a subsequent single-blind, cross-over trial[41] involving 11 patients, it was discovered that haloperidol was just as effective as TBZ, with less severe side effects in the haloperidol group. However, three of the 11 patients had tardive dyskinesia, which made it difficult for them to take haloperidol. Barr and co.[42] report that in an open-pilot research, low-dose haloperidol >10 mg/day was shown to be beneficial in reducing chorea with little extra therapeutic benefit on dosages. Two further type-III studies[43] and three case reports[44] revealed similar favourable outcomes in favour of haloperidol. Older reports also point to its efficacy.[45]

Additional conventional antipsychotic, fluphenazine, was successful in decreasing chorea in a small type II study[46], which was validated by type III data[47] as well as a case report.[48] Drug was commonly used in the 1960s[47], as well as all reports date from that time period. A handful Review publications from the 1960s and 1970s identify thiopropazate as an important conventional antipsychotic that has been shown to be beneficial in the treatment of chorea.[49] Trifluperidol[50], thioproperazine[51], phenothiazine[52], trifluoperazine[53], perphenazine[54] chlorpromazine[55], and melperon trials were equivocal in terms of therapeutic benefits and are no longer in use. Tiapride trials in HGD yielded inconsistent outcomes. A type-Ib research[56], which was validated by a type II study[57], indicated antichoreatic effects; however, these findings were refuted by another type-Ib article[58] and two type-III[59] investigations. In contrast, there are 4favourable small type-III studies[60] as well as one negative case report on pimozide.[61] The pathogenic mechanism explained in Fig 2.

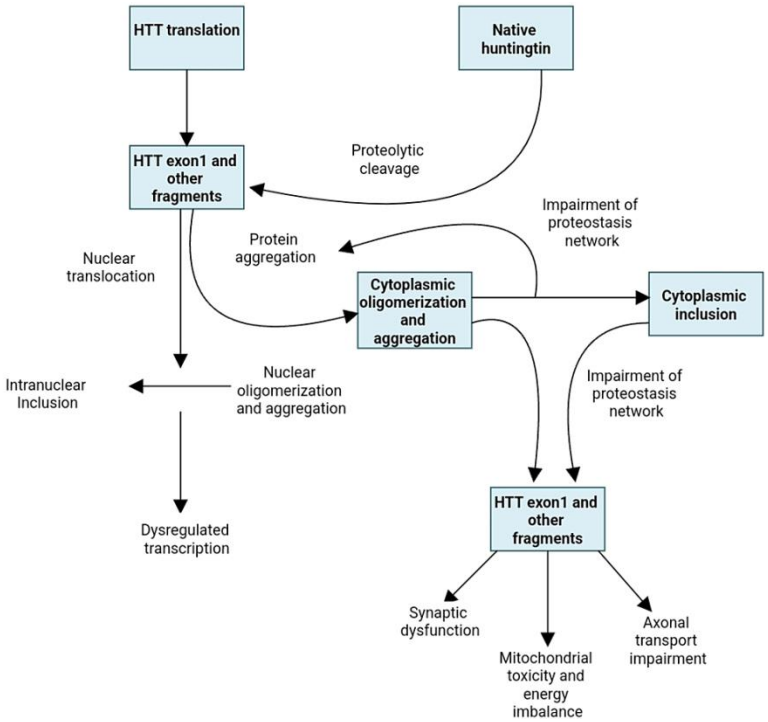

Figure 2: Pathogenetic cellular mechanisms of Huntington's disease HTT and huntington.

Finally, Sulpiride decreased chorea scores in a type II study[62], despite no functional improvement; an additional case report demonstrated high effectiveness.

Therefore, high-dose antipsychotics are ineffective and may impair oculomotor[63], orolingual[64], motor control, and cognitive function. Low-dose dopamine depleting antipsychotics are well tolerated and may lessen the severity of choreatic hyperkinesias. Additionally, these neuroleptics might exacerbate functional decline[65], as well as trigger tardive dystonia[66] In fact, the use of an antidopaminergic medication has been linked to the severity of dystonia in HGD[67], although further research is needed on this subject.It is worth noting that, although being a documented side result of conventional antipsychotics, neuroleptic malignant syndrome has never been observed in HGD patients on this drug class.

1.3. Neuroleptics

Chorea and psychosis in HGD can be treated with both traditional and atypical neuroleptics. Both are DAD2 antagonists.

Typical Neuroleptic

For the treatment of chorea HGD, typical neuroleptics such as haloperidol, pimozide, fluphenazine, thioridazine, sulpiride, as well as tiapride have been used. With the exception

of clozapine, neuroleptic medicines have not been examined in type I or type II studies, but they are drugs for treating movement abnormalities associated with HGD. In two type III investigations, behaviouralsubscores improved with modest dosages (5 mg/d). Three RCTs on atypical neuroleptics that matched the inclusion standards of the present systematic literature review were discovered. Clozapine, an atypical neuroleptic, is utilised in RCT trials on 33 HGD patients have a less favourable effect on chorea.[29] However, because so many individuals had adverse effects, the recommended amount of 150 mg per day was not reached (which may have resulted in greater effectiveness). Furthermore, adverse effects (drowsiness, exhaustion, anticholinergic symptoms, and difficulty walking) required the experiment to be terminated in six individuals as well as dose reduced in another 8. A level II[70] as well as a level III[71] investigation yielded comparable results. Another case report[73] and type III research[72], on the other hand, demonstrated favourable benefits on chorea. In a second RCT evaluation of atypical neuropeptics, tiapride (3g/day) was shown to have a significant favourable impact on chorea in a placebo-controlled crossover trial of 29 patients.. In contrast, a 2-week research on tiapride[30] was also done in which participants took. The smaller dosage, as well as the differences in evaluation and rating scales, might have contributed to the disparities in results. Recent research on pridopidine, a dopaminergic stabiliser, revealed it to be as effective as placebo.[31] In a type III study, olanzapine at high dosages (up to 30 mg/d) significantly improved gait, finger dexterity, orolingual dysfunction, and chorea. Risperidone appears to be helpful in the treatment of HD-related psychosis and chorea in a number of case studies. Further case studies show that quetiapine, zotepine[68], and ziprasidone[69] considerably enhance motor (UHDRS).

1.4. GABAergic Therapy

Three key groups of medications have been explored to enhance GABAergic neurotransmission in HGD because GABA, an inhibitory neurotransmitter, is decreased in HGD brains[74] and CSF.[75] GABA precursors like glutamate, GABAmimetic medicines like gammavinyl-GABA, muscimol, Examples include baclofen, also known as THIP (4,5,6,7-tetrahydroisoxazolo-5,4,-c pyridin-3ol), and GABA transminase inhibitors such isoniacid.. Isoniazid markedly elevated levels of free and conjugated GABA in human CSF[76], but was ineffective in HGD in a number of type II and type III investigations.[77][78] Baclofen was discovered to be an antichoreic agent in a type III[79] as well as a case report (mixed with lithium)[80] investigation, but it did not demonstrate effectiveness in a larger type I trial.[81] In two case studies, valproate had no positive impact on involuntary movements.[82] In an open

label experiment, five patients were administered L-glutamate and pyridoxine for two years with no motor or behavioural effects.[83] In an HGD patient, levetiracetam significantly decreased chorea but caused parkinsonism and lethargy.[84] Because benzodiazepines include anxiolytic, sedative, hypnotic, and anticonvulsant characteristics, they may provide generalised suppression of hyperkinesias in HD patients. Other studies are based on patients who were given clonazepam[86], diazepam[87], or chlordiazepoxide.[88]

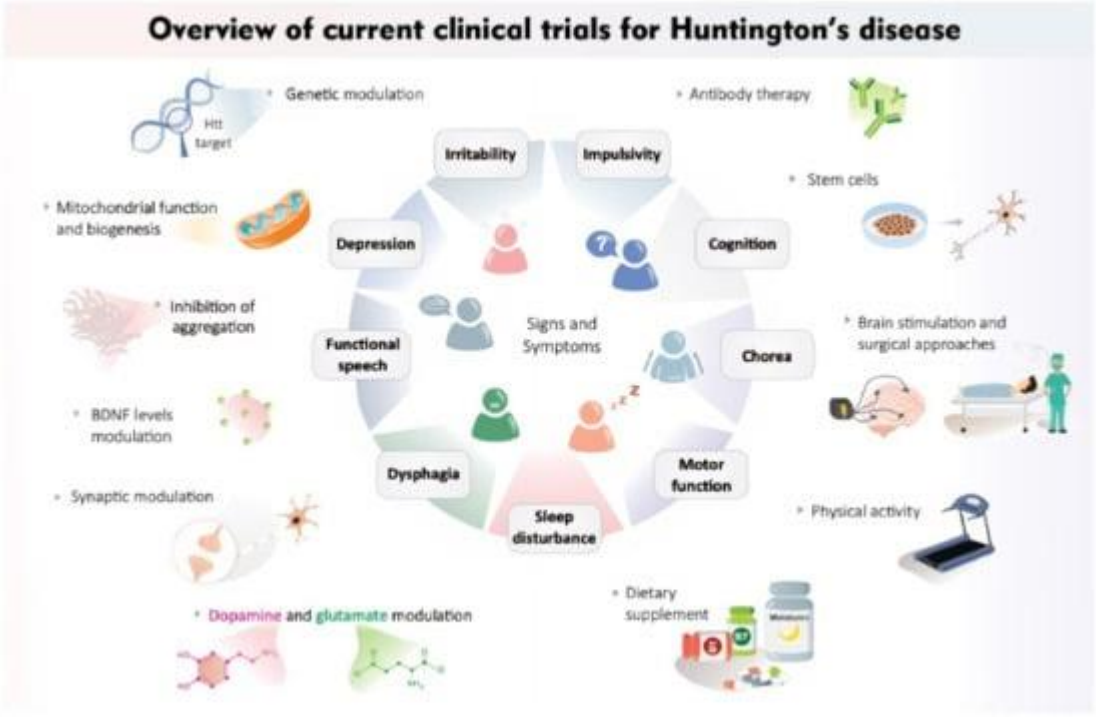

Figure 3: An overview of the current Huntington's disease clinical trials.

1.5. Glutamatergic agents

Amantadine was the subject of two comparable randomised controlled trials (a NMDA-receptor antagonist). Both trials comprised 24 patients for a four-week period and used identical dosages, but the outcomes were different. Verhagen-Metmanet al. conducted the first case study.[89] On Amantadine 400mg/day were given and had a good effect on cholea with minimal bad effects, but in a second case study done by O'Suilleabhainbesides Dewey[90] when Amantadine 300 mg/day were given shows no effect on chorea when it was compared to the placebo, and it shows more side effects. While, 19 different individuals reported subjective improvement following the therapy period, whwn it is compared to 6 after the placebo phase.

A non-competitive NMDA-receptor antagonist is remacemide, Kieburtz et al.[91] conducted randomised controlled trials on Remacemide 200 mg/day dosage and found an overall improvement in chorea level. The HSG[92] conducted a bigger multicenter trial comprising 347 patients to examine the effects of remacemideas well as coenzyme Q10 (a neuroprotective drug) on functional decline in early HGD. No medicine was shown to be statistically beneficial, as judged largely by the change in Total Functional Capacity (TFC). Another glutamate release inhibitor is riluzole. There were two double-blind, placebo-controlled RCTs looking at its impact on chorea in HGD.. Landwehr Meyer et al.[93] conducted studies on 537 individuals who were randomly assigned to receive riluzole 50 mg/day or placebo in a 2:1 ratio for three years. Other antichoreic medications were not permitted, which increased the study's trustworthiness. Only 71% of individuals finished the clinical study, with the major cause being withdrawal owing to concurrent medication rather than bad effects. There were no positive effects on chorea observed. The dosage impact HSG[94] conducted Riluzole investigations on 63 patients, yielding findings that differed from earlier research. When compared to a placebo after 8 weeks of treatment, riluzole 200 mg/day reduced chorea. Last but not least, Kremer et al.[94] conducted a randomised controlled study with lamotrigine. The results showed improvement in chorea in the active arm and a patient-reported improvement in symptoms, but these findings were not statistically significant. There have been published three more case reports of positive effects on chorea.

1.6. Other Medications for the Treatment of Chorea

Fluoxetine[96], Cysteamine[97], FK 33-824[98], Lithium[99], and Cannabidiol exhibit negative outcomes in type-Ib and type II chorea therapy studies. In open label studies, choline[100] and prednisolone[101] administered to two patients for ten weeks were shown to be clinically ineffective in reducing chorea. Piracetam[102] exacerbated chorea in two 1-day level II studies. Apomorphine was found to be efficacious in multiple level II[103], level III[104] trials, as well asreports of the case.[105] Dopaminergic autoreceptors are stimulated by low doses of apomorphine. Two level II trials on bromocriptine, whwreone positive[106], one negative. [106[107] Bromocriptine articles with lower evidence levels are also split.[108] Other antidopaminergic drugs, such as trans-Dihydrolisuride[109], lisuride[110], and SKF-39393[111], have had equivocal results.

2. Treatment of other Neurological Features

Dystonia develops when functional ability deteriorates.[112] The incidence of dystonia in HGD of any severity is greater than 80%[113]; roughly 12% of individuals have dystonia-predominant HGD.[114] Although dystonia is not troublesome for the majority of HGD patientsothers, resulting in functional impairment that calls for therapeutic intervention..In HGD research, dystonia treatment is generally difficult and frequently ignored..Surprisingly, no pharmacological intervention has ever been associated with HGD dystonia as the main consequence. Many prosecutions examining amantadine[115], riluzole[116], or olanzapine[117] in HGD used the UHDRS as an end measure and found no significant change in dystonia sub scores. Gait problem in HGD reduces the patient's quality of life and independence severely. Pharmacological treatments in HGD gait abnormalities has received little attention thus far. In a level-II experiment including 13 HGD patients, haloperidol therapy reduced chorea but had no effect on gait patterns. [118] A modest and brief level-III investigation with high-dose olanzapine[119] produced significant (35%) improvement in UHDRS-defined gait impairment in 9 HGD patients. Other medications have not yet been examined.

In the akinetic-rigid Westphal variety pramipex in HGD, rigidity and akinesia are primary causes of motor impairment. Levodopa (up to 1000 mg/day) and pramipexole (normal dose scheme) have been shown to have antiparkinsonian effects in open label case reports or case series. In a recent case report, amantadine and was effective, while it failed in an earlier one.Despite being a typical feature of adult HGD[120], bradykinesia has never been the focus of therapy. Epilepsy can occur in adults with HGD, however it is more prevalent in the Westphal-variant[121] Numerous HGD patients with myoclonus and epilepsy responded to treatment with valproate[122] or clonazepam.[123] A detrusor hyperreflexia is typically the cause of urinary incontinence, which is a common but generally ignored problem in late-stage HGD.[124] Three HGD patients' responses to carbamazepine (200 mg/day) were noted.[125] Botulinum toxin was successful in treating the bruxism of one patient.[126]

3. TREATMENT OF PSYCHIATRIC SYMPTOMS

The UHDRS behavioural examination takes into account a person's mood, sense of guilt or low self-esteem, anxiety, suicidal thoughts, disruptive or aggressive behaviour, irritable behaviour, obsessions, compulsions, delusions, and hallucinations.[127] These are the most common mental difficulties seen in therapeutic practise. There has been no single type I or II study in this area.

3.1 Dementia

One of the three essential clinical characteristics of HGD is dementia. The clinical stage of the illness affects prevalence..Asyptomatic gene carriers may also have minor cognitive impairments. For HGD patients, there is no level-I dementia therapy present. In level-III studies[128] and a case report, choline esterase inhibitors were shown to be ineffective.[129] Unsaturated fatty acids[130], riluzole[131], and minocycline[132], on the other hand, have been found in open label trials to produce minor cognitive advantages (secondary endpoints).

3.2 Psychotic Symptoms

In HGD patients, psychotic symptoms seem to be prevalent.[133] Three percent to twelve percent of HGD patients who underwent eleven studies were found to have psychosis, which can range from vague paranoia to symptoms similar to schizophrenia. There are just two case studies on risperidone and psychotic symptoms, and they are based on clinic outcomes. Pychiatric Disease Symptoms On neuropsychological tests, HGD patients with obsessive or compulsive symptoms had much poorer executive function impairment than those without these symptoms.[134] Two case studies have demonstrated the efficacy of sertraline[135] and paroxetine[136] in treating obsessive behaviour in HGD. Olanzapine[137] has level-III evidence for obsessions in HGD, according to a prior publication.Anxiety, on the other hand, was reported in a case report as being treated with diazepam and amitryptiline.[138] Propranolol was effective in treating hypomania in an HGD patient.[139]

3.3. Behavioral Disturbance

Increased irritation, loss of control, and violence are all likely indications of frontal lobe disfunction. Irritability as well as emotional dyscontrol are typical present in HGD patients as well as they can create significant disruption in their relations or alivecircumstances. Male patients' crime rates are much greater than those of their first-degree relatives and controls.[140] Haloperidol was successful in treating irritability, violent outbursts, and depression in a level II study (double-blind, crossover in 6 patients).[141] In two short level-III studies, olanzapine showed a significant improvement in the UHDRS mental subscores for sadness, anxiety, irritability, as well asobsessions.[142] No patients mentioned any negative consequences. Stewart claimed that propranolol was effective in treating aggression in one patient[143], despite the fact that he had previously written about the paradoxical aggressive effects of propranolol in a patient with HGD[144]; a similar case had previously been written up with pindolol.[145] Other case reports relate to buspirone[148], sertraline[146], fluoxetine[147],

and olanzapine with valproate.[148][149] However, a multimodality treatment plan is required for severe behavioural instability.[150] According to DSMIII-R criteria, 82 percent of HGD patients have one or more sexual disorders[151], most frequently sexual hypoactivity, however some people may display hypersexuality.The little information known on the management of hypersexuality in HGD comes from case reports. Leuprolide, a gonadotropin-releasing hormone agonist, was effectively used to treat a patient with HGD and exhibitionism.[152] Medroxyprogesterone was utilised by a different group to lessen hypersexuality.[153]

3.4.Anti Depressants

On non-depressed patients, antidepressant medications like fluoxetine were employed to assess their effectiveness. For a 4-month research, Como et al.[154] randomly assigned 30 non-depressed HGD patients to receive fluoxetine or a placebo for measuring the drug's clinical effect. The TFC has changed, and other ratings of cognitive, behavioural, and neurological alterations are also evident in the results. Fluoxetine was not demonstrated to significantly lessen these symptoms, despite the fact that there was a slight drop in agitation in the treatment arm.. There were no RCTs on the subject of treating depression in HGD patients. EthylEPA is another antidepressant in use. On ethylEPA, two multicenter RCTs were discovered. In neither trial—Puri et al.[155] nor HSG[156]—was ethyl-EPA proven to be more effective. For cognitive dysfunction, atomoxetine[157], creatine[158], as well as modafinil[159] have all been studied in RCTs. Latrepirdine (Kieburtzetal.,[160]) has been evaluated for cognitive, behavioural, and motor symptoms. Modafinil and latrepirdine exhibited only marginally good benefits, whereas atomoxetine and creatine had no positive effects.

3.5. Acetylcholinesterase inhibitors

Since cognitive decline is the HGD patient population's most prevalent symptom, antidementia medications such acetylcholinesterase inhibitors have been employed to treat these symptoms. Donepezil, the first acetylcholinesterase inhibitor utilised, was tested on 30 non-dementia HGD patients (with genetic confirmation or a family history of HGD).[161] Donepezil was given to the patients in two doses: 5 mg/day at first for 6 weeks, and then 10 mg/day for an next 6 weeks. 24 out of 30 patients When the trial was over, it shows no discernible difference between the active group as well as the placebo group in terms of chorea motor (UHDRS) scale, quality of life (Sickness Impact Profile), or cognitive ADAS.Negative effects were virtually evenly distributed between the two groups, with the exception of one study where the donepezil group had suicidal thoughts (two patients

reported suicidal ideation). The lack of dementia was one of the exclusion criteria, thus it was challenging to understand how the cognitive had improved.

8 patients having HGDas well as moderate to severe cognitive changes were selected for an open-label trial and donepezil 5 mg/day for the first six weeks and then 10 mg/day for the upcoming six weeks.[162] Due to this, a study on 50% of patients has recently been finished (Within 4 days of increasing the dose, four patients suffered adverse effects that included worsened chorea with more falls, severe diarrhoea, irritability, and anxiety). The motor UHDRS subcategories, including chorea, did not show any statistically significant improvement (Two patients experienced increasing chorea, which improved with medication removal in both cases). On 5 mg/day, 2 patients showed a little improvement in their memory as well as focus, but there was no statistically significant change between their baseline and 6-week neuropsychological test results. At 12 weeks, there weren't enough patients available to obtain statistical power that would have allowed for any analysis. Once the trial was over, just one patient was still taking donepezil.

In a potential, open-label, randomized, controlled research, rivastigmine was examined in 21 individuals with genetically proven HGD.[163] Additionally, they either got no therapy at a 2:1 ratio for 2 months or rivastigmine at a dosage of 1.5 mg twice daily for the first 2 months, escalating to 3 mg twice daily for the next 6 months. They were then continuously evaluated until the end of the study using the TFC score, AIMS score, and MMSE, with the clinical evaluation performed on a blinded rate basis. One patient left the study early due to side symptoms (nausea and diarrhoea), while the other three participants were not found. However, patients who were randomly allocated to the rivastigmine group saw a statistically significant 1-point improvement on the MMSE in comparison to the control group (p 0.05).Although marginally significant in clinical practise, the difference does not justify the use of this medicine for HGD patients. The other assessments showed no change.

Over a two-month period, the same patient's TFC and MMSE scores revealed improvement in the treated group against a trend toward decrease in the untreated group..The untreated group's AIMS scores dramatically degraded in comparison to scores in the active group, which shown a considerable reduction in the involuntary movements in a prior assessment at 12 months. The untreated group's AIMS scores considerably declined as compared to the active group's scores, which revealed a considerable reduction in the involuntary movements in a prior assessment at 12 months.

Galantamine was given as a substitute drug after a month of therapy with haloperidol decanoate for an acute psychotic episode.[164] A dosage (24 mg/day) was administered to a 35-year-old man with genetically determined HGD, and it was shown to treat both the chorea and the psychotic symptoms.. The ability to think clearly was unaffected. The medication was favourably received.

Acetylcholinesterase inhibitors do not have a specific prescription for the management of HGD since their usage in treatment did not significantly alleviate motor symptoms, cognitive decline, or have a significant impact on patients' everyday life. However, the treated group shows more favourable motor results in HGD when compared to the control group.

After receiving haloperidol decanoate medication for a severe psychotic episode for a month, galantamine was administered as a replacement medication.[164] It was administered to a 35-year-old man with genetically determined HGD in a dosage (24 mg/day), which was seen to reduce both the chorea and the psychotic symptoms.The ability to think clearly was unaffected. The medication was favourably received.

Because the treatment of HGD with acetylcholinesterase inhibitors did not significantly improve the motor symptoms or cognitive impairment or have a major influence on patients' daily lives, these medications do not have a particular indication for the management of this disease refer fig 4.

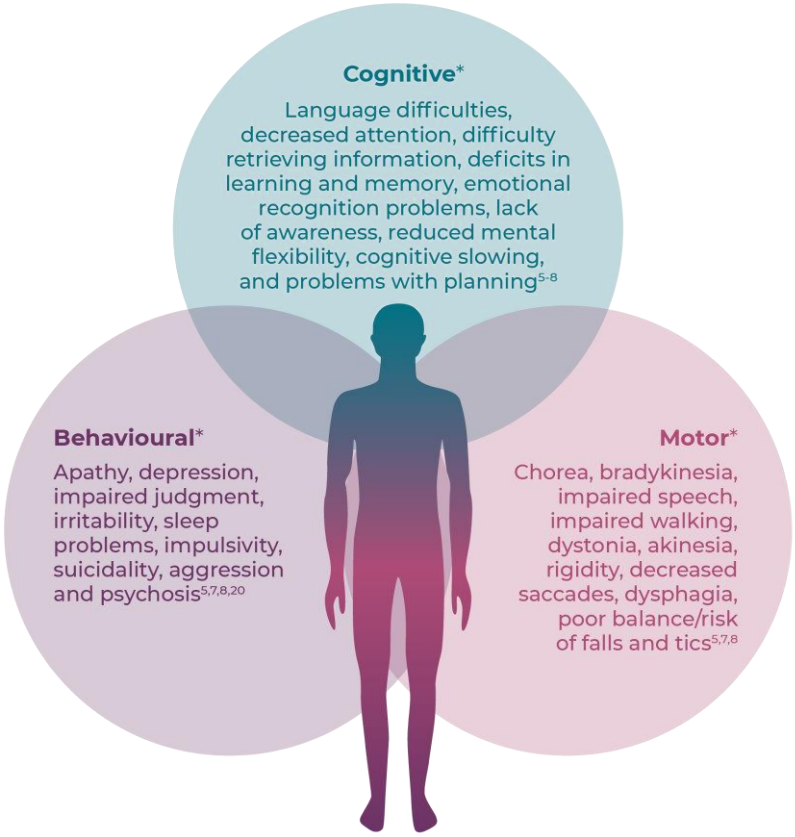

Figure 4: Since each person experiences these symptoms differently, HD is frequently challenging to diagnose. This indicates that patient treatment can sometimes be difficult, and a multidisciplinary approach could aid in better illness management.

3.6. Psychiatric Symptoms

Neuropsychological tests evaluating executive function reveal a much larger deficit in HGD patients with obsessive or compulsive symptoms compared to individuals without these symptoms. Sertraline[165] and paroxetine[166] have been proven to be effective at reducing obsessive behaviour in HD in two case studies. Olanzapine[167] for obsessions in HD has Level-III evidence, as was previously indicated. On the other hand, amitryptiline and diazepam[168] were described as effective treatments for anxiety in a case report. Taking propranolol helped an HD patient who had hypomania.[169]

4. Neuroprotective Treatment Strategies

Understanding of the illness process has increased as a result of the HGD gene's discovery nas well as huntingtin, its byproduct, which also opened up new therapeutic avenues.[170] Some of these problems have recently been resolved in research employing transgenic mice and Drosophila, giving optimism for the discovery of therapeutic targets.[171] Up until now,

the majority of neuroprotective research have used treatments that reduce or modify glutamatergic neurotransmission, improve bioenergetic systems, or have antioxidative effects.[172] Based on evidence showing that creatine, like coenzyme Q10, increased mitochondrial oxidative processes lacking in HGD as well as being inspired by hopeful results in the transgenic mouse model, Tabrizi and colleagues undertook an open label study utilising creatine on nine HGD patients.[173] Using TMS, functional capacity scores, or cognitive assessments, the UHDRS) did not significantly worsen after 24 months of creatine therapy, which is actually what should be anticipated after 2 years. Bender et al. found no motor effects in a subsequent brief level IIIresearch but did see aalteration in brain metabolite levels after 8 weeks of therapy as determined by proton magnetic resonance spectroscopy.[174] Unfortunately, further results from a level II (non-randomized) 1-year double-blind placebo-controlled trial of creatine in 41 patients with HGD (stage I through III) have been found.[175] Between the start of the experiment and its conclusion, both groups saw a drop in functional UHDRS scores, maximal static torque, and peak oxygen intake.. In two brief, quick, double-blind, placebo-controlled investigations, extremely unsaturated fatty acids were shown to be supportive.[176] The rationale was based on how cell membranes operate, which may have an effect on a cell's propensity to go through apoptosis and may be helpful in reducing the rate of neuronal cell death in HGD both inside and outside the striatum.[177] However, given that just three and nine patients, respectively, were treated, these findings should be regarded with care..Unfortunately, a Level-I study with 61 HGD patients that was just published contradicts these earlier findings.[178] According to the researchers, there was no noticeable difference between the placebo and unsaturated fatty acids on the motor score.. However, certain subanalyses offer cause for optimism. However, far more extensive level I research are in progress. Minocycline, an inhibitor of caspase and neuronal apoptosis, has been demonstrated to decrease disease progression and increase lifespan by 14% in the R6/2 transgenic mouse model of HGD.[179] The first open-label pilot study on minocycline in HGD was completed after six months.[180] revealed a considerable improvement in a number of motor and cognitive markers.Contrary to what the predicted natural course of HGD predicts, patients showed stability in overall motor and cognitive performance at endpoint after 2 years.[181] Furthermore, after 24 months, there had been a considerable improvement in the patient's psychological problems. In contrast, a level III trial with a comparable design was unable to detect any impact after six months.[182] In the USA, level I clinical research is now being carried out, and revealed minocycline to be harmless and well tolerated in HGD patients.[183] Before beginning long-term neuroprotective trials, it is important to do proper safety and

tolerability tests, as highlighted by an intriguing case study involving many people who received OPC-14117. On free-radical scavengers, two further label I clinical studies have been conducted. A one-year, placebo-controlled study of alphatocopherol in 73 HGD patients (n=40 on the active medication) failed to demonstrate any improvements. Idebenone, an antioxidant, did not slow the course of HGD in 91 HGD patients (n=48 on active medication) in a label I study conducted over a year. Anti-glutaminergic tactics were tried in three label-Ia trials. Baclofen and lamotrigine are thought to lessen glutamate neurotransmission by blocking the release of corticostriatal glutamate. However, a baclofen trial in 60 individuals for up to 42 months and a placebo-controlled study of lamotrigine[184] in 64 patients were both followed for 30 months.both failed to demonstrate any advantage for slowing the development of the functional loss in HGD.Remacemide, a glutamate antagonist, and coenzyme Q10, an activator of bioenergetics, were both investigated After remacemide was deemed safe in a safety level I trial, the Huntington Study Group conducted two level III open-label investigations.[186] The researchers carried out a double-blind, randomised, 2 x 2 factorial, multicenter clinical study. 347 HGD patients were randomly assigned to receive either coenzyme Q10 300 mg twice day, remacemide hydrochloride 200 mg three times daily, both drugs, or none. For a total of 30 months, patients underwent frequent evaluations every four to five months. Coenzyme Q10 users, however, had a trend in that way, despite the fact that neither intervention appreciably slowed the UHDRS's reduction in overall functional capacity.

CONCLUSION

Huntington's disease has a genetic basis, a diagnosis, symptoms, and a treatment regimen. It is an inherited autosomal dominant syndrome. Testing for the HGD gene can reveal the hereditary nature of this incurable disease. The illness is diagnosed using both physical and mental symptoms, such as uncontrollable jerking and writhing movements. There is still a rapidly expanding field of investigation even though there is now no therapy to address the sudden rise in chorea and behavioural disturbance. However, new technical developments that allowed researchers to locate and understand the disease-causing gene provide a great deal of hope for the future therapy.

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