The Pharmacological Therapies of Huntington's Chorea

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Huntington's Disease (HD) is an autosomal, dominantly inherited neurodegenerative disorder caused by an expansion of the CAG repeat in the huntingtin (HTT) gene. The disease generally manifests during mid-life and is clinically characterized by involuntary movements (chorea), psychiatric and behavioral symptoms, and cognitive decline. To this date, no cure or disease-modifying therapy exists. However, a wide variety of pharmacological therapies are used to improve quality of life.

Keywords: Huntington's Disease ; pharmacological therapies ; Tiapride

1. Introduction

Huntington's Disease (HD) is an autosomal, dominantly inherited neurodegenerative disorder caused by an expansion of the CAG repeat in the huntingtin (HTT) gene [1][2]. The disease generally manifests during mid-life and is clinically characterized by involuntary movements (chorea), psychiatric and behavioral symptoms, and cognitive decline [3][4][5]. To this date, no cure or disease-modifying therapy exists [6][7]. However, a wide variety of pharmacological and non-pharmacological therapies are used to improve quality of life [7][8][9][10][11][12].

Traditionally, dopamine-blocking agents have been used to treat chorea [13][14]. Haloperidol, developed in the mid-20th century, was one of the first treatments [15][16][17]. In the mid-1980s, tiapride became available [18][19]. Tiapride was originally developed to counteract abnormal involuntary movements in various disorders [20][21][22]. Tiapride is marketed under various brand names, such as tiapridal, tiaprida, hipokin, sereprile, and tiaprid, and is highly affordable at approximately €0.55/day for 200 mg [23][24]. As an antipsychotic and benzamide derivate, tiapride acts by selectively blocking dopamine D_2- and D_3-receptors [25][26]. Blocking these dopamine receptors improves the regulation of behavioral, sleep, and motor function disturbances [26][27]. Therefore, tiapride is appealing to prescribe in clinically heterogeneous movement disorders such as HD and has been widely prescribed by European HD experts over the last 40 years [28][29][30].

In March 2020, Sanofi S.A. withdraw tiapride from the Dutch market abruptly [31]. This was the only company that supplied this medicine, which was covered by health insurance, in the Netherlands [31][32]. No major safety concerns were reported, whereas many HD patients reported benefits from tiapride [28][33]. The unexpected and sudden shortage of tiapride caused much distress among patients and their caregivers, as illustrated by three representative cases below [34]. Pharmacological alternatives, which had to be introduced quickly, were not always suitable and led to disease aggravation or (severe) side effects in several patients.

2. Safety and Side-Effect Profile of Tiapride

Treatment with tiapride is generally well tolerated, particularly in HD patients (**Table 1**). Side effects are often rare and mild. After four decades of tiapride use in clinical practice, the most reported (in 1–10% of patients) side effects are somnolence, apathy, agitation, and during the beginning of treatment, rigidity, hypokinesia, and hypersalivation [19][24][35][36][37][38]. Less commonly (0.1–1%) reported side effects are akathisia and symptoms that are a consequence of elevated prolactin levels, such as gynecomastia, galactorrhea, and weight increase [24][36][37]. For detailed descriptions of rare side effects, please refer to the package leaflet [39]. In VigiAccess, 1897 reports of suspected potential side effects were present since tiapride became available. This is a relatively small number of reports considering that tiapride has been available for over four decades and is also used in psychiatric patients. Only those symptoms that were reported 25 times or more (arbitrarily chosen) and that are not otherwise mentioned in the patient leaflet are listed here: confusional state (*n* = 94), hyponatremia (*n* = 36), urinary retention (*n* = 34), loss of consciousness (*n* = 33), bradycardia (*n* = 27), thrombocytopenia (*n* = 26), increased serum creatine phosphokinase (*n* = 26), aspiration pneumonia (*n* = 26), and rash (*n* = 25). Simultaneous use of tiapride with antidepressants, benzodiazepines, analgesics, opiates, or alcohol might increase

its sedative side effects [24]. Simultaneous use of tiapride with substances that might prolong QT-interval, such as class IA and III antiarrhythmic agents, domperidone, haloperidol, and pimozide, should be avoided [39].

3. Expert Opinions

Three expert surveys were included in here. Two studies focused on pharmacological chorea control [28][40]. One article summarized preferred treatment options for irritability in HD [29]. A summary of the included expert opinions can be found in **Table 1**. The survey with the most respondents (*n* = 200) was conducted among USA neurologists and describes pharmacological treatment options for HD [40]. At the time of publication, solely tetrabenazine was FDA-approved for HD chorea control. Tiapride was and is still not available in North America. However, 54% of respondents perceived tetrabenazine as having minimal or no effectiveness in suppressing HD chorea. Antipsychotics (26%) and amantadine (9.3%) were reported as off-label alternatives. The most commonly prescribed antipsychotics were risperidone (6.9%), quetiapine (6.7%), and haloperidol (5.8%). Burgunder et al. conducted a multinational survey among North American, European and Australian physicians [28]. Regional differences were visible since respondents from North America and Australia equally favored off-label antipsychotics (58%) or tetrabenazine (56%), while European respondents evidently preferred antipsychotics (87%) and specifically tiapride (50%) as initial monotherapy. Tetrabenazine was considered an alternative monotherapy by 67% of European respondents. All experts preferred antipsychotic monotherapy when comorbid behavioral symptoms were present. A combination of tetrabenazine and an antipsychotic was prescribed when symptoms were inadequately controlled by monotherapy. Efficacy and side-effect profiles were considered similar for antipsychotics and tetrabenazine, except that depression is more prevalent in the latter.

Table 1. Summary of included expert surveys.

Reference	*n* Respondents	Practice Based in	HD Symptom	Initial Monotherapy without Comorbidities Present	Side Effects of Tiapride
Sung et al., 2018 [40]	200	100% USA	Chorea	Respondents preferred tetrabenazine (50%). Antipsychotics (26%) were considered off-label alternatives.	NA *
Burgunder et al., 2011 [28]	52	42% EU 54% USA/Canada 4% Australia	Chorea	Worldwide respondents preferred antipsychotics (58%) as a first choice, and tetrabenazine (56%) as an alternative monotherapy. Fifty percent of EU respondents preferred tiapride. * Risperidone (43%) and olanzapine (39%) were also preferred. ×	Sedation, Parkinsonism
Groves et al., 2011 [29]	55	47% EU 49% USA/Canada 4% Australia	Irritability	Respondents preferred an SSRI (57%) as first choice, and antipsychotics (31%), mirtazapine (28%), or anti-epileptic drugs (27%) as alternative monotherapy. Twenty-seven percent of EU respondents preferred tiapride. *	None reported

Legend: * Tiapride is not available in North America; × The total is more than 100% since each respondent could check more than one option.

One expert opinion focused on the pharmacological treatment of irritability [29]. Worldwide respondents preferred antipsychotics (77%) for severe aggression. In case of milder irritability symptoms, SSRIs (57%), antipsychotics (31%), and mirtazapine (28%) were endorsed. Olanzapine, risperidone, and, to a lesser extent, tiapride are specific drugs from the antipsychotic class that were favored. None of the studies reported sex differences in tiapride treatment response [28][29][40].

References

1. MacDonald, M.E.; Ambrose, C.M.; Duyao, M.P.; Myers, R.H.; Lin, C.; Srinidhi, L.; Barnes, G.; Taylor, S.A.; James, M.; Groot, N.; et al. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 1993, 72, 971–983.
2. Caron, N.S.; Wright, G.E.B.; Hayden, M.R. Huntington Disease. In GeneReviews(®); Adam, M.P., Ardinger, H.H., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Gripp, K.W., Mirzaa, G.M., Amemiya, A., Eds.; University of Washington: Seattle, WA, USA, 1993.

3. Folstein, S.E.; Folstein, M.F. Psychiatric features of Huntington's disease: Recent approaches and findings. Psychiatr. Dev. 1983, 1, 193–205.
4. Roos, R.A.C. Clinical neurology. In Huntington's Disease, 4th ed.; Bates, G.P., Tabrizi, S.J., Jones, L., Eds.; Oxford University Press: New York, NY, USA, 2014; pp. 25–35.
5. Baake, V.; Reijntjes, R.; Dumas, E.M.; Thompson, J.C.; Roos, R.A.C. Cognitive decline in Huntington's disease expansion gene carriers. Cortex 2017, 95, 51–62.
6. Rook, M.E.; Southwell, A.L. Antisense Oligonucleotide Therapy: From Design to the Huntington Disease Clinic. BioDrugs 2022.
7. Ferreira, J.J.; Rodrigues, F.B.; Duarte, G.S.; Mestre, T.A.; Bachoud-Levi, A.C.; Bentivoglio, A.R.; Burgunder, J.M.; Cardoso, F.; Claassen, D.O.; Landwehrmeyer, G.B.; et al. An MDS Evidence-Based Review on Treatments for Huntington's Disease. Mov. Disord. 2022, 37, 25–35.
8. Coppen, E.M.; Roos, R.A. Current Pharmacological Approaches to Reduce Chorea in Huntington's Disease. Drugs 2017, 77, 29–46.
9. Bilney, B.; Morris, M.E.; Perry, A. Effectiveness of physiotherapy, occupational therapy, and speech pathology for people with Huntington's disease: A systematic review. Neurorehabil. Neural Repair 2003, 17, 12–24.
10. Nance, M.A. Comprehensive Care. In Huntington's Disease, 4th ed.; Bates, G.P., Tabrizi, S.J., Jones, L., Eds.; Oxford University Press: New York, NY, USA, 2014; pp. 393–409.
11. Quinn, L.; Kegelmeyer, D.; Kloos, A.; Rao, A.K.; Busse, M.; Fritz, N.E. Clinical recommendations to guide physical therapy practice for Huntington disease. Neurology 2020, 94, 217–228.
12. Zarotti, N.; Dale, M.; Eccles, F.; Simpson, J. Psychological Interventions for People with Huntington's Disease: A Call to Arms. J. Huntington's Dis. 2020, 9, 231–243.
13. Cepeda, C.; Murphy, K.P.; Parent, M.; Levine, M.S. The role of dopamine in Huntington's disease. Prog. Brain Res. 2014, 211, 235–254.
14. Bashir, H.; Jankovic, J. Treatment options for chorea. Expert Rev. Neurother. 2018, 18, 51–63.
15. Buis, C.; Flohil, J.M. CLINICAL EXPERIENCES WITH HALOPERIDOL (SERENASE). Ned. Tijdschr. Geneeskd. 1964, 108, 796–800.
16. Koller, W.C.; Trimble, J. The gait abnormality of Huntington's disease. Neurology 1985, 35, 1450–1454.
17. Siegel, G.J.; Mones, R.J. Modification of choreiform activity by Haloperidol. JAMA 1971, 216, 675–676.
18. Chouza, C.; Romero, S.; Lorenzo, J. Clinical trial of tiapride in patients with dyskinesia. Sem. Hop. 1982, 58, 725–733.
19. Deroover, J.; Baro, F.; Bourguignon, R.P.; Smets, P. Tiapride versus placebo: A double-blind comparative study in the management of Huntington's chorea. Curr. Med. Res. Opin. 1984, 9, 329–338.
20. Roos, R.A.C.; de Haas, E.J.M.; Buruma, O.J.S.; de Wolff, F.A. Pharmacokinetics of tiapride in patients with tardive dyskinesia and Huntington's disease. Eur. J. Clin. Pharmacol. 1986, 31, 191–194.
21. Eggers, C.; Rothenberger, A.; Berghaus, U. Clinical and neurobiological findings in children suffering from tic disease following treatment with tiapride. Eur. Arch. Psychiatry Neurol. Sci. 1988, 237, 223–229.
22. Lněnicka, J.; Stará, V. The therapeutic effect of tiapride in the treatment of dyskinetic forms of cerebral palsy in children. Cesk. Pediatr. 1992, 47, 670–672.
23. Tiapride. Available online: https://www.drugs.com/international/tiapride.html (accessed on 11 February 2022).
24. Farmacotherapeutisch Kompas. Tiapride. Available online: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/t/tiapride (accessed on 20 July 2020).
25. National Center for Biotechnology Information. PubChem Compound Summary for CID 5467, Tiapride. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Tiapride (accessed on 4 September 2020).
26. Dose, M.; Lange, H.W. The benzamide tiapride: Treatment of extrapyramidal motor and other clinical syndromes. Pharmacopsychiatry 2000, 33, 19–27.
27. Steele, J.W.; Faulds, D.; Sorkin, E.M. Tiapride. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in geriatric agitation. Drugs Aging 1993, 3, 460–478.
28. Burgunder, J.M.; Guttman, M.; Perlman, S.; Goodman, N.; van Kammen, D.P.; Goodman, L. An International Survey-based Algorithm for the Pharmacologic Treatment of Chorea in Huntington's Disease. PLoS Curr. 2011, 3, RRN1260.
29. Groves, M.; van Duijn, E.; Anderson, K.; Craufurd, D.; Edmondson, M.C.; Goodman, N.; van Kammen, D.P.; Goodman, L. An International survey-based algorithm for the pharmacologic treatment of irritability in Huntington's disease. PLoS

Curr. 2011, 3, RRN1259.

30. Bachoud-Lévi, A.C.; Ferreira, J.; Massart, R.; Youssov, K.; Rosser, A.; Busse, M.; Craufurd, D.; Reilmann, R.; de Michele, G.; Rae, D.; et al. International Guidelines for the Treatment of Huntington's Disease. Front. Neurol. 2019, 10, 710.
31. Van Ark, T. Regulation of the Minister for Medical Care of January 22, 2021, Reference 217289-1815434-Z, Amending Annexes 1 and 2 of the Health Insurance Scheme in Connection with the Change in the Entitlement to Registered Medicines; Staatscourant: The Hague, The Netherlands, 2021; p. 17.
32. Zorginstituut Nederland. Reimbursement per DDD 2016-2020 for ATC-subgroup N05AL03: Tiapride. Available online: https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel_g_00-totaal=B_01-basis&tabel_h_00-totaal=B_01-basis&geg=vg&spec=vg_ddd&item=N05AL03 (accessed on 16 March 2022).
33. Lindquist, M. VigiBase, the WHO Global ICSR Database System: Basic facts. Drug Inf. J. 2008, 42, 409–419.
34. Vereniging van Huntington. . Available online: https://www.huntington.nl/nieuws/682-oproep-tot-actie-tiapridal-is-van-de-markt-gehaald.html (accessed on 16 March 2022).
35. Girotti, F.; Carella, F.; Scigliano, G.; Grassi, M.P.; Soliveri, P.; Giovannini, P.; Parati, E.; Caraceni, T. Effect of neuroleptic treatment on involuntary movements and motor performances in Huntington's disease. J. Neurol. Neurosurg. Psychiatry 1984, 47, 848–852.
36. Mathe, J.F.; Cler, J.M.; Venisse, J.L. Therapeutic use of tiapride in movement disorders. Sem. Hop. 1978, 54, 517–520.
37. Petit, H. Les indications du Tiapride en pathologie extrapyramidale. Lille Med. 1979, 24, 339–344.
38. Roos, R.A.C.; Buruma, O.J.S.; Bruyn, G.W. Tiapride in the treatment of Huntington's chorea. Acta Neurol. Scand. 1982, 65, 45–50.
39. Sanofi Winthrop Industrie. Tiapridal (Tiapride) ; Sanofi Winthrop Industrie: Quetigny, France, 2013.
40. Sung, V.W.; Iyer, R.G.; Gandhi, S.K.; Shah-Manek, B.; DiBonaventura, M.; Abler, V.; Claassen, D.O. Physician perceptions of pharmacologic treatment options for chorea associated with Huntington disease in the United States. Curr. Med. Res. Opin. 2018, 34, 643–648.