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Review

Effects of Exercise Environment and Protocol Intensity on the Efficacy of Rehabilitation Care for Patients with Huntington's Disease: A Comprehensive Review

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ABSTRACT

International Journal of Exercise Science 12(3): 456-470, 2019. Huntington's disease (HD) is a neurodegenerative disease caused by astrogliosis of the putamen and caudate nucleus. Motor symptoms include progressive chorea, leading to deficits in gait, motor function, and quality of life. While many studies have examined the effects of therapeutic exercise on these factors in individuals with HD, the efficacy of such protocols has yet to be analyzed. Purpose: The purpose of this review is to analyze trends in efficacy reported by studies examining the effects of exercise on motor function, gait quality, and quality of life in individuals with HD. Methods: A literature search was performed by the primary author in September 2017. Databases include PubMed, Google Scholar Article Library, and The Cochran Article Library. Results: Though there is intrinsic variability between studies, therapeutic outcomes can be compared between settings and protocols. The increases in exercise duration/frequency and utilization of multiple supervised rehabilitation modalities in clinical/intensive inpatient-based programs resulted in greater function and psychological improvements in individuals with HD compared to those in the home/community-based programs. However, the adherence rates of high-intensity, multi-disciplinary protocols are lower than less intensive regimens. Conclusion: The results of this review suggest that rehabilitation exercise protocols held in a clinical and moderately intensive inpatient setting may provide the greatest functional and psychological outcomes for those with HD as evidenced by consistent patient benefit and high adherence rates. Furthermore, the high physical and time demands of high-intensity protocols may make them less practical than less intensive protocols, though more study is needed for confirmation.

KEY WORDS: Huntington's Disease, rehabilitation, exercise

INTRODUCTION

Huntington's disease (HD) is a multimodal, autosomal dominant neurodegenerative disease caused by a repeated CAG expansion in the IT15 gene of the short arm of chromosome 4, also known as the Huntington's gene (19, 43). Clinical presentations of HD are caused by astrogliosis and neuronal degeneration of the putamen and caudate nucleus (9, 39). Psychomotor symptom presentation typically begins during the third and fourth decade of life and is commonly characterized by a combination of progressive cognitive, behavioral, and motor dysfunction.

(7,44). The most common motor dysfunction characteristics associated with HD are chorea and dystonia, causing deficits in gait, motor function, and balance (4, 23). These psychomotor deficiencies progress to cause choreic involuntary movements, weight loss, slowness of voluntary movement, increased fall risk, impaired activities of daily living, and a lower quality of life (QoL) (12, 17).

Motor disturbances associated with chorea have earlier onset in less physical activity individuals with HD (42). Many studies have shown the benefits of exercise and environmental enrichment in HD animal models (26, 37), as well as in similar neurodegenerative diseases (11, 33, 36). Pharmacological intervention for the treatment of HD has yielded mixed results, with the majority of treatment focusing on physical symptom relief (38). While in general, physiotherapy and rehabilitation techniques utilized to assuage the symptoms of HD most commonly take place in a specialized therapeutic facilities, home-base exercise programs have shown to aid in the engagement and self-management of those with neurological injury and disease (21,25).

Within the past 5 years, many studies have been published studying the effects of exercise on balance, gait, and motor function in individuals with HD. However to date, no review has been published on the trends found in these studies as a whole. Previous reviews either pre-date the majority of these new studies, or consist of primarily abstract-form study information (2,4). The purpose of this review is to analyze the trends in efficacy reported by clinical and non-clinical studies on the effects of exercise on balance, motor function, gait quality, QoL in individuals with HD. Specifically, the intent of this review is to examine the differences in therapeutic environment and protocol of these studies as a whole, and explore the effectiveness of each to improve motor, balance, and QoL in patients with HD. This review includes studies performed in both clinical and in-home settings, as well as studies that utilized a wide range of therapeutic modalities including traditional physiotherapy, community-based exercise, multidisciplinary intensive rehabilitation, and DVD/video game-based exercise.

METHODS

Search Strategy: The literature search was performed by the primary author in September 2017. Databases include PubMed (1975 to September 2017), Google Scholar Article Library (1975 to September 2017), and The Cochran Article Library (1975 to September 2017). Searched keywords include: Huntington('s) disease/Huntington('s) chorea and physiotherapy or therapy or physical therapy or rehabilitation or gait or robotic or exercise or walking or body-weight supported treadmill training or aquatic or sports or activity or intensive or home-based or balance or treadmill or quality of life or activities of daily living or ergometry. Synonym and thesaurus suggestions were used in this literature search when recommended by the searched databases. Inclusion Criteria: 1) Articles and studies must include a physical activity-based intervention or measurement thereof, either supervised or unsupervised by a medical professional, with at least one measured variable outcome characterizing motor, proprioception, or QoL. 2) All or a substantial amount of study participants had received a diagnosis of HD with no preference given to the amount of CAG repeats in participants. 3) Utilization of a performance or status measurement that has been shown accurate in the disabled population. Exclusion Criteria: 1) Studies solely examining the use of leisure-based activities or activities not regularly associated with eliciting an excitatory cardiorespiratory response in the participant (i.e. meditation, yoga, etc.), or increases in metabolic status. 2) Studies not published in the English language. 3) Studies only published in abstract form. Some relevant studies were excluded from this review due to low subject number or an insufficient description of the therapeutic protocol utilized. (20, 27, 34).

A total of 9 studies resulted after inclusion and exclusion criteria were added, and these studies are analyzed in this review. Given the extensivity of the keywords searched over 3 large-scale research databases, considerable result overlap occurred in the resulting found articles. Due to this overlap, a total number of the resulting searched articles can not be accurately reported.

RESULTS

Functional Effects of Home- and Community-Based Exercise Programs for HD: There are many cognitive and motivational factors that play a role in the adherence of individuals with HD to supervised exercise programs (30). Similar to individuals with other neurological injury and disease, the adherence of individuals with HD to an exercise plan tends to decrease rapidly after cessation of clinical or professional supervision (5). Home-based, audio-visually-aided (DVD/videotape) exercise programs have shown to increase both the performance and adherence of healthy individuals and those with HD (14, 16, 31, 45). Though some reviewed studies utilized exercise protocols taking place within an outpatient clinic, the following studies were categorized as "home-based" or "community-based" due to the majority of the time spent exercising having taken place in the residence of the participant, or in a community-oriented exercise facility. A total of 4 studies analyzing, with exercise protocols ranging from in-home audio/video aided exercise to supervised exercise in a community setting were found and included. All included studies reporting on home- and community-based exercise programs are included in Table 1.

A study performed by Khalil et al. examined the effects of a home-based exercise program in 25 subjects with early to mid-stage Huntington's disease (13). Participants were randomly divided into an exercise group (n=13, mean age 54.2+9.9, Unified-Huntington's-Disease-Rating-Scale-Total-Motor-Score (UHDRS-TMS) [31] 51.6+15.9) and control group (n=12, mean age 51.3+16.9, UHDRS-TMS 50.5+19.3). Participants in the exercise group completed 8 weeks of 3x/week in-home exercise using a specifically designed exercise DVD in addition to 1 light-intensity walk per week for a maximum of 30 minutes. This DVD was created in accordance with physiotherapist-recommended exercise routines, and was prescribed specifically for individuals with HD. Though the study authors did not specify the length of time of the DVD exercise sessions, each session contained various exercises to help flexibility, balance, strength, and coordination. Exercise protocols were regularly monitored and augmented to adjust to new participant abilities (14). Participants in the control group were instructed not to change their physical activity or exercise routines during the course of the study. Post-study results revealed that, compared to the control group, the exercise group showed statistically significant improvements in gait speed (m/s), balance as assessed by the Berg Balance Scale (BBS), and functional activity as assessed by the 30 Second Chair Sit to Stand Test (30SCSST) and the Physical Performance Test (PPT) (15). No significant between-group difference were observed in healthy-related quality of life. No improvements were shown in any variable for the control group.

Table 1. SS: Statistically Significant, H-B: Home-Based, C-B: Community-Based, NCPA: No Change in Physical Activity, OPC: Out-Patient Clinic, E vs. C: Exercise Group compared to Control Group, E vs. B: Exercise Group compared to Control Group, LTF: Lost to Followup.

Table 1		**Home and Community-Based Exercise Protocols**			
Study Ref.	**Setting**	**Exercise Protocol**	**Participants**	**Improvements** (Test/measurement) *Only SS results shown*	**Adherence Rate**
Khalil 2013 (13)	H-B C-B	**Exercise:** DVD: 8 wks, 3x/wk Walking: ≤ 30 min. walk 1x/wk. **Control:** NCPA	**Exercise:** n=13, age: 54.2±9.9, UHDRS-TMS: 51.6±15.9 **Control:** n=12, age 51.3±16.9, UHDRS-TMS: 50.5±19.3	**<u>E vs. C</u>** **Exercise:** Gait Speed (m/s) Balance (BBS) Functional Activity (30SCSST, PPT)	**Exercise:** 11/13 completed 2 LTF Mean Adh: 29.4±1.8 of 32 sessions (72% completed 80% of sessions) **Control:** 10/12 completed. 2 LTF
Thompson 2013 (40)	H-B OPC	**Exercise:** Supervised-OPC Therapy: 9 months, 1x/wk Unsupervised H-B Exercise: 6-months, 3x/week OT: 2x/month (all at same time) **Control:** NCPA	**Exercise:** n=9, age 53.8 ± 2.9 UHDRS-TMS: ≤ 5 **Control:** n=11, age 52.2 ± 2.6 UHDRS-TMS: ≤ 5	**<u>E vs.C</u>** **Exercise:** Upper/lower body strength and fat-free mass (DEXA) Up- and down-stair walking ability (ABC)	**Exercise:** 85% OPC therapy 56% H-B Exercise
Busse 2012 (6)	H-B C-B	**Exercise:** Supervised C-B aerobic and strength training: 12 wks, 1x/wk Unsupervised Walking: 12 wks, 2x/wk, ≥ 10 min. **Control:** NCPA	**Exercise:** n=16, age 53.3±12.5, UHDRS-TMS: 32.4 ± 15.5 **Control:** n=15, age 47.4 ± 9.5, UHDRS-TMS: 35.2 ± 20.5	**<u>E vs.C/E vs. B</u>** No SS differences	**Exercise:** 9/16 completed 5 LTF 2 left mid-study **Control:** 13/15 completed 2 LTF **Total** 71% completed study.
Kloos 2013 (18)	H-B	**Exercise:** Unsupervised Video game-based Exercise: 6 wks, 2x/wk **No Control Used**	**Exercise:** n=18, age 50.7 ± 14.7 UHDRS-TMS: 6-65 (no mean given) **Control:** N/A	**<u>E vs. B</u>** Dynamic balance while walking (GAITRite)	**Exercise:** 18/18 completed 100% sessions

A similar study was performed by Thompson et al. examining the effects of a multidisciplinary and dual-environment exercise protocol consisting of both supervised clinical and unsupervised at-home exercise sessions (40). In this study, 20 patients with UHDRS-TMS of > 5 were matched based on functional and cognitive ability, and divided into a control group (n=11, mean age 52.2 + 2.6) or an exercise group (n=9, mean age 53.8 + 2.9). The exercise group completed 9 months of 1x/week physiotherapist-supervised in-clinic exercise for 1 hour, during which these participants also completed 6-month of 3x/week unsupervised home-based exercise in accordance with therapist recommendations. Participants in the exercise group also received occupational therapy (OT) 2x/month during the same 6 months. No exercise program was given to the control group. Post-study results showed that compared to the control group, those in the exercise group showed significant improvements in upper/lower body strength and fat-free mass as measured by dual-energy X-ray absorptiometry (DEXA). Statistically significant improvements were also found in up- and down-stair walking ability as measured by the Activities-specific Balance Confidence scale (ABC) (29). Additionally, these results showed an attenuation of motor and balance loss in the exercise group compared to the control group. Only minor and statistically insignificant improvements in depression and QoL were seen in either group and were reported to be associated with functional improvements.

One study by Kloos et al. investigated the therapeutic effects of participation of individuals HD in home-based video game play (Dance Dance Revolution) (18). This game play requires the participant to respond to both visual and rhythmic cues by moving their body as directed by the game. Successful execution of these cued movements incorporates attentional strategy, balance training, synchronized/multidirectional stepping, and biofeedback. The 18 participants in this study had a UHDRS-TMS of 6-65 (no mean given), and an average age of 50.7 + 14.7. The home-based game play was performed 2x/week for 6 weeks and was supervised via weekly participant phone calls and electronic session data monitoring. No control group was used in this study. Post-study results showed significant improvement in dynamic balance while walking, however no significant improvements were seen in balance confidence, functional mobility, or quality of life.

With community integration and social activity participation both being large known effectors of QoL in the disabled population, the community integration of an exercise protocol may play a key role in both psychological and physiological therapeutic outcomes. A study performed by Busse et al. tested the cognitive and functional effects of integrating a physiotherapist-supervised community-based exercise program with an in-home walking-program for individuals with HD (6). In this study, 31 participants were divided into a control group (n=15, mean age 47.4 + 9.5, UHDRS-TMS 35.2 + 20.5) who did not participate in study specific exercise, and an exercise group (n=16, mean age 53.3 + 12.5, UHDRS-TMS 32.4 + 15.5) who participated in 12 weeks of a dual-environment exercise program. This exercise program consisted of weekly aerobic and resistance training at a local community-based gymnasium and supervised by an exercise physiologist, in addition to a twice weekly at-home unsupervised, self-directed walking program. All aerobic and resistive exercise was progressive in nature, augmented to the ability of each participant, and were performed for a maximum of 30 minutes for each aerobic exercise session. Supervised aerobic exercise was performed at 55%-75% of the participants' agepredicted maximum heart rate (APMHR) and resistive exercise repetitions were performed at 60%-70% of the 1 repetition maximum (1RM) of each participant. Post-study results showed statistically insignificant improvements or attenuation of loss in the exercise group compared to the control group in tests of walking distance and standing balance. Only one of multiple QoL assessment subsets, the mental component summary, showed statistically significant improvement after group comparison, and thus will be omitted from Table 1.

Functional Effects of Moderate to Intensive Inpatient/Clinic-Based Exercise Programs for HD: Of all of the therapies and protocols utilized for patients with HD, intensive in-patient therapies show the most promise. As can be seen from the studies analyzed in this review, in-patient therapy often provides a patient a wide-variety of different therapeutic modalities, techniques, and technologies, as well as an opportunity for much needed patient progress monitoring. Differing from the previously examined studies, the following studies employ therapeutic protocols in which the patient performed the physical therapy protocol primarily or solely in an in-patient clinic environment, under constant supervision of a medical or rehabilitation professional. A total of 5 studies analyzing, with exercise protocols ranging from traditional physiotherapy to highly intensive supervised exercise in a clinical setting were found and included. All included studies reporting on intensive/clinic-based exercise programs are included in Table 2.

A recent study performed by Bohlen et al. examined the effects of 6 weeks of a twice weekly physical therapy program in an in-clinic environment for HD patients (n=12, mean age 52.2, UHDRS-TMS 41.4) (3). Each physical therapy session lasted approximately 1 hour and consisted of 40 minutes of supervised exercises specifically focusing on transfer and position changing, postural stability, gait training, and motor coordination, with 20 minutes reserved for pre-exercise warm-up and post-exercise relaxation. Gait performance and analysis was performed using a GAITRite mat (CIR Systems, Inc., Sparta, NJ, USA) (32). Post-study results showed that patients exhibited statistically significant improvements in % time of the gait cycle spent in two leg support, stride length, and gait speed. Additionally, statistically significant improvements were reported in Timed Up and Go test (TUG) and the BBS, however no significant improvements were shown in static stability as measure by force plate posturography or UHDRS-TMS scores.

Further study of the effects of in-clinic physical therapy utilizing proprioceptive neuromuscular facilitation (PNF) (1) for patients with HD was performed by Mirek et al. (24). In this study 30 patients with HD (mean age 43.4 + 13.8, UHDRS-TMS 40.8 + 20) completed 3 weeks of intensive 5x/week physiotherapy sessions. Each session was 90 minutes in duration and consisted of a 10-minute warm up emphasizing body awareness, 70 minutes of PNF-based physical therapy emphasizing balance reactions, gait training, and seated exercises, and 10-minute post-exercise relaxation. Post-study results showed statistically significant improvements in anticipatory, static, and dynamic balance, as tested by the Functional Reach Test (FRT), Pastor Test, and the BBS. Additionally, significant improvements were seen in all gait tests, including the 10-meter and 20-meter Timed Walking Test (10/20m TWT), TUG, and the Tinetti Gait Assessment Tool.

Balance and gait improvements were greater in participants with more severe HD motor symptoms.

Table 2. SS: Statistically Significant, Cl-B: Clinic-Based, IP: In-Patient, E vs. B: Exercise Group compared to Control Group, PT: Physiotherapy, RT: Respiratory Therapy, ST: Speech Therapy

Table 2		**Clinical and Intensive-Based Exercise Protocols**			
Study Ref.	**Setting**	**Exercise Protocol**	**Participants**	**Improvements** (Test/measurement) *Only SS results shown*	**Adherence Rate**
Bohlen 2013 (3)	Cl-B	**Exercise:** Physiotherapy: 6 wks, 2x/wk, 1 hr **No Control Used**	**Exercise:** n=12, mean age 52.2 UHDRS-TMS 41.4 **Control:** N/A	**E vs. B** % time in two leg support, stride length, gait speed (GAITRite) Mobility/Balance (TUG, BBS)	**Exercise:** 12/12 completed Mean PT attendance: 90%
Mirek 2013 (24)	Cl-B	**Exercise:** PNF-Intensive Physiotherapy: 3 wks, 5x/wk, 90 min **No Control Used**	**Exercise:** n=30, age 43.4±13.8, UHDRS-TMS: 40.8 ± 20 **Control:** N/A	**E vs. B** Anticipatory, static, and dynamic balance (FRT, Pastor, BSS) All Gait Measures (10/20m TWT, TUG, Tinetti)	**Exercise:** 30/30 completed. No further data reported
Ciancarelli 2013 (8)	IP	**Exercise:** Intensive Physiotherapy/OT: 3 wks, 6x/wk, 2x/day, 2 hrs/session **No Control Used**	**Exercise:** n=34, 12 M/22 FM, age 48.2 ± 7, UHDRS-TFCS: 5.65 ± 1.89 **Control:** N/A	**E vs. B** ADLs (BI, UHDRS-TFCS) Balance and gait (16 item TS) Functional motor performance (PPT)	**Exercise:** 34/34 completed. 100% sessions
Zinzi 2007 (46)	IP	**Exercise:** Intensive PT, OT, cognitive rehabilitation, ST and RT: 2 years, 3 visits/yr, 3 wks/visit, 6 days/wk, 8 hrs/day **No Control Used**	**Exercise:** n= 40, 17 M, 23 FM, age 52.0 ± 3.3, Shoulson and Fahn Rating Scale 1-3 **Control:** N/A	**E vs. B** Each 3 wk period: Motor Performance and ADL (Tinetti and PPT) No motor decline over entire 2 years	**Exercise:** 11/40 attended all 6 visits over 2 years. Other participants had a variable number of subsequent visits
Piira 2014 (28)	IP	**Exercise:** Intensive PT, OT, ST and Aquatic Therapy: 2 years, 3 visits/yr, 3 wks/visit, 6 days/wk, 8 hrs/day **No Control Used**	**Exercise** n=10, age 50.0±14.0, UHDRS-TMS: 47.4 ± 9.8 **Control:** N/A	**E vs. B** No gait or balance decline over entire 2 years (TUG, 6-min walk test, 10-meter walk test, BBS and ABC, No ADL, cognitive function, anxiety, depression loss over 2 years (BI, MMSE, HADS)	**Exercise:** 6/10 completed the entire 2-year program

Ciancarelli el al. conducted a study examining a 3-week intensive neurorehabilitation program held in a rehabilitation-centered nursing home (8). In this study, patients with HD (n=34, 12 male/22 female, mean age 48.2 + 7, UHDRS-Total Functional Capacity Scale (TFCS) 5.65 + 1.89) (35) completed sessions lasting 2 hours in duration, held twice per day and 6 days per week. The rehabilitation protocol aimed to improve patient gait, posture, balance, strength, and coordination through a combination of global neuromotor exercises including treadmill walking, ball drills, and fine motor exercises including small object movements training and object stacking. Both global and fine motor movement exercise protocols were highly eclectic and the study authors reported 28 different types of exercises in these categories all centered in physical therapy and OT. Additionally, static and dynamic balance exercises were performed using a Biodex Balance System (Biodex Medical System Inc, Shirley, NJ, USA). All patient rehabilitation protocols were individualized to the functional abilities of the patient, and progressive in difficulty as new abilities were gained. Post-study results showed that all study patients showed statistically significant improvement in activities of daily living (ADL) as measured by the Barthel Index (BI) (22) and UHDRS-TFCS, balance and gait as evaluated by the 16-item Tinetti Scale (TS) (41), and functional motor performance as tested by PPT. Additionally, the study found that there was no difference in any improvements in patients that were being treated with tetrabenazine (n=12) and those that were not (n=22) , showing that there is likely little to no negative physical implications to the use of this drug while concurrent in a similar neurorehabilitation program. Improvements in independence and ADL were reported to have returned to pre-study values during a follow-up evaluation using the BI 3 months after the patient was discharged.

Further study on the effects of an intensive inpatient clinic rehabilitation program for individuals with HD was performed by Zinzi et al. (46). In this study, 40 patients with early to mid-stage HD (17 men, 23 women, mean age 52.0 + 3.3, Shoulson and Fahn Rating Scale 1-3) completed an individualized and group exercise program. Physical and occupational therapy primarily focused on gait, balance, strength and transfer training completed while lying, sitting and standing. Additionally, stationary bikes, treadmills, and common gym equipment were used during training. The rehabilitation protocol was performed at an intensity of 8 hours per day, five days per week, and an additional day per week for 4 hours. This treatment period lasted 3 weeks, and was performed 3 times per year, for 2 years (6 treatment periods total). Post-study results showed that while no significant difference was shown in depression as a result of each individual 3-week session as tested by Zung Depression Scale (ZDS) (47), cognition as tested by the Mini-Mental State Examination (MMSE) (10) or ADL as measured by BI. Each 3-week session showed a statistically significant improvement in motor and functional performance as measured by TS and PPT respectively. Interestingly however, results in all 5 tests over the entire 2-year course of treatment showed no significant differences from baseline values, suggesting that this treatment protocol is possibly sufficient in allowing patients with HD to maintain a constant level of cognitive, functional, and motor abilities while in treatment.

The results of the study are similar to those found by Piira et al. that also examined the effects of a 2-year intensive multidisciplinary rehabilitation protocol with patients with early to mid-stage HD (n=10, mean age 50.0 + 14.0, UHDRS-TMS 47.4 + 9.8) (28). Both the exercise frequency and duration were identical to the above study by Zinzi et al., however the wholistic rehabilitation approach by this study utilized aquatic therapy in addition to PT, OT and speech therapy. Post-study results showed that, similar to Zinzi et al., no significant differences were found in gait or balance as measured by TUG, 6-minute walk test, 10-meter walk test, BBS and ABC over the course of the study. Additionally, no significant differences were found in ADL as measured by BI, not in cognitive function as measured by MMSE over the course of the study. Post-test results also showed that no significant differences were found in anxiety and depression as measured by the Hospital Anxiety and Depression Scale (HADS). The results of this study may show that this rehabilitation program protocol is sufficient to preserve and maintain a level of physical and cognitive ability in patients with HD.

Adherence rates of studies examining rehabilitation protocols performed in an in-home/in-community therapeutic environment ranged from 56% (6) to 100% (18). Though the studies were developed by or in accordance with a physical therapy or rehabilitation specialist, little significant improvement was reported by these studies as a result of the utilized rehabilitation protocols. Adherence rates of studies examining rehabilitation protocols performed in an intensive or clinically-based environment ranged from 27.5% (46) to 100% (3, 8, 24).

DISCUSSION

This review presents research performed on the effects of various rehabilitation modalities for individuals with HD. Specifically, the intent of this review is to examine the differences in therapeutic environment and protocol of these studies as a whole, and explore the effectiveness of each to improve motor, balance, and QoL in patients with HD. Individuals with HD often experience wide-ranging physical and psychological disabilities dependent upon the severity of CAG repeats and speed of neurological degeneration concomitant with HD (7, 9, 19, 39, 43, 44). While the progressive psychological and body compositional symptomology of HD can be variable, motor symptoms including choreic movement and dystonia are signature of HD and cause deficits in gait, motor function, and balance (4, 23). The progressive nature of these symptoms often also often have severe implications for the ADL and QoL of individuals with HD (12, 17).

In the studies examining the effects of home- and community (H/C) based exercise regimens on individuals with HD (Table 1) no definitive trends can be identified in efficacy of treatment when comparing duration, frequency, modality, or participant characteristics. However, these studies suggest that the frequency and duration of physical activity may play a role in motor and balance improvements as the studies that mandated the least amount of physical activity per week (6,18) showed the least improvements, and those that offered longer duration and higher frequency showed greater improvements in multiple variables (13, 40). Furthermore, while all of the studies utilizing H/C based physical activities examined their effects on QoL, none of them with the exception of a small subgroup in (6) showed a statistically significant improvement in any QoL variable. Although only a small subgroup showed statistical significance in QoL variables, the individual clinical significance of each patient, in regards to QoL measures, should not be overlooked.

Of these studies utilizing H/C based exercises, 2 included audio-visual aids in the form of video games (18) or workout DVDs (8) and 2 included unsupervised walking regimens performed once (13) and twice (6) per week. While the effectiveness of an unsupervised walking program or inclusion of audio-visually aided exercise cannot be determined, it may be notable that both studies utilizing audio-visually aided exercise showed statistically significant improvements in balance. These results are, however, incomparable as only one of these studies included a control group (13) and there are important differences in the nature of the exercises. Additionally, nothing can be determined about the effectiveness of supervised vs. unsupervised exercise due to the paucity and nonuniformity of exercise protocols.

In the studies examining the effects of clinical and inpatient (Cl/IP) exercise regimens on individuals with HD (Table 2), several trends can be identified and comparisons made. It should first be noted that all CL/IP based exercise programs produced multiple statistically significant improvements in numerous areas. In terms of exercise duration and frequency, these studies ranged from 3 to 104 weeks and from 2-6 sessions/week respectively. Additionally, the duration of each rehabilitation session varied widely from 1-8 hours/day. While each of these studies reported multiple statistically significant improvements, the studies with the longest session and study duration, as well as highest exercise frequency (28, 46) showed the most remarkable outcomes. These studies performed by Zinzi et al. (46) and Piira et al. (28) explored an intensive inpatient and multidisciplinary wholist approach to participant exercise including physiotherapy, OT, RT, aquatic therapy, cognitive therapy, and speech therapy. What is remarkable about these studies is that they not only showed statistically significant improvements at the end of each 3 week visit, but also described that over the course of the 2 year study, each reported an absence of motor skills decline. Furthermore, Piira et al. (28) reported an absence of decline in participant ADLs, cognitive function, anxiety, and depression. Authors of these studies also suggested that their substantial findings may represent a sufficient exercise protocol for the maintenance of motor, (46) proprioceptive, functional, and cognitive function (28) in individuals with HD.

Studies examining the use of Cl/IP exercise protocols have limitations, as none of them included a control group for comparison and the assessment tools used to determine participant disability level varied between studies disallowing cross-study comparisons. Though between-study measurements vary widely, two studies (28,46) utilized the same exercise and study durations and frequencies. While they differed slightly in the intervention therapies used, these studies showed considerably similar results.

In making comparisons between H/C based and Cl/II based therapeutic exercise protocols, several experimentally intrinsic differences must be identified. The average number of participants in H/C based exercise is 14 while the average for participants in CL/IP based is 25. While this may suggest more reliability for the latter, no CL/IP based included a control group for comparison. Study and session duration, as well as exercise frequency also varied widely between each exercise environment. Conversely, as a whole, studies in each exercise setting measured outcome variables using the same measurement scales and tools.

In comparing the study adherence of each therapeutic environment, a few trends can be identified. The highest percentages of participants completing the studies were seen in home-based, audio visually aided, therapies (13, 18), and in uni-disciplinary, intensive, clinically-based therapy programs (3, 8, 24). Low adherence rates were reported in programs utilizing both supervised and unsupervised components, and requiring the majority of sessions to be completed at home (6, 40). Additionally, low and highly varying adherence rates were reported in therapeutic protocols utilizing multi-disciplinary intensive inpatient protocols spanning long durations (28,46). The difference in adherence rate among these studies may be the result of lack of supervision and monitoring to help encourage participants in a home-based setting, as well as the considerably high time and energy requirements of the multidisciplinary, intensive inpatient protocols. It also may be important to note that home-based exercise sessions were self-directed and self-reported, leading to the possibility of reporting bias.
Additionally, studies involving intensive inpatient protocols showed a considerably high participant dropout rate that was reported to increase over the course of the studies (28,46). The dropout rate was shown to be independent of sociodemographic and clinical characteristics and could possibly be explained by the programs' extensive duration and intensity (46). Overall, clinically-based and short-term inpatient based-programs have the best adherence rates and show the best overall participant improvements (3, 8, 24). Although the intensive inpatient-based program demonstrated the capability of a rigorous and long-term protocol to maintain the physical and cognitive ability of participants, the reported adherence rates of these studies may indicate a lack of feasibility of such a program for individuals with HD (28,46). It is also important to note that more studies are needed to obtain a more accurate representation of the protocol- and environmental-specific adherence rates. None of the reviewed studies reported any adverse effects as a result of the studied protocols, nor commented on the monetary cost of such therapeutic regimens to the patient or providing facility. While there may be benefits and disadvantages to both the home and clinical environment, due to the similar reported benefits of therapeutic exercise completed in each, no definitive trends can be determined for safety or adherence rates.

Comparing solely the number and amplitude of the outcomes of the studies in each therapeutic environment as a whole, the improvements shown in participants in Cl/IP based compared to those in H/C based exercise appear more substantial and wide-ranging. Cross-comparison of these settings may also suggest that supervision of therapeutic exercise may be more beneficial to the patient than unsupervised exercise. These findings, in addition to those found in cross-comparison of the outcomes of each therapeutic setting may suggest that due to the considerably more rigorous and lengthy exercise protocols employed by Cl/IP based therapy, these exercise are considerably more effective than those studied in a H/C based environment at improving motor and proprioceptive function and QoL in individuals with HD. Though studies with the most demanding exercise protocols showed the lowest adherence rates, overall, clinically-based and short-term inpatient based-programs have the best adherence rates and show consistent overall participant improvements (3, 8, 24).

As one looks to the future of HD rehabilitation, prospective studies could focus on categorizing rehabilitation protocols and UHDRS-TMS scores. It would be of interest, if those with lower UHDRS-TMS scores would be more adherent to the more intensive inpatient protocols, compared to those with higher UHDRS-TMS. This information would allow rehabilitation professionals to tailor specific rehabilitation protocols for each HD patient, based upon their UHDRS-TMS score. This specialization would allow for optimization of rehabilitation needs, functional outcomes and QoL measure. As this specification would allow for more targeted rehabilitation protocols, the current research can have great clinical implication. The current information as outlined above allows the therapeutic care team to outline rehabilitation protocols with the best adherence rates, greatest functional and psychological outcomes.

Though there is considerable intrinsic variability to studies examining the use of H/C based, and CL/IP based exercise for individuals with HD, therapeutic outcomes can be compared between each setting. The implicit increases in exercise duration and frequency as well as the utilization of multiple supervised, rehabilitation modalities and disciplines appear in these studies to result in functional and psychological outcomes that are greater than those found in a H/C based setting. However these highly demanding studies report the lowest adherence rates. The results of this review suggest that rehabilitation exercise protocol held in a clinical, moderate-intensity inpatient setting may provide greater functional and psychological outcomes than those performed in a non-clinical setting. Additionally, short-term, inpatient programs may provide a helpful medium in terms of time and physical demand on the patient. More research on exercise in both settings is needed to confirm these findings.

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