Telemedicine for neurologic diseases: A systematic review and meta-analysis

Short running title: Telemedicine for neurologic diseases

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Background: To systematically review the effectiveness and safety of telemedicine combined with usual care (in-person visits) compared to usual care for the therapeutic management and follow-up assessment of neurologic diseases.

Methods: The electronic databases MEDLINE, EMBASE, WOS, and Cochrane Central Register of Controlled Trials were searched (June 2021). We considered randomized controlled trials (RCTs) on patients of any age with neurologic diseases. Two reviewers screened and abstracted data in duplicate and independently and assessed risk of bias using the Cochrane risk-of-bias tool for randomized trials (RoB 2). When possible, pooled effect estimates were calculated.

Results: Of a total of 3018 records initially retrieved, 25 RCTs (n=2335) were included: 11 (n=804) on stroke, 4 (n=520) on Parkinson's disease, 3 (n=110) on multiple sclerosis, 2 (n=320) on epilepsy, 1 (n=63) on dementia, 1 (n=23) on spina bifida, 1 (n=40) on migraine, 1 (n=22) on cerebral palsy, and 1 (n=433) on brain damage. Types of telemedicine assessed were: online visits (11 studies), tele-rehabilitation (7 studies), telephone calls (3), smartphone apps (2), and online computer software (2). The evidence was quite limited except for stroke. Compared to usual care alone, telemedicine plus usual care was found to improve depressive symptoms, functional status, motor function, executive function, generic quality of life, health care utilization, and healthy lifestyle in patients in post-stroke follow-up.

Conclusions: Well-designed and executed RCTs are needed to confirm our findings on stroke and to have more scientific evidence available for the other neurologic diseases.

International Prospective Register of Systematic Reviews (PROSPERO) number: CRD42021262578 (https://www.crd.york.ac.uk/PROSPERO/).

Keywords. Effectiveness, Meta-Analysis, Neurologic diseases, Safety, Telemedicine, Teleneurology.

1. INTRODUCTION

Hundreds of millions of people around the world suffer from neurologic disease (1). According to World Health Organization data, more than 50 million people have epilepsy, and almost 48 million suffer from dementia. Alzheimer's disease is the most common cause of dementia and may account for to 60% to 70% of cases. Migraine is the second most common disease in humans (after tooth decay) (2,3), with a global prevalence of more than 10% (1).

The quality of life of patients with neurologic diseases may be affected in many ways due to the symptoms and sequelae these diseases may cause (4). Today, neurologic diseases are the second leading cause of deaths (90 million; 95%CI 247-308 million) and the leading cause of disability globally when measured in disability-adjusted life years (DALYs) (276 million; 95% CI 247-308 million). Of this total figure, stroke, migraine, meningitis, Alzheimer's disease, and other dementias account for the highest number of deaths and dependencies (5,6).

The neurological diseases can be acute or chronic, and due to the differences between them, their care setting can be different (inpatient vs. outpatient). Patients with chronic neurological diseases, such as Alzheimer or Parkinson diseases, usually receive outpatient care but those with acute neurological diseases that require immediate attention, such as stroke, must be managed in a hospital setting. In either case, patients have to travel to receive neurologic care.

As in other diseases, initial management of neurologic diseases involves taking a patient's clinical history and performing a physical examination to diagnose the disorder. This is followed by a request for further tests to ascertain the disorder to offer the most appropriate treatment to each patient.

As more information and communications technologies (ICTs) are being developed and gradually incorporated into healthcare (7), healthcare professionals are increasingly providing remote health services, known as telemedicine. The application of telemedicine in the field of neurology is called teleneurology and has been defined as the use of ICTs in enabling the provision of neurologic care when patients and/or healthcare professionals are not present in the same location and/or at the same time (6). Telemedicine has been applied for different purposes which has led to the use of specific terms such as telemetry (in situ collection of measurements or other data at remote points and their automatic transmission for monitoring), teleconsultation (interactions that happen between a clinician and a patient for the purpose of providing diagnostic or therapeutic advice through electronic means), telediagnosis (the detection of a disease by evaluating data transmitted to a receiving station from instruments monitoring a distant patient), telerehabilitation (the delivery of rehabilitation services over telecommunication networks and internet) or telegenetics (the process of providing genetic counseling services remotely online). Although in-person consultation has been, and continues to be, fundamental to healthcare and practitioner–patient relationships, ICTs are utilized to complement healthcare provision, without displacing in-person attendance.

Teleneurology has been increasingly used in neurocritical care and emergency cerebrovascular accidents, particularly in cases where there is no direct access to a neurology department (8). In recent times, teleneurology has also been incorporated into routine follow-up assessments of outpatients with chronic neurologic disorders (8), such as Parkinson's disease (9), multiple sclerosis (10), and Alzheimer's disease (11), among others; especially following the outbreak of the COVID-19 pandemic.

Teleneurology offers specialists the chance to provide continuing healthcare to patients without being hindered by distance, access difficulties, patients' mobility difficulties or the COVID-19 pandemic (12). Patients and healthcare professionals alike have indicated the clinical utility of implementing teleneurology while also stressing the importance of maintaining the possibility of in-person visits (13). However, the development of teleneurology have to face the possible limitations and minimum technical requirements necessary for its implementation, such as data protection, cybersecurity problems and confidentiality of the consultation, lack of training in digital skills, poor management of technologies of certain groups or impossibility of carrying out a complete neurological examination (12).

The aim of this study was to identify, critically assess and synthesize the available scientific evidence on safety and clinical effectiveness of the strategy of combining in-person visits and telemedicine for the therapeutic management and/or follow-up assessment of people with neurologic diseases. This study is based on a Health Technology Assessment (HTA) report requested from the Spanish HTA Network (RedETS) by the Spanish Ministry of Health to inform health policy decisions and guide clinical decisions to improve the clinical management of patients with neurologic diseases.

2. METHODS

A systematic review (SR) of the scientific literature was conducted according to the methodology developed by the Cochrane Collaboration with reporting in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (14). The review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under reference number CRD42021262578.

2.1. Information sources and search strategy

The following electronic databases were searched (June 2021): Medline (OVID), EMBASE (Elsevier), Web of Science (Clarivate Analytics) and the Cochrane Central Register of Controlled Trials (Wiley). The strategy was developed initially in Medline and then adapted for each of the other databases. The search strategy included both controlled vocabulary search terms and text-word terms. It combined telemedicine-related terms with neurology-related terms. Searches were restricted to studies published from the last 10 years onwards and either in English or Spanish. The search strategies are available in Supplementary Material 1.

To complete the systematic search, the reference lists of all relevant papers were examined to identify all possible additional studies that met the selection criteria but were not retrieved by means of electronic search.

2.2. Selection criteria

Studies were eligible for inclusion if they fulfilled the following criteria:

a) Type of study: we included randomized controlled trials (RCTs).

b) Population: we included studies that assessed patients with any neurologic disease.

c) Intervention: we included studies that assessed interventions with the following characteristics: 1) Any synchronous or asynchronous teleneurology intervention used in addition to usual standard of care (teleneurology group); 2) Any teleneurology intervention applied to diagnosis, therapeutic management or follow-up assessment; 3) Any intervention of teleneurology applied by any health professional (neurologists, rehabilitators, nurses, etc.). We excluded studies: 1) assessing teleneurology not delivered alongside usual care; 2) assessing telecommunications technology not linked to direct patient care; 3) assessing teleneurology only used for educational or administrative purposes; 4) the patient was not physically present at any point of care, e.g. studies evaluating the electronic transmission of X-ray images or pathology results for routine reporting, 'store and forward' systems without patient-caregiver interaction; 5) assessing patient monitoring systems where the patient only received an automated voice response; 6) assessing interventions aimed exclusively at caregivers; 7) comparing teleneurology to other alternative or complementary interventions different from usual care.

d) Comparator: usual standard of care alone (usual care group).

e) Outcome measures: studies had to report on safety (i.e., adverse events) and/or any disease management (diagnostic agreement, request for complementary tests, hospitalizations, emergency visits, transfers, waiting lists, number of consultations, etc.) and/or health outcome measure, and/or satisfaction or acceptability of care received and/or satisfaction or acceptability of care by professionals.

f) Timing: we did not exclude any study based on duration of follow-up.

g) Setting: studies conducted in primary or secondary healthcare were included.

h) Language: we only included studies published in Spanish or English.

2.3. Selection process

Two reviewers addressed eligibility independently and in duplicate. First, the titles and abstracts of all records identified by searches were screened. Subsequently, full text of all articles deemed potentially relevant were assessed for inclusion according to pre-specified eligibility criteria. Any disagreements were resolved by discussion until consensus was reached with the participation of a third reviewer when necessary.

2.4. Data collection process and assessment of risk of bias

Data extraction and assessment of risk of bias were also conducted independently and in duplicate by two reviewers. Discrepancies were consulted with a third reviewer. Data extracted include general study characteristics (first author, publication year, country, study design), sample characteristics (i.e., age, sex, neurologic disease), intervention details (i.e., type of teleneurology, number of sessions, duration), comparator details and results. Risk of bias was assessed according to the Cochrane risk of bias tool for randomized trials (RoB 2) (15). RoB 2 is structured into five bias domains, focusing on different aspects of trial design, conduct, and reporting. A proposed judgement about the risk of bias arising from each domain is generated by an algorithm, based on answers to each domain's signaling questions. Judgement can be 'Low' or 'High' risk of bias, or can express 'Some concerns'. These response options for individual domains are the same for the overall risk-of-bias judgment. The overall risk of bias generally corresponds to the worst risk of bias in any of the domains. The high risk of bias rating in any of the domains assessed or the uncertain risk of bias rating in three or more domains leads to qualify the study as having a high overall risk of bias (15).

2.5. Assessment of publication bias

According to Cochrane Collaboration recommendations (16), publication bias was examined by computing the Egger test. Statistical significance was set at 0.05 using meta bias commands in Stata Statistical Software (STATA 17. StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

2.6. Analysis and synthesis of results

When possible, a meta-analysis was performed for each outcome and according to each neurologic disease using the Review Manager computer software (RevMan, version 5.4.1. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2020).

The Mantel-Haenszel method was used to estimate the pooled risks ratio (RR) for each dichotomous variable. Continuity correction was used for studies with zero events in one or both groups. The generic inverse variance method and mean difference (MD) or standard mean difference (SMD) were used to combine continuous variables (17). Heterogeneity was assessed using the Higgins I^2 statistic. When there was heterogeneity ($I^2 \geq 50\%$ or $P < 0.1$), meta-analyses were performed using a random-effects model. A sensitivity analysis was conducted by omitting each study individually to determine the stability of the effect's overall estimate if the meta-analysis had 3 or more studies. When there was neither clinical nor statistical heterogeneity, a fixed-effect statistical model was used (18).

Subgroup analyses were performed to investigate how pooled effects vary across different teleneurology systems (videoconsulting, software, telerehabilitation, telephone).

2.7. Certainty of evidence assessment

We performed an assessment of the overall certainty of evidence, based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach by evaluating the evidence for each key outcome on the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (19). We developed evidence profile tables and rated the overall certainty of evidence as high (we are very confident that the true effect lies close to that of the estimate), moderate, low or very low (very little confidence in the effect estimate).

3. RESULTS

3.1. Search results

The results of the literature search and study selection process are shown in Figure 1. The initial search in the electronic databases yielded 3018 references after removing duplicates. Manual examination and the Google Scholar search did not lead to locating any additional articles. A total of 25 studies (n=2335 participants), reported in 26 articles, were finally eligible for inclusion according to the pre-established selection criteria (20,21,30–39,22,40–44,23–29). Excluded studies are listed in Supplementary Material 2 by reason for exclusion.

3.2. Description of studies included

The main characteristics of selected studies are summarized in Table 1. All of them were RCTs published in English between 2011 and 2021. The following types of teleneurology were used: videoconference/online visit (11 studies) (20,21,30,22–29), telerehabilitation (7) (31–37), phone calls (3) (38–40), an application for mobile phones (2) (41,42) and online tools or computer software (2)(43,44). The neurologic diseases of the participants were: stroke (11 studies) (22,31,44,32–37,39,40), Parkinson disease (4) (21,23,29,42), multiple sclerosis (3) (20,28,30), epilepsy (2) (26,43), and one study in each of the following diseases: traumatic brain injury (38), dementia (25), spina bifida (41), migraine (24) and cerebral palsy and dysarthria (27). In most studies the purpose of teleneurology was therapeutic management/follow-up assessment. No studies were found that used teleneurology for diagnosis.

Only one study did not report teleneurology provider (22). In eight studies teleneurology was performed by a therapist (occupational, speech therapist) (23,25,31–33,41,44), in three studies by psychologists/psychiatrists (20,38,45), in four studies by neurologists/neuropsychologists (21,24,28,34), in three by a multidisciplinary team (37,39,42,43), in two by nursing (30,40), in one by a health professional (specialty not specified) (29), in one by physical therapist (36), in one by a speech-language pathologist (35), in one by a clinical pediatrician (27) and, finally, one study implemented an automated intervention where help messages are received via a computer (26). For more teleneurology intervention details see Table 1.

3.3. Risk of bias in studies included

Only two (21,36) of the 25 studies were assessed at a low risk of bias. Risk of bias was considered high in half of the studies (20,22,34,39,42,43,23,25–29,31,33) and uncertain bias in the remaining nine (24,30,32,35,37,38,40,41,44). The detailed judgements for each risk of bias domain criteria are shown in Figure 2.

3.4. Publication bias

Funnel plots analysis and Egger's test could not be performed because the minimum number of studies necessary to be able to assess the publication bias in any of the outcomes was not attained (n=10).

3.5. Summary of results

Meta-analysis with two or more studies was only possible with outcomes of stroke and Parkinson's disease. The results of all meta-analysis and subgroup analysis are available in the Supplementary Material 3.

Evidence profile was also undertaken for stroke and Parkinson's disease related to important and critical outcomes. The evidence profiles are available in the Supplementary Material 4.

3.5.1. Stroke

Eleven studies assessed teleneurology addressed to patients in post-stroke follow-up (n=804) (22,31,44,32–37,39,40) but one of them could not be included in the meta-analysis due to lack of data (33). Seven studies were on telerehabilitation (simultaneously includes various teleneurology systems such as videoconsultations, calls, SMS, mobile phone applications, virtual reality or computer software) (31–37,46), two on telephone calls (39,40), one on videoconference (22) and one on computer software (44). Table S4.1 of Supplementary Material 4 provides the evidence profile. The quality of evidence of important outcomes ranged from moderate to very low.

An effect in favor of teleneurology compared to usual care alone was observed in the following outcomes: functional state (five studies, n=384; SMD=0.27; 95%CI=0.06 to 0.48; P<0.01; I^2=9%), depression (two studies, n=79; SMD=–1.01; 95%CI=–1.98 to –0.05; P<0.04; I^2=0.04), motor function (one study, n=61; MD=9.85; 95%CI=8.36 to 11.34; P<0.00001), executive function (one study, n=94; MD=2.49; 95%CI=–3.01 to 7.99; P=0.37), generic quality of life (three studies, n=3; MD=7.64; 95%CI=0.98 to 14.31; P=0.02; I^2=64%), health care utilization (one study, n=49; MD=–0.82; 95%CI=–1.56 to –0.08; P=0.03); healthy lifestyle (one study, n=80; MD=0.22; 95%CI=0.02 to 0.42; P=0.03).

No statistically significant differences were found in terms of mortality (two studies, n=293; RR=0.66, 95%CI=0.18 to 2.47; P=0.54; I^2=0%), adverse events (three studies, n=341; RR=1.15, 95%CI=0.97 to 1.38; P=0.11; I^2=0%), language disorders (three studies, n=257; SMD=0.73; 95%CI=–0.22 to 1.67; P=0.13; I^2=90%), gait (two studies, n=187; SMD=0.68; 95%CI=–1.65 to 3.02; P=0.57; I^2=98%), balance (three studies, n=166; SMD=0.61; 95%CI=–0.38 to 1.60; P=0.23; I^2=93%), specific quality of life (two studies, n=144; SMD=1.64; 95%CI=–1.55 to 4.83; P=0.31; I^2=98%).

Subgroup analysis did not reveal any significant differences by type of teleneurology.

3.5.2. Parkinson's disease

Four studies assessed teleneurology in patients with Parkinson disease (n=520) (21,23,29,42). Three studies (21,23,29) were on videoconference and one on mobile application (42). Table S4.2 of Supplementary Material 4 provides the evidence profile. The quality of evidence of important outcomes ranged from moderate to very low.

An effect in favor of teleneurology was observed in the following outcomes: generic quality of life "mental domain" (one study, n=90; MD=15.13; 95%CI=5.69 to 24.57; *P*=0.002) and "physical domain" (one study, n=90; MD=3.85; 95%CI=1.06 to 6.64; *P*=0.007) and adherence to treatment (one study, n=97; MD=0.35; 95%CI=0.08 to 0.62; *P*=0.01).

No statistically significant differences were found in functional state (two studies, n=215; MD=0.29; 95%CI=–0.44 to 1.02; *P*=0.44; I^2=0%), depression (four studies, n=462; SMD=–0.14; 95%CI=–0.67 to 0.40; *P*=0.61; I^2=85%), anxiety (two studies, n=247; SMD=–2.09; 95%CI=–6.51 to 2.33; *P*=0.35; I^2=99%), movement disorders (two studies, n=215; MD=–0.97; 95%CI=–3.26 to 1.33; *P*=0.41; I^2=0%), cognitive state (one study, n=215; MD=0.40; 95%CI=–0.37 to 1.17; *P*=0,31), specific quality of life (3 studies, n=372; MD=0,40; 95%CI=–0.37 to 1.17; *P*=0.31; I^2=0%), quality of health care received (two studies, n=352; SMD=0.21; 95%CI=–0.21 to 0.63; *P*=0.33; I^2=0%), caregiver burden (one study, n=195; MD=–0.20; 95%CI=–4.41 to 4.01; *P*=0.16), emergency room visits (one study, n=195; MD=–0.20; 95%CI=–0.56 to 0.16; *P*=0.27) and hospital admissions (one study, n=195; MD=–0.10; 95%CI=–0.24 to 0.04; *P*=0.16).

The effect of teleneurology on mortality and adverse events could not be estimated as there were no events in the study assessed reporting these outcomes(21).

Subgroup analysis only revealed a significant difference by type of teleneurology system for anxiety estimates. Anxiety outcomes improved more in users of videoconference than users of mobile application (Chi^2=112.43, *P*<0.00001).

3.5.3. Multiple sclerosis

Three studies assessed teleneurology (videoconference) in patients with multiple sclerosis (n=110) (20,28,30).

An effect in favor of teleneurology was observed in severity of symptoms (one study, n=39; MD=–0.31; 95%CI=–0.38 to –0.24; *P*<0.00001) and depression (one study, n=27; MD=–2.42; 95%CI=–4.65 to –0.19; *P*=0.03).

No statistically significant differences were detected between the teleneurology group and the usual care group in terms of number of relapses (one study, n=39; RR=1.68; 95%CI=0.67 to

4.24; *P*=0.27), disability status (one study, n=39; MD=–0.40; 95%CI=–0.88 to 0.08; *P*=0.10), catastrophizing pain (one study, n=27; MD=1.46; 95%CI=–5.31 to 8.23; *P*=0.37), pain intensity (one study, n=27; MD=–0.20; 95%CI=–1.35 to 0.95; *P*=0.73), pain interference (one study, n=27; MD=–1.45; 95%CI=–6.71 to 3.81; *P*=0.59) and satisfaction with the health care received (one study, n=38; *P*<0.05).

3.5.4. Epilepsy

Two studies assessed teleneurology in patients with epilepsy (n=320) (26,43). One study assessed the use of videoconference (26) and the other one online software (42).

An effect in favor of teleneurology was observed in the severity of epilepsy (one study, n=103; MD=–5.91; 95%CI=–8.75 to –3.07; *P*<0.00001), functional status (one study, n=200; MD=–0.31; 95%CI=–0.38 to –0.24; *P*<0.00001), depression (two studies, n=303; MD=–1.79; 95%CI=–2.69 to –0.90; *P*<0.0001; I^2=0%), generic quality of life “mental domain” (one study, n=103; MD=0.42; 95%CI=0.07 to 0.77; *P*=0.02), specific quality of life (two studies, n=303; SMD=0.42; 95%CI=0.06 to 0.77; *P*=0.02; I^2=54%), epilepsy self-efficacy (one study, n=103; MD=23.22; 95%CI=3.39 to 43.05; *P*=0.02) and epilepsy self-management (one study, n=103; MD=9.53; 95%CI=3.64 to 15.42; *P*=0.002). Subgroup analysis did not reveal any significant differences by type of teleneurology.

No statistically significant differences were detected between the groups in anxiety (one study, n=200; MD=–0.79; 95%CI=–1.83 to 0.25; *P*=0.14) and generic quality of life “physical domain” (one study, n=103; MD=0.24; 95%CI=–0.12 to 0.60; *P*=0.20).

3.5.5. Dementia

One study assessed teleneurology (videoconference) in patients with dementia (n=63) (25).

An effect in favor of teleneurology was observed in the quality of health care received (MD=0.20; 95%CI=0.04 to 0.36; *P*=0.01), behavior disorders (MD=–2.40; 95%CI=–2.54 to –2.26; *P*<0.00001) and therapist’s travel time (MD=–178.70 minutes; 95%CI=–257.45 to –99.95; *P*<0.00001).

An effect against teleneurology was observed in perceived change by patients (MD=–2.00; 95%CI=–2.33 to –1.67; *P*<0.00001) and functional status (MD=–4.00; 95%CI=–4.57 to –3.43; *P*<0.00001).

No statistically significant differences were detected between the teleneurology group and the usual care group in face-to-face time (MD=–29.50 minutes; 95%CI=–130.53 to 71.53; *P*=0.57).

3.5.6. Spina bifida

Only one study assessing the use of a mobile application in patients with spina bifida (n=23) (41) was considered.

An effect in favor of teleneurology was observed in disease self-management (MD=0.70; 95%CI=0.01 to 1.39; *P*=0.05).

No statistically significant differences were detected in functional status (MD=–2.40; 95%CI=–10.67 to 5.87; *P*=0.57), depression (MD=–7.30; 95%CI=–15.47 to 0.87; *P*=0.08), quality of life “physical domain” (MD=–0.30; 95%CI=–0.73 to 0.13; *P*=0.17), quality of life “psychological domain” (MD=3.10; 95%CI=–6.23 to 12.43; *P*=0.51), quality of life “social domain” (MD=–5.90; 95%CI=–14.45 to 2.65; *P*=0.18), quality of life “environment domain” (MD=–2.00; 95%CI=–11.43 to 7.43; *P*=0.68), number of urinary tract infections (RR=0.62; 95%CI=0.22 to 1.71; *P*=0.35), wounds (RR=0.44; 95%CI=0.18 to 1.09; *P*=0.08), quality of health care received (MD=–0.40; 95%CI=–0.83 to 0.03; *P*=0.07), number of emergency department visits (RR=1.15; 95%CI=0.24 to 5.65; *P*=0.86), number of scheduled hospitalizations (RR=2.31; 95%CI=0.28 to 18.99; *P*=0.44) and number of unscheduled hospitalizations (RR=0.38; 95%CI=0.04 to 3.67; *P*=0.44).

3.5.7. Migraine

One study assessed teleneurology (videoconference) in migraine patients (n=40) (24).

No statistically significant differences were detected between the teleneurology group and the usual care group in any of the reported measures: headache severity (MD=0.00; 95%CI=–1.57 to 1.57; *P*=1.00), headache days (MD=10.00; 95%CI=–25.8 to 5.80; *P*=1.00), disability (MD=–4.30; 95%CI=–31.66 to 23.06; *P*=0.76), number of emergency department visits (RR=2.00; 95%CI=0.23 to 17.03; *P*=0.53), and hospitalizations (RR=1.33; 95%CI=0.29 to 6.17; *P*=0.71).

3.5.8. Cerebral palsy

One study assessed teleneurology (videoconference) in patients with cerebral palsy (n=22) (27). No health outcomes were reported.

All participants in the teleneurology group rated the intervention as effective 12 months later. No statistically significant differences were found between the groups in number of recordings made/total possible (RR=0.94; 95%CI=0.81 to 1.10; *P*=0.45), number of listeners hearing recordings/total possible (RR=0.96; 95%CI=0.85 to 1.08; *P*=0.46) and number of questionnaires completed/total possible (RR=1.20; 95%CI=0.52 to 2.79; *P*=0.67).

3.5.9. Traumatic brain injury

One study (n=433) assessed teleneurology (telephone calls) in patients with traumatic brain injury (38). According to the results offered by the study, no statistically significant differences (*P*>0.05) were observed between the participants of the teleneurology group and those of the usual care only group in terms of quality of life, emotional state, functional state or disability.

4. DISCUSSION

No SRs were found that assessed telemedicine delivered together with usual care versus usual care alone for neurologic diseases, whereby the results obtained in our SR could have been compared. The use of ICTs such as videoconference, mobile applications, and computer software has made remote neurologic care of patients possible. Some SRs have assessed the effects of using telemedicine versus usual care to manage patients suffering from various diseases, including neurologic diseases (47,48). Nevertheless, the work reported in this paper is, to the best of our knowledge, the first SR with scope on the use of telemedicine together with usual care in the management of neurologic diseases. Therefore, our work provides initial pooled estimates of the effect of teleneurology for patients with neurologic diseases in addition to an innovative subgroup analysis by type of teleneurology.

The studies considered (25 RCTs, n=2335) assessed the use of teleneurology to manage patients suffering from nine different neurologic diseases. Although the use of ICTs is spreading in neurology, well-conducted RCTs evaluating the use of teleneuroloy are not available for all neurological diseases, perhaps due to the characteristics of each disease and its treatment. Five of these diseases were assessed by a single study while the remaining four diseases (stroke, Parkinson disease, multiple sclerosis, and epilepsy) were assessed by more than one study. Among studies considered for all diseases, four different types of teleneurology system were evaluated: telerehabilitation and videoconference/online visit were the most commonly assessed but phone calls, applications for mobile phones, and online tools or software for computers were also assessed.

The results of our meta-analysis revealed that telemedicine, delivered together with usual care, presents varying effects depending on the neurologic disease and the outcomes evaluated. The evidence is quite limited except for stroke and Parkinson disease. Specifically, the greater number of studies on stroke, mainly assessing telerehabilitation, may be due to the fact that it is a more frequent disease whose sequelae can also be treated. Stroke has the unique characteristic of presenting a therapeutic window of several years after the acute episode. Within that window, rehabilitation and control of vascular risk factors are crucial to regain functionality and improve patient's quality of life. Since teleneurology is suitable for rehabilitation and vascular risk factors control, the research becomes especially attractive, considering the potential benefits for patients and society.

For stroke, a significant effect in favor of teleneurology (tele-rehabilitation) was observed on functional state, motor function, executive function, generic quality of life, health care utilization, and healthy lifestyle. Previous meta-analyses on telerehabilitation in stroke survivors (49,50) did not detect any statistically significant differences in functional state, emotional state, balance, specific quality of life, caregiver burden or satisfaction with care. The difference in results may be due to the fact that, in these cases, teleneurology fully replaced usual care instead of complementing it.

For Parkinson disease, an effect in favor of teleneurology was observed in terms of generic quality of life and adherence to treatment. In a previous meta-analysis (11 RCTs and 10 cohort studies; n=903) (51), teleneurology compared to usual care was found to be effective in reducing the motor impairment of patients diagnosed with Parkinson's disease. However, no statistically significant differences were found in emotional state, functional state, cognitive state, complications, quality of life or balance.

Regarding safety, only four studies reported on adverse events or direct harm of the intervention, such as falls during online consultation or issues concerning the privacy of the data, without detecting any statistically significant differences. Although serious adverse events are unlikely to occur during follow-up assessment and therapeutic management of patients by teleneurology, future research should systematically evaluate the occurrence of these events.

Finally, no significant differences in pooled estimates were shown by type of teleneurology system, likely because most studies included were focused on telerehabilitation, a form of telemedicine that includes several types of combined interventions (e.g., videoconferences, SMS, calls, etc.). Further studies assessing the independent effects of different telemedicine systems are needed to examine the superiority of any of them over others.

A recently published SR performed by the Agency for Healthcare Research and Quality (AHRQ) (48) included 233 comparative studies on the use of any ICTs to facilitate hospital consultations, hospital emergencies and outpatient care (54, 73 and 106 studies evaluated hospital consultations, emergency care and outpatient care, respectively). For emergencies, telestroke was evaluated and no statistically significant differences were detected in terms of mortality (hospital and at three months), administration of thrombolytic therapy, time to treatment or complications (bleeding). For hospital consultations, 11 clinical topics were established, among which neurologic diseases were not found to make results comparable.

Although research on telemedicine in general, and teleneurology in particular, has been performed for two decades, a technology that continues to develop and expand is being evaluated while barriers and technical limitations in its implementation are being resolved. With the onset of COVID-19, the use of ICTs in medical consultations has been promoted in the last two years. Therefore, it is conceivable that scientific production on these technologies will continue to be developed.

Our findings support the incorporation of telemedicine into the management of patients' post-stroke as part of routine care in Spain and we recommend waiting for future studies in the case of Parkinson's disease and the other diseases evaluated.

4.1. Study limitations

Our results must be interpreted cautiously due to several reasons that may limit the confidence placed in them. The main limitations of this review are the quality of most studies included and the low number of studies tackling some neurologic diseases where teleneurology was assessed, which also prevented performing Funnel plots analysis and Egger test. Blinding was difficult to achieve in the studies included due to the nature of the intervention. Finally, one last limitation derived from the methodology applied is the possibility that relevant studies were not included in the analysis as a result of their non-publication, being published in a language other than English or Spanish, or because they were published in non-indexed journals.

Despite all these limitations, this study provides an assessment of the effectiveness and safety of teleneurology to manage patients with neurologic diseases supported by meta-analyses and according to rigorous and transparent methods. Further well-designed randomized controlled trials are needed to confirm our findings, especially for those neurologic diseases where scientific evidence was very scarce.

5. CONCLUSION

The available evidence on telemedicine combined with usual care for the management of neurologic diseases is quite limited except for stroke. Our study suggests that telemedicine delivered with usual care is effective in improving depressive symptoms, functional status, motor function, executive function, generic quality of life, health care utilization, and healthy lifestyle of stroke patients; and it is not inferior to usual care alone for mortality, adverse events, language disorders, gait, balance, and specific quality of life.

However, our review highlights the absence of high-quality evidence due to the methodologic limitations of available studies. Therefore, well-designed and executed RCTs are needed to confirm our findings for stroke and to have more scientific evidence available for other neurologic diseases, where the evidence was very scarce.

ACKNOWLEDGEMENTS

The authors would like to thank Carlos González Rodríguez for his support in the documentation and editing tasks. We are also grateful to Jason Willis-Lee for native English language editing support with the final manuscript.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare with the subject matter or materials discussed in the manuscript.

AUTHOR CONTRIBUTIONS

All authors 1) made substantial contributions to research design, analysis and interpretation of data; 2) drafted and critically reviewed the paper, and 3) approved the final version.

FUNDING

This work was supported by the Spanish Ministry of Health in the framework of activities developed by the Spanish Network of Agencies for Health Technology Assessment for the National Health Service (RedETS).

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LIST OF ABBREVIATIONS AND OTHER FOOTNOTES

ICTs: Information and Communications Technologies

MD: Mean Difference

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: International Prospective Register of Systematic Reviews

RCT: Randomized Clinical Trial

RR: Risk Ratio

SD: Standard Deviation

SMD: Standard Mean Difference

SR: Systematic Review

95% CI: 95% confidence interval

Table 1. Main characteristics of studies included

First author, year, country	N	Patient				Teleneurology				Follow-up time (months)
		Age (years)†	**Sex** (% female)	**Diagnosis**	**Disease duration** (years)†	**Teleneurology system**	**Purpose of teleneurology**	**Provider**	**Sessions, frequency, and duration**	
Alschuler 2021 (20) USA	27	39.9±11.75	33.3	Multiple Sclerosis	2.17±1.03	Videoconference	Therapeutic management	Psychologist	1 session of 120 min.	3
Asano 2021 (31) Singapore	124	64.1 (41-90)	47.6	Stroke	NR	Tele-rehabilitation (The Singapore Tele-technology Aided Rehabilitation)	Therapeutic management	Therapist	1 session weekly	6
Beck 2017 (21) USA	195	66.4±8.1	46.7	Parkinson's disease	8±5.6	Virtual calls	Therapeutic management/follow-up assessment	Neurologist	4 sessions weekly	12
Bell 2011 (38) USA	433	38.1±18	25.4	Traumatic brain injury	NR	Telephone calls	Therapeutic management/follow-up assessment	Psychologist/psychiatrist	11 sessions, telephone calls at 2 and 4 weeks and at 2, 3, 5, 7, 9, 12, 15, 18 and 21 months	24
Bishop 2014 (39) USA	49	70.1±11.6	65.3	Stroke	NR	Telephone calls (Telephone tracking FIIT)	Therapeutic management/follow-up assessment	Multidisciplinary team (psychiatrist, family therapist and nurse rehabilitation)	26 sessions. 1 session weekly for 6 weeks; every fifteen days during the following 2 months; and then monthly for 2 months	6
Chapman 2021 (22) Austria	45	64.61±10.	45.8	Stroke	NR	Videoconference (Zoom)	Therapeutic management/follow-up assessment	NR	NR	2 weeks
Chumbler 2012 (32) USA	48	67.4±9.8	2.1	Stroke	NR	Tele-rehabilitation (STeleR) (virtual visit+ SMS + telephone call)	Follow-up assessment	Therapist	3 online visits every 12-16 days	6
Dicianno 2016 (41) USA	23	29.6±5.9	43.5	Spina Bifida	NR	Mobile Health and Rehabilitation system (iMHere)	Therapeutic management/follow-up assessment	Occupational therapy	Request	12
Dobkin 2021 (23) USA	90	66.8±8.7	0	Parkinson's disease	5.4±5.1	Video-to-home cognitive-behavioral therapy (V-CBT))	Therapeutic management	Therapist	10 sessions, 1 session of 2.5 hours weekly during first months and optionally monthly for 6 months of follow-up	6
Friedman 2019 (24) USA	40	41 (21-67)	97.5	Migraine	NR	Videoconference (Zoom)	Therapeutic management/follow-up assessment	Neurologist, medical doctor	6 sessions. 1 visit at 4-6 weeks, and 1 visit at 3, 6, 9 and 12 Months.	12
Kamwesiga 2018 (33) Uganda	30	59.7±14.5	75	Stroke	NR	Mobile phone application (App F@ce)	Therapeutic management/follow-up assessment	Occupational therapy	16 sessions. 2 daily SMS (morning and night), 2 weekly calls and 1 call on demand if needed	2

Lakshminarayana 2017 (42) United Kingdom	215	60.3±9.7	39.3	Parkinson's disease	5.5±4.6	Mobile phone application (Pakinson's Tracker App)	Therapeutic management/follow-up assessment	Multidisciplinary team	1 call two weeks after starting the intervention	16 weeks
Laver 2020 (25) Australia	63	80±6.9	39.7	Dementia	NR	Videoconference	Therapeutic management/follow-up assessment	Occupational therapist	6 sessions.	4
Maresca 2019 (34) Italy	30	51.2±11.3	53.3	Stroke	NR	Virtual reality rehabilitation system (VRRS-Tablet)	Therapeutic management/follow-up assessment	Neurologist	50-minute sessions 5 days a week. Videoconference 2 times a week	6
Meyer 2019 (26) United Kingdom	200	40.3±13.12	63.5	Epilepsy	>18	Electronically delivered cognitive behavioral therapy (eCBT)	Therapeutic management	Automatic intervention	Request	9
Øra 2020 (35) Norway	62	64.9±23.9	33.9	Stroke	NR	Tele-rehabilitation ((software LogMeIn) + videoconference)	Therapeutic management/follow-up assessment	Speech and language therapist	Telerehabilitation of 5 hours per week. 16 language sessions by videoconference over 32 days.	4
Palmer 2020 (44) United Kingdom	169	64.9±13	40.3	Stroke	2.9±2.8	Computerized therapy (Specialist aphasia software (StepByStep)	Therapeutic management/follow-up assessment	Speech and language therapist	1 daily session of 20 to 30 min.	12
Pennington 2019 (27) United Kingdom	22	8.8±3.2	8	Cerebral palsy	NR	Videoconference (Skype)	Therapeutic management/follow-up assessment	Pediatrician	18 sessions. 3 times a week	3
Robb 2019 (28) USA	43	50.6±NR	61	Multiple Sclerosis	< 10 years = 16(42%) ≥ 10 y ≤ 20 years = 13 (34%) > 20 years = 9 (24%)	Videoconference	Therapeutic management/follow-up assessment	Neurologist	1 session every 3 months	6
Sajatovic 2018 (43) USA	120	41.3±18.8	68.1	Epilepsy	20.6±15.2	Software online (SMART)	Therapeutic management/follow-up assessment	Educator and nurse	8 sessions in 8-10 months	6
Saywell 2021 (36) New Zeeland	95	73.5±11.7	48.4	Stroke	0.7±0.3	Tele-rehabilitation (ACTIV videoconference+ telephone call + SMS)	Therapeutic management	Physiotherapist	NR	12
Sekimoto 2019 (29) Japan	10	53.5±5.5	30	Parkinson's disease	7.3±6	Videoconference	Therapeutic management/follow-up assessment	Health professional	3 sessions. 1 session every 2 months	12
Wan 2016 (40) China	91	59.7±12.5	28.75	Stroke	NR	Telephone calls	Follow-up assessment	Nurse	3 calls 1st week and month 1 and month 3 after high	6
Wu 2020 (37) China	61	57.7±10.2	25	Stroke	NR	Tele-rehabilitation (Internet-based TCMeeting v6.0 conferencing system)	Therapeutic management/follow-up assessment	Multidisciplinary team	2 sessions. 1 session weekly.	3

Zissman 2012 (30) Israel	40	43.8±11.5	85	Multiple Sclerosis	6.8±5.2	Videoconference (call center Telemed)	Therapeutic management/follow-up assessment	Nurse	On demand, operational 24 hours a day, 7 days a week	6

NR: not reported; USA: United States of America

†Mean±standard deviation

Figure 1. PRISMA flow chart of the study selection process

Figure 2. Risk of bias summary of studies included