Published in final edited form as:

Mov Disord. 2016 September ; 31(9): 1327–1336. doi:10.1002/mds.26671.

Transducer-based evaluation of tremor

Dietrich Haubenberger, MHSc, MD[1], **Giovanni Abbruzzese, MD**[2], **Peter G Bain, MD**[3], **Nin Bajaj, MD PhD**[4], **Julián Benito-León, MD, PhD**[5,6,7], **Kailash P Bhatia, FRCP**[8], **Günther Deuschl, MD**[9], **Maria João Forjaz, PhD**[10], **Mark Hallett, MD**[11], **Elan D Louis, MD**[12], **Kelly E Lyons, PhD**[13], **Tiago A Mestre, MSc, MD**[14], **Jan Raethjen, MD**[9], **Maria Stamelou, MD, PhD**[15], **Eng-King Tan, MD**[16], **Claudia M Testa, MD, PhD**[17], and **Rodger J Elble, MD, PhD**[18]

[1]Clinical Trials Unit, Office of the Clinical Director, National Institutes of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

[2]DINOGMI University of Genoa, Italy

[3]Department of Neurology, Imperial College London, Charing Cross Hospital, London, United Kingdom

[4]Department of Neurology, Nottingham University Hospitals NHS Trust, Nottingham, UK

[5]Department of Neurology, University Hospital “12 de Octubre”, Madrid, Spain

[6]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Spain

[7]Department of Medicine, Complutense University, Madrid, Spain

[8]Sobell Department for Movement Neuroscience, UCL, Institute of Neurology, Queen Square, London WC1N 3BG

[9]Department of Neurology, Christian-Albrechts-University Kiel, Kiel, Germany

Corresponding Author: Dietrich Haubenberger, MHSc MD, NINDS Intramural Research Program, National Institutes of Health, 9000 Rockville Pike, Building 10, Rm 6-5700, Bethesda, MD, 20892, USA, office phone: +1 (301) 496-7563, cell phone: +1 (301) 633-3429, dietrich.haubenberger@nih.gov.

Financial Disclosures / Conflict of Interest concerning the research related to the manuscript:
Dietrich Haubenberger is involved in the development of Neuroglyphics for tremor assessment and collaborates with Portland State University to develop sensors to measure tremor.
Giovanni Abbruzzese none
Peter Bain none
Nin Bajaj none
Julián Benito-León none
Kailash Bhatia none
Guenther Deuschl none
Maria João Forjaz none

Mark Hallett is involved in the development of Neuroglyphics for tremor assessment and has a collaboration with Portland State University to develop sensors to measure tremor.
Elan Louis none
Kelly Lyons none
Tiago Mestre none
Jan Raethjen none
Maria Stamelou none
Eng-King Tan none
Claudia Testa none
Rodger Elble has collaborated with Great Lakes NeuroTechnologies and APDM Wearable Technologies in the development of their motion transducers.

[10]National School of Public Health and Red de Investigación en Servicios Sanitarios y Enfermedades Crónicas (REDISSEC), Carlos III Institute of Health, Madrid, Spain

[11]Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

[12]Departments of Neurology and Chronic Disease Epidemiology, Yale School of Medicine and Yale School of Public Health, Yale University, New Haven, CT, USA

[13]University of Kansas Medical Center, Kansas City, Kansas

[14]Parkinson's disease and Movement Disorders Center, Division of Neurology, Department of Medicine, University of Ottawa, The Ottawa Hospital Research Institute, Ottawa Brain and Mind Research Institute, Ottawa, Ontario, Canada

[15]Neurology Department, University of Athens, Greece and Neurology Department, Philipps University, Marburg, Germany

[16]Department of Neurology, National Neuroscience Institute (SGH campus), Duke NUS Medical School, Singapore General Hospital, Singapore

[17]Department of Neurology and Parkinson's and Movement Disorders Center, Virginia Commonwealth University, Richmond, Virginia, USA

[18]Department of Neurology, Southern Illinois University School of Medicine, Springfield, Illinois, USA?

Abstract

The Movement Disorder Society (MDS) established a task force on tremor that reviewed the use of transducer-based measures in the quantification and characterization of tremor. Studies of accelerometry, electromyography, activity monitoring, gyroscopy, digitizing tablet-based measures, vocal acoustic analysis, and several other transducer-based methods were identified by searching PubMed.gov. The availability, use, acceptability, reliability, validity, and responsiveness were reviewed for each measure using the following criteria: 1) used in the assessment of tremor, 2) used in published studies by people other than the developers, and 3) adequate clinimetric testing. Accelerometry, gyroscopy, electromyography, and digitizing tablet-based measures fulfilled all three criteria. Compared to rating scales, transducers are far more sensitive to changes in tremor amplitude and frequency, but they do not appear to be more capable of detecting a change that exceeds random variability in tremor amplitude (minimum detectable change). The use of transducer-based measures requires careful attention to their limitations and validity in a particular clinical or research setting.

Keywords

tremor; transducers; accelerometry; electromyography; reproducibility of results

INTRODUCTION

Clinical rating scales are the most popular method of assessing tremor, but transducer-based methods are increasingly appealing. Rapidly advancing technologies have made transducers more precise, affordable, portable, and capable of long-term recording. Here we define transducer as any sensor that converts a physical property of tremor into an electrical signal. Devices are instruments equipped with one or more types of transducer, being deployed for a specific methodology.

Transducer-based methods and rating scales should fulfill similar standards of validity, reliability, and sensitivity to change. The Movement Disorders Society (MDS) Task Force on Tremor recently published its review of tremor rating scales,[1] and a comparable review of transducers is needed. Therefore, we examined the validity, reliability and responsiveness of transducer-based methods in the detection and quantification of abnormal tremor. We did not review the use of transducer-based methods in differentiating different forms of tremor on a diagnostic or phenomenological level (rest, posture, action, intention) because these applications depend primarily on complex computer algorithms and data interpretation that have not been sufficiently studied or developed and are beyond the scope of this review.

The aim of this review is to discuss the methodology of measuring tremor with transducers. The studies selected for this review used various specific devices that shared common methodologies (e.g., accelerometry). We aimed to summarize the findings for each common methodology, while referring to specific devices only in the context of specific studies. The authors stress that this approach is not intended to recommend any specific commercial product The assessment of a methodology is only as good as the specific transducers and devices used in published studies, and it is important to state that inferences onto a common methodology are often based on data available from actually applied transducers and devices, and therefore inherently limited.

METHODS

Measures using transducers in published clinical assessments of tremor were considered for this review. Medline was searched via PubMed.gov in March 2014 and in February 2015 using Boolean expressions of “tremor” AND each of the following: “device”, “measurement”, “transducer”, “accelerometer”, “accelerometry”, “electromyography”, “electromagnetic”, “goniometer”, “goniometry”, “gyroscope”, “inertial measurement unit”, “photogrammetric”, “test-retest reliability”, “digital”, “acoustic analysis” and “motion analysis”. Publications relevant for this review were selected based on an evaluation whether any of the formal evaluation criteria (see Appendix 1) were addressed in the manuscript. Furthermore, any secondary references cited in these publications were also reviewed for selection using the same criteria for inclusion in this review.

The evaluation form used in the assessment of tremor rating scales[1] was adapted for this study (Appendix 1). This form captured relevant properties of the specific device used in this study, including analysis methods, the designed and intended use, acceptability in different populations, and clinimetric properties including validity, reliability, and responsiveness. If

not explicitly reported in the literature, minimum detectable change (MDC) was computed using published data if available: $\mathrm{MDC}=1.96\cdot\sqrt{2}\cdot\sigma\cdot\sqrt{1-\mathrm{ICC}}$, where σ=standard deviation of the group of measurements and ICC is the intraclass correlation of the two measurements, or $MDC = 1.96 \cdot SD_d$, where SD_d=standard deviation of the difference between the two assessments.[2]

Transducers were reviewed by at least two Task Force members, one being the Task Force chair (RJE). Consensus reviews and initial draft of this manuscript were sent to all members of the Task Force. The final assessment was based on three criteria: 1) used in the assessment of tremor (Y/N), 2) used in published studies by people other than the developers (Y/N), and 3) adequate clinimetric testing (Y/N). Transducers were evaluated for use in tremor based on whether 3, 2 or 1 criteria were met.

Adequate clinimetric testing was defined as follows. For reliability, we required estimates of test-retest reliability, which is a measure of the consistency of a test administered two or more times over a period of time to the same group of individuals. Test-retest reliability is a function of random variability in the measurement system (i.e., transducer and data analysis) and in the phenomenon being measured (tremor). For validity, face validity and statistically significant correlations with clinical ratings (convergent validity) were required. Face validity is a subjective judgement of the extent to which a transducer appears to measure tremor. For sensitivity to change (responsiveness), the detection of change in at least one clinical trial was required, and estimates of MDC were either published or computed with published data.

RESULTS

The following transducer-based methodologies are included in this report because each has published validity, reliability and responsiveness data: accelerometry, electromyography, gyroscopy, activity monitoring, digitizing tablets, and acoustic analysis of voice tremor. The availability, use and acceptability, clinimetric properties, and proposed areas of application are summarized for each methodology. Devices that appeared in isolated reports or have had limited use or clinimetric testing are reviewed in Appendix 2.

Accelerometry

Availability—Accelerometry has been applied in tremor studies for more than 50 years.[3] Limited tremor analysis software is packaged with some commercially available transducers, but it is often necessary to develop additional custom software for tremor analysis. Accelerometry as discussed in this section is aimed at recordings of pre-specified limb positions or movements for seconds to minutes. Accelerometers, among other sensors, are also used in activity monitors (a.k.a. actigraphs), which record spontaneous activity continuously for hours or days. Due to the conceptually different approaches to tremor characterization, activity monitors are discussed separately below.

Use and acceptability—Body motion has 6 degrees of freedom, consisting of three-dimensional translation and rotation in space. Most body parts rotate about a joint, so motion (e.g., tremor) is primarily rotational. Accelerometry measures translations, but

accelerometers will also detect rotation, depending on their location with respect to the axis of rotation (joint).[4] Accelerometer output is proportional to both inertial acceleration (the measure of interest) and gravitational artifact.[4] Gravitational artifact cannot be removed by filtering, and multiple strategically-placed accelerometers are needed to capture inertial acceleration, free of gravitational artifact.[4] We found only one instance of this being done in a clinical study of tremor.[5]

Accelerometry has been used to assess tremor amplitude and frequency in all age groups.[6–8] Accelerometry in combination with EMG is also used to detect pathologic central neurogenic oscillation, which is characteristic of essential tremor, Parkinson tremor, orthostatic tremor and dystonic tremor.[9] This form of tremor oscillation has a frequency that is independent of mechanical loading and reflex arc length.[9–13] Spectral analysis of accelerometer recordings is frequently used to estimate tremor amplitude and frequency, and algorithms that distinguish oscillation from other movement are used to determine tremor presence.[14, 15]

Clinimetric properties—Measures obtained with accelerometers have good face validity when they are mounted appropriately and have recording specifications that are adequate for the tremor in question. For example, a specific accelerometer (or any other transducer) may not have sufficient sensitivity to measure physiologic tremor or may not have sufficient range to capture severe pathologic tremor (floor and ceiling effects). Face validity is reduced when accelerometers are not mounted optimally (e.g., when a wrist-worn accelerometer is used to measure hand tremor or when an accelerometer axis is not in the primary direction of motion) and when limb motion is too complex to be captured by one transducer.[3, 4]

Tremor acceleration is roughly equal to tremor displacement times the square of tremor frequency in radians/second. Therefore, displacement can be derived from acceleration by double integration[13] or by dividing acceleration by the square of tremor frequency in radians/second.[16] The reporting of spectral analysis measures has varied greatly among investigators: spectral peak amplitude,[17] log peak power,[18] area under the peak,[19, 20] and area under the spectrum.[19–23] Regardless, tremor amplitudes are logarithmically correlated with clinical ratings.[14, 24–26]

Test-retest linear correlations for upper extremity postural tremor in essential tremor (ET), assessed minutes apart, were >0.9,[11] and test-retest intraclass correlation coefficients (ICC) for same-day measurements of amplitude and occurrence (fraction of recording with tremor) were >0.8.[14] These values may vary with the etiology of tremor, the range of tremor amplitudes,[27] and the time between tremor measurements. In ET, tremor frequency varied <1 Hz in repeated measures over hours and over several weeks, but variability in amplitude was considerable (coefficient of variation ≈30%), and there was a downward trend in tremor amplitude over 5 weeks, suggesting a practice effect or habituation.[28] Test-retest reliability of clinician ratings and of ratings generated from accelerometry did not differ statistically for ET (ICC>0.8)[27] or Parkinson disease (PD) (ICC≈0.6–0.7).[29]

Accelerometry has been applied in the measurement of treatment effects in ET,[17, 20, 21, 23, 30–41] multiple sclerosis,[42] PD[43–46] and various drug- and toxin-induced

conditions.[14] In patients with ET, the sensitivity to change appears to be comparable to that of the Fahn-Tolosa-Marín scale (FTM),[47] Bain and Findley Spiral and Handwriting scales,[48] and the Essential Tremor Rating Assessment Scale (TETRAS).[27] However, in a study of 3,4-diaminopyridine, the FTM was sensitive to a practice/learning effect, but accelerometry was not, and the test-retest variability was greater for accelerometry.[49] In another study of ET, TETRAS was slightly more sensitive than accelerometry to an ethanol treatment effect.[25] However, in a study of zonisamide, postural hand tremor measured with accelerometry revealed a small treatment effect, while the FTM did not.[50] MDC for postural hand tremor was 73% of the baseline mean for ET patients assessed a few minutes apart.[51] MDCs for ratings derived from accelerometry were comparable to those derived from physician ratings in patients with ET[27] and PD.[29]

Applicability—Accelerometry can be used in the measurement of tremor amplitude, frequency and occurrence.

Electromyography

Availability—Tremor analysis with electromyography (EMG) is usually accomplished with surface skin electrodes mounted over the muscle belly in a bipolar configuration. Modern surface EMG systems allow portable multichannel recordings with wireless data transmission to a computer. Commercially available portable wireless EMG systems are equipped with software, but additional programming for tremor analysis is usually necessary.

Use and acceptability—EMG is used primarily for upper limb tremor, but electrodes can be applied over any muscle that is accessible with skin electrodes (e.g. over leg muscles to document the characteristic 13–18 Hz muscle activity in orthostatic tremor).[9] Most muscle electrodes have wired connections to recording or transmission units, and this may be restrictive during some activities.

EMG output is the voltage difference between two surface electrodes. Therefore, EMG does not measure tremor amplitude per se, rather it measures the occurrence and intensity of the underlying motor unit entrainment. EMG rectification and low-pass filtering ("demodulation") produces a signal that is proportional to muscle force.[52] However, demodulated EMG is only a rough surrogate for tremor amplitude, and EMG amplitudes may vary with electrode positioning and soft tissue impedance. Spectral analysis of demodulated EMG is used to determine the occurrence, frequency and intensity of motor unit entrainment.[53–55] Surface EMG is used to detect abnormal central neurogenic oscillation in pathological tremors[9] and to document entrainment, coherence, and movement disruption by distracting movements in functional (psychogenic) tremor.[22] EMG recordings can range from seconds to 24 hours or more.

Clinimetric properties—Rhythmic entrainment of motor unit discharge is the *sine qua non* of pathologic tremor, so the face validity of EMG in detecting tremor is not disputed. Occurrence of pathological tremor is validated by the observation that rhythmic EMG activity is absent in the majority of healthy controls with physiological tremor.[12] Test-retest

reliability (ICC) over 3 consecutive days was 0.8–0.9 for tremor occurrence, intensity and frequency in PD and ET.[56]

Tremor occurrence, but not intensity, correlated moderately well (r=0.7–0.8) with clinical ratings in ET and PD.[55] Long-term EMG recording was used to detect a significant 45.7% change in tremor occurrence in 84 PD patients treated with pramipexole.[57] This change was comparable to a 34.7% change in the Unified Parkinson Disease Rating Scale (UPDRS) tremor score.[57] The calculated MDC for occurrence of tremor was 64% of baseline in ET and 48% in PD.[58]

Applicability—EMG can be used to identify and quantify pathological tremor.

Gyroscopy

Availability—Gyroscopic transducers are comparable in size to accelerometers and provide a linear measure of angular velocity (degrees/sec or radians/sec) of a body part rotating in space. Triaxial gyroscopes are often paired with triaxial accelerometers in so-called inertial measurement units. Inertial measurement units are widely available and used in many industrial and medical applications, including human motion analysis. Limited tremor analysis software is packaged with commercial devices, but it is often necessary to develop additional custom software for tremor analysis.

Use and acceptability—Most devices using gyroscopes can transmit data wirelessly to a computer. Some manufacturers provide centralized data analysis for their devices (e.g., www.glneurotech.com), but most devices require the user to develop customized software for data analysis. Gyroscopy has been used to quantify Parkinson tremor and ET[27, 29, 59–61] and to identify central neurogenic tremor.[62, 63] In contrast to accelerometers, gyroscopic transducers have very small gravitational artifact that is only significant when the signal is integrated over time.[63, 64] Gyroscopes record angular velocity independently of location on a rotating body part.

Clinimetric properties—Most tremors are primarily rotational motion of a body part, so gyroscopes have good face validity for recording tremor. Moreover, log-transformed measurements are strongly correlated with clinical tremor ratings.[24, 65] Clinical ratings of ET and PD generated from transducer recordings had comparable test-retest reliability (intraclass correlations 0.5 to 0.98) and MDC estimates as ratings produced by clinicians.[27, 29]

Applicability—Gyroscopes can be used for the measurement of tremor amplitude, frequency and occurrence.

Activity monitoring

Availability—Activity monitors (a.k.a., actigraphs) are wearable motion transducers that are attached to the wrist or other body part to record spontaneous body motion continuously for 24 hours or more. The original actigraphs contained uniaxial accelerometers and were designed primarily for quantifying time spent in sleep versus other activity. The

Tremorwatch® (a.k.a., Actiwatch®, Cambridge Neurotechnology Ltd., Cambridge, UK) was an actigraph equipped with an algorithm to distinguish tremor from other movement, and it was capable of recording tremor presence and intensity for more than 24 hours.[66] The Tremorwatch® was used to assess ET, PD, and functional tremor.[67] but is no longer commercially available. Modern activity monitors are equipped with triaxial accelerometers, triaxial gyroscopes or both and have enough internal memory to store unprocessed digitized motion data continuously for at least 24 hours.

Many activity monitors are now commercially available,[i] but most were not designed for tremor analysis. Those adapted for this purpose must have a sampling (digitizing) rate of at least twice the frequency of the tremor and must have sufficient sensitivity and amplitude range to record tremor. Some activity monitors may have optional recording modes in which sampling rate, sensitivity, frequency range, and amplitude range are adequate for recording tremor. At the time of this review, Kinesia™ (Great Lakes Neurotechnologies, Cleveland, OH) was the only commercially available activity monitor for tremor analysis, and this software is designed for Parkinson disease. Kinesia™ software uses a computer algorithm that converts transducer recordings to clinical ratings. Other devices and algorithms are being developed.[68]

Use and acceptability—Most activity monitors are the size of a watch. Distinguishing tremor from other movement is accomplished by spectral analysis or by some other analysis algorithm that identifies oscillation.[63] Activity monitors can be used to measure tremor amplitude, frequency and occurrence over extended periods of time, during unconstrained spontaneous activity, or during specific activities.

Clinimetric properties—The face validity of activity monitors is good for devices with suitable recording capabilities and tremor analysis algorithms. Face validity depends on the ability to mount the device in a location suitable for the measurement of tremor. For example, devices worn on the wrist may detect the presence of upper limb tremor but will provide only a rough measure of tremor amplitude when tremor is primarily rotation of the hand about the wrist. Furthermore, tremor generated in neighboring body parts can be transmitted to the transducer.

The Tremorwatch® was not sensitive enough to detect physiological tremor, and tremor was erroneously detected in only 6% of normal people (specificity 0.94).[66] The sensitivity for detecting Parkinson tremor in the upper limb was 0.7.[66, 69] Using spectral analysis and three-dimensional accelerometry, the sensitivity and specificity for detecting Parkinson tremor was approximately 0.84 and 0.94.[70]

Activity monitors can produce reliable and valid measures of tremor severity. A patient diary on tremor correlated significantly with PD tremor duration (r=0.62) and amplitude (r=0.55) measured with the Tremorwatch®,[71] and the UPDRS rest tremor item 20 also correlated with duration (r=0.85) and amplitude (r=0.71).[69] Sensitivity to change was demonstrated by a 44.5% reduction in tremor duration and 29.7% reduction in tremor amplitude in a study of

[i] http://www.sleepreviewmag.com/2015/03/actigraphy-comparison-guide-march-2015/

cabergoline for PD.[71] In a study of 50 early unmedicated PD patients, the Tremorwatch® was sensitive to disease progression over 6 months but no more sensitive than the UPDRS.[72] MDC has not been reported for these devices. Test-retest variability is greater when ET upper extremity tremor is recorded during spontaneous activity, compared to specific assessment protocols.[61]

Applicability—Studies of tremor analysis were performed with two technically differing activity monitors (Tremorwatch®, Kinesia™), and the Tremorwatch® is no longer available. No other activity monitor has been evaluated for measurement of tremor, but the limited published data suggest that other commercially available activity monitors can be used for detecting pathologic tremor and for measuring change in tremor amplitude and frequency due to treatment and disease progression. However, the application of activity monitors for these purposes will require the development of valid and reliable computer software algorithms.

Digitizing tablet-based tremor measures

Availability—Action tremor is commonly assessed in writing and drawing (e.g., Archimedes spirals) and can be quantified using a digitizing tablet, connected to a computer. Modern digitizing tablets are portable and come in sizes that accommodate a standard piece of writing paper. While several commercial graphics tablets are available on the market, Wacom Intuos® (Wacom Technology Corporation, Vancouver, WA) tablets have been used most commonly in studies of tremor. Their accuracy (±0.25 mm) and recording frequency (≥100 Hz) are sufficient to quantify tremor visible to the unaided eye, but not all tablets have these capabilities. Time-series data collected via digitizing tablets require processing and analysis to generate measures of interest (e.g., measures of frequency amplitude, irregularity, etc.). The platforms mentioned here have been used in tremor studies. No commercially available software is available to process tremor data obtained with digitizing tablets, but a free Windows-based program to collect, visualize, store and analyze spiral drawings has been used in several studies[20, 25, 73, 74] and is publicly available for download.[ii] VBTablet[iii] is a free Windows-based platform that that can be used to capture the pen coordinates, which can be analyzed with custom software.[75] Interfacing a tablet with custom software requires programming effort and industry-standard tablet software drivers.

Use and acceptability—Most pens for digitizing tablets are wireless and have a pressure-sensitive tip. However, the pressure sensor is nonlinear and must be calibrated, so this sensor can be used to detect tremor but has not been used to quantify tremor. The x-y displacements of the pen can be converted into velocity and acceleration by numerical differentiation, and frequency and amplitude measurers can be derived mathematically by spectral (Fourier) analysis.[75, 76]

There is no standard for how to process digitized writing or drawings. Software packages such as Neuroglyphics perform spectral analysis on the digitized drawing, but the user is responsible for interpretation. While tremor is most commonly quantified with spectral

[ii] www.neuroglyphics.org
[iii] greenreaper.co.uk

analysis, Rudzinska and coworkers converted the measurements into a 0–10 clinical score using an artificial neural network algorithm.[77] Data analysis is usually performed by the user, but it is possible to have raw data processed and analyzed at a central location.[78]

While digitizing tablets are routinely used in tremor, they have not been approved by regulatory bodies for tremor analysis. Tablets have been used to quantify tremor severity in several published treatment trials,[73, 78–80] to screen for pathologic tremor in genetic studies,[81] and to study patients with functional tremor, neurodegenerative ataxia, Huntington disease, tic disorders, and Niemann-Pick type C.[82–84] A single spiral can be collected and analyzed in a few minutes.

Potential ambiguities can arise from several sources. The instructions for writing and drawing have varied (e.g., direction of spiral drawing, template vs. no-template drawing, forearm supported or not, number of spiral turns, number of trials, etc.). Ambiguities in the analysis can arise in situations where tremor is very mild or intermittent, producing no unequivocal tremor spectral peak. Ambiguities also arise when the tablet recordings contain discontinuities due to the pen leaving the tablet surface, a common occurrence in severe tremor. Also, the start of a drawing can be overlain by irregularities introduced by intention tremor and dysmetria, and one may or may not choose to remove this portion of the drawing prior to tremor quantification.[80] Furthermore, the normal oscillations in cursive handwriting must be distinguished from tremor,[75] so spiral drawings may be the preferred task to assess tremor during penmanship-tasks.[85]

Clinimetric properties—Modern tablets have sufficient sensitivity to detect pathologic tremor that is visible to the unaided eye but have the floor effect of being unable to measure physiologic tremor and very mild pathologic tremor.[75] A ceiling effect is present when tremor is so severe that patients cannot keep the pen within 1 cm of the tablet surface.

Tablet analysis has good face validity, and log-transformed tablet measures of drawing tremor have high correlations with clinical ratings.[24, 75, 80, 86] Using spectral analysis, tablet-based measures are useful in distinguishing non-rhythmic irregularities in drawings from mild tremor.[86]

Test-retest analysis of two drawings of cursive e, and cursive l, and Archimedes spirals collected 3 minutes apart produced MDC estimates of 50%, 56% and 59% of the baseline means in patients with mild-moderate ET.[51] MDCs for the tablet and FTM part B were computed using baseline data from a crossover trial of pregabalin in ET,[78] and the MDC of the tablet (71% of baseline mean) was comparable to that of the FTM part B (64%).[87] Feys and coworkers[86] reported a mean (SD) ≈ 28 (20) and test-retest Spearman correlation ≈ 0.85 for patients with tremor due multiple sclerosis, and from these data, the $\mathrm{MDC} = 1.96 \cdot \sqrt{2} \cdot 20 \cdot \sqrt{1 - 0.85} = 21.5 \text{ or } 77\%$ of the baseline mean. More data are needed on test-retest reliability and MDC for repeated measures over longer intervals (e.g., 1–4 weeks) that are comparable to the measurement intervals in most clinical trials.

Applicability—Tremor measures derived from digitizing tablets can be used to quantify tremor and to detect pathologic tremor in spiral drawings. Inherent limitations to the

methodology are ceiling effects in severe tremors, in which patients may not be able to complete the task. Similar to visual ratings of handwriting and drawings, tablet-based measures of tremor are capable of quantifying tremor intensity, but are not useful in diagnosing different types of pathological tremor.

Acoustic analysis of voice tremor

Availability—Vocal tremor is recorded with wired or wireless microphones while patients perform standardized speech tasks such as emitting prolonged vowels (e.g., “aah”, “eee”, “ooh”) or repeating standardized sentences.[88–93] Sound pressure changes associated with voice tremor can be analyzed with commercial software or with generic signal processing platforms.[94]

Use and acceptability—Tremor is quantified by trained personnel using a measure of log-percent modulation (rhythmic fluctuation) of the fundamental frequency and sound pressure level.[94] The recording may require a sound booth, and data analysis is time consuming. Ambiguities in recordings and analysis stem from variation in loudness and duration of prolonged vowels, variation in vowel- and sentence-pronunciation across languages, and variation in speech output. Tremor in the head, mouth, or jaw can confound the analysis of laryngeal tremor.[88, 95]

Clinimetric properties—No data are available on floor or ceiling effects. This method has obvious face validity for identifying tremor,[96] and construct validity is documented by a correlation of the depth of frequency modulation with a 0–7 clinical rating scale.[97] Tremor measures probably vary with the patient’s language and age, and validation studies are needed in different language populations and age groups.

Depth of frequency modulation improved slightly in ET patients treated with methazolamide.[90] Acoustic analysis was either less sensitive or no better than clinical ratings in studies of botulinum toxin for voice tremor.[88, 98] A study by Warrick and coworkers revealed considerable repeated measures variability, but the test-retest reliability was not specifically estimated.[99] MDC has not been estimated.

Applicability—Acoustic analysis can be used for detecting and characterizing tremor, but there are insufficient clinimetric data to demonstrate the applicability of acoustic tremor analysis in assessment of tremor severity.

DISCUSSION

Based on the criteria set forth in this review, accelerometry, gyroscopes, electromyography, and digitizing tablets met all three criteria for use in the quantification and detection of abnormal tremor. Presently, there are no activity monitors fulfilling these criteria, but there are ample data supporting the feasibility of this approach. Acoustic analysis is useful for detecting vocal tremor, but there are insufficient clinimetric data for the application of acoustic analysis in assessing tremor severity.

Transducer-based measures are blind to the diagnosis and are only capable of measuring the symptomatic “output” of a movement disorder, independent of the underlying etiology. Most transducers used for tremor analysis were not developed for specific diseases, and the applicability of each device depends in the target signal for which it was developed. There is no evidence that a particular type of tremor is more amenable to measurement with transducers. Due to the rapid development in the field of sensor-based measurement-technology, it is important to point out that the specific transducer-based devices and analysis platforms are presented as methodological examples that have been applied to collect and analyze accelerometry, EMG, digitizing-tablet based measures, etc. in tremor. The aim of this review was to discuss the different techniques available for objective quantification of tremor, not to recommend specific devices or software platforms.

Transducers provide objective, precise linear measurements of tremor amplitude, frequency and occurrence, without the potential bias introduced by perceptions of patients and clinical raters. Wearable devices can be used to continuously record tremor, without the presence of a clinician. However, the application of transducers in tremor has significant limitations. Their use and data analysis require training, and a single transducer may not adequately capture the complex motion of a body part. The use of multiple transducers is feasible, but this approach is expensive and time-consuming, and data analysis is complex.[62] Floor and ceiling effects may exist with any transducer, so users must select transducers with a sensitivity, frequency bandwidth and amplitude range suitable for the tremor being studied (Appendix 3).

The use of transducers does not eliminate user bias. Selecting recordings to analyze, trimming “bad data” from recordings, and interpreting results from spectral analysis can be affected by user bias. Therefore, strict standardization of data sampling and analysis is needed for all methods (Appendix 3), including blinded data analysis.

Transducers produce linear measures of tremor amplitude, while visual rating scales are inherently non-linear, as predicted by the Weber-Fechner law of psychophysics.[24] Based on the log-relationship between clinical ratings and transducer measures, a 1-point reduction on a 0–4 tremor rating scale corresponds to a 50% or greater reduction in tremor amplitude.[24] This is comparable to the MDC estimates reported for a variety of tremors and transducers.

Given their precision and sensitivity, one might expect transducers to have a lower MDC than clinical ratings. However, there is considerable test-retest random variability in tremor amplitude. Additional variability might come from variations in how and where the transducer is mounted and in signal acquisition and analysis. Regardless, in most clinical studies, investigators are interested in changes in tremor amplitude or occurrence that exceed random variability. The MDC is the smallest change exceeding random variability that a transducer or rating scale can detect. Currently, there is no evidence that the MDC is smaller when transducers are used.[1] When data from transducer-based tremor recordings are converted to ratings, clinical and computer-generated ratings have been statistically equivalent. [27, 29] Standardization across protocols would facilitate the comparison of results.

The minimum clinically important difference (MCID) has not been computed for transducers and tremor rating scales. MCID is to a large extent subjectively defined and may vary with subjects' daily activities and social behaviour. The preferred method of computing MCID is unclear.[100] MCID may increase in proportion to baseline tremor severity[100] and needs to be defined for various patient populations. Based on aggregated data from studies in ET, reducing tremor amplitude to a rating of 1 on a 0–4 clinical scale is associated with high patient satisfaction,[101] and this magnitude of change is within the capabilities of the transducer-based measures that fulfilled the evaluation criteria of this review.

The use of scales vs transducer-based measures will depend on the type of tremor, experimental goals and design, and resources. Sensor-based measures frequently will be used to complement the clinical examination and are an obvious choice when the goal is to measure tremor in the absence of a clinician. The episodic measurement of tremor using transducers has established utility in clinical trials, but scales and transducer-based measures appear to have comparable MDC. Continuous measurement of tremor using wearable devices is a promising approach to capture tremor in natural settings that are functionally relevant, but this approach has not been shown to be more sensitive to change than periodic assessments with rating scales. The utility of long-term recordings will depend on the development of valid computer algorithms for identifying and quantifying tremor against a background of other voluntary and involuntary movement. The precision and objectivity of transducer-based measures may not be sufficient to justify the cost and complexity of devices and associated software, vis-à-vis available rating scales. Lastly, the use of transducer-based measures requires careful attention to their limitations and validity in a particular clinical setting (Appendix 3).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding sources: Movement Disorders Society

Appendix

Author Roles (Research project: A. Conception, B. Organization, C. Execution; Statistical Analysis: A. Design, B. Execution, C. Review and Critique; Manuscript Preparation: A. Writing the first draft, B. Review and Critique)

Dietrich Haubenberger: research project (A, B, C), statistical analysis (C), manuscript preparation (A)

Giovanni Abbruzzese: manuscript preparation (B)

Peter Bain: research project (B, C), statistical analysis (A, C), manuscript preparation (B)

Nin Bajaj: manuscript preparation (B)

Julián Benito-León: manuscript preparation (B)

Kailash Bhatia: manuscript preparation (B)

Guenther Deuschl: manuscript preparation (B)

Maria João Forjaz: research project (A, B, C), statistical analysis (C), manuscript preparation (B)

Mark Hallett: manuscript preparation (B)

Elan Louis: manuscript preparation (B)

Kelly Lyons: manuscript preparation (B)

Tiago Mestre: statistical analysis (C), manuscript preparation (B)

Jan Raethjen: manuscript preparation (B)

Maria Stamelou: manuscript preparation (B)

Eng-King Tan: manuscript preparation (B)

Claudia Testa: research project (A, B, C), manuscript preparation (B).

Rodger Elble: research project (A, B, C), statistical analysis (A, B, C), and manuscript preparation (B).

Full financial Disclosures:

Dietrich Haubenberger: none

Giovanni Abbruzzese received speaker honoraria from Abbvie and Lundbeck and serves on the advisory board of Zambon.

Peter Bain is a consultant for the Royal College of Physicians, London (Chair of Tremor Map) and serves on the advisory board of DENDRON (Dementia and & Neurodegenerative Diseases Research Network, UK). He received grants from the Medical Research Council, National Tremor Foundation, Parkinson's Disease Society, Rosetree's Trust, and BUPA Foundation. He is employed by the Imperial College London and holds and honorary contract with Imperial College Healthcare NHS Trust. He received royalties from Oxford University Press, and he is a trustee to the National Tremor Foundation (UK registered charity).

Nin Bajaj has received grant support from Medical Research Council (UK), Wellcome Trust, National Institute of Health Research (UK), Parkinson's UK, GE Healthcare; honoraria for lectures from GE Healthcare.

Julián Benito-León: none

Kailash Bhatia received funding for travel from Ipsen, Merz Pharmaceuticals and Sun Pharma; is a co-editor in chief of Movement Disorders Clinical Practice (MDCP) Journal and on the editorial board of Therapeutic Advances in Neurological Disorders; receives royalties from the publication of Oxford Specialist Handbook of Parkinson's Disease and Other Movement Disorders (Oxford University Press, 2008); receives a stipend for editorship for MDCP; received speaker honoraria from GSK, Ipsen, Merz Pharmaceuticals, LLC, and Sun Pharmaceutical Industries Ltd.; received personal compensation for advisory board from Ipsen, and Boehringer-Ingelheim; received research support from the Wellcome Trust Medical Research Council (MRC) strategic neurodegenerative disease initiative award (no. WT089698), a grant from the Dystonia Coalition, and a grant from Parkinson's UK (no. G-1009), Gossweiller Foundation, and NIHR.

Günther Deuschl has received lecture fees from Medtronic and Desitin and has been serving as a consultant for Medtronic, Sapiens and Boston Scientific. He received royalties from Thieme publishers. He is a government employee and receives through his institution funding for his research from the German Research Council, the German Ministry of Education and Health, and Medtronic.

Maria João Forjaz: none

Mark Hallett is involved in the development of Neuroglyphics for tremor assessment, and has a collaboration with Portland State University to develop sensors to measure tremor. He serves as Chair of the Medical Advisory Board for and may receive honoraria and funding for travel from the Neurotoxin Institute. He may accrue revenue on US Patent #6,780,413 B2 (Issued: August 24, 2004): Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders, and US Patent #7,407,478 (Issued: August 5, 2008): Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. He is on the Editorial Board of 20 journals, and received royalties and/or honoraria from publishing from Cambridge University Press, Oxford University Press, John Wiley & Sons, Wolters Kluwer, Springer, and Elsevier. He has received honoraria for lecturing from Columbia University. Dr. Hallett's research at the NIH is largely supported by the NIH Intramural Program. Supplemental research funds have been granted by BCN Peptides, S.A. for treatment studies of blepharospasm, Medtronics, Inc., for studies of deep brain stimulation, Parkinson Alliance for studies of eye movements in Parkinson's disease, UniQure for a clinical trial of AAV2-GDNF for Parkinson Disease, Merz for treatment studies of focal hand dystonia, and Allergan for studies of methods to inject botulinum toxins.

Elan Louis: none

Kelly Lyons received consulting fees from Adamas and US WorldMeds.

Tiago Mestre has been a consultant for CHDI Foundation and AbbVie. He has received honoraria from AAN, Novartis, AbbVie and Teva and grants from the Parkinson Society Canada, Parkinson study group/National Parkinson Foundation and the University of Ottawa.

Jan Raethjen is a paid advisory board member for Novartis.

Maria Stamelou serves on the editorial boards of Movement Disorders Journal and Frontiers in Movement Disorders, received travel and speaker honoraria from Actelion and AbbVie Pharmaceuticals; receives research support from the Hellenic Ministry of Education (THALIS) and from the Michael J Fox Foundation (Prodromal PPMI).

Eng-King Tan has received honoraria as an editor of European Journal of Neurology (Wiley) and Parkinsonism and related disorders (Elsevier). He is also an editor of Journal of Parkinson's disease, Basal Ganglia and Annals Academy of Medicine. He is supported by research funds from the National Medical Research Council and Duke NUS Medical School. His programs have also been supported by educational grants from Novartis and GlaxoSmithKline.

Claudia Testa is employed by Virginia Commonwealth University (VCU). She received honoraria from MedLink Neurology, Society for Neuroscience, and Lundbeck Pharmaceuticals. She received grants or contracts from the Huntington Study Group and Auspex Pharmaceuticals, the CHDI Foundation, Teva Pharmaceuticals, and the NIH/NORD grant 5 U54 NS065701 (Dystonia Coalition).

Rodger Elble received grant support from the National Institutes of Health and the Spastic Paralysis Research Foundation of Kiwanis International, Illinois-Eastern Iowa District. He received consulting fees from Sage Therapeutics and is a paid video rater for InSightec.

REFERENCES

1. Elble R, Bain P, Forjaz MJ, et al. Task force report: scales for screening and evaluating tremor: critique and recommendations. Mov Disord. 2013; 28(13):1793–1800. [PubMed: 24038576]
2. Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. J Strength Cond Res. 2005; 19(1):231–240. [PubMed: 15705040]
3. Elble, RJ. Accelerometry. In: Hallett, M., editor. Handbook of Clinical Neurophysiology. New York: Elsevier Science B. V.; 2003. p. 181-190.
4. Elble RJ. Gravitational artifact in accelerometric measurements of tremor. Clin Neurophysiol. 2005; 116(7):1638–1643. [PubMed: 15905122]
5. Sprdlík O, Hurák Z, Hoskovcová M, Ulmanová O, Ruzicka E. Tremor analysis by decomposition of acceleration into gravity and inertial acceleration using inertial measurement unit. Biomedical Signal Processing and Control. 2011; 6(3):269–279.
6. Marshall J. Physiological tremor in children. J Neurol Neurosurg Psychiatry. 1959; 22:33–35. [PubMed: 13642074]
7. Despres C, Richer F, Roberge MC, Lamoureux D, Beuter A. Standardization of quantitative tests for preclinical detection of neuromotor dysfunctions in pediatric neurotoxicology. Neurotoxicology. 2005; 26(3):385–395. [PubMed: 15935210]
8. Fusco C, Valls-Sole J, Iturriaga C, Colomer J, Fernandez-Alvarez E. Electrophysiological approach to the study of essential tremor in children and adolescents. Dev Med Child Neurol. 2003; 45(9): 624–627. [PubMed: 12948330]
9. Elble, RJ.; Deuschl, G. Tremor. In: Brown, WF.; Bolton, CF.; Aminoff, M., editors. Neuromuscular Function and Disease: Basic, Clinical and Electrodiagnostic Aspects. Philadelphia: W. B. Saunders Co; 2002. p. 1759-1779.
10. Elble RJ. Physiologic and essential tremor. Neurology. 1986; 36:225–231. [PubMed: 3945394]

11. Elble RJ, Higgins C, Leffler K, Hughes L. Factors influencing the amplitude and frequency of essential tremor [published erratum appears in Mov Disord 1995 May;10(3):411]. Mov Disord. 1994; 9(6):589–596. [PubMed: 7845397]
12. Elble RJ. Characteristics of physiologic tremor in young and elderly adults. Clin Neurophysiol. 2003; 114(4):624–635. [PubMed: 12686271]
13. Louis ED, Pullman SL. Comparison of clinical vs. electrophysiological methods of diagnosing of essential tremor. Mov Disord. 2001; 16(4):668–673. [PubMed: 11481690]
14. Caligiuri MP, Tripp RM. A portable hand-held device for quantifying and standardizing tremor assessment. J Med Eng Technol. 2004; 28(6):254–262. [PubMed: 15513743]
15. de Lima ER, Andrade AO, Pons JL, Kyberd P, Nasuto SJ. Empirical mode decomposition: a novel technique for the study of tremor time series. Med Biol Eng Comput. 2006; 44(7):569–582. [PubMed: 16937193]
16. Elble, RJ.; Koller, WC. Tremor. first. Baltimore: The Johns Hopkins University Press; 1990.
17. Calzetti S, Findley LJ, Perucca E, Richens A. Controlled study of metoprolol and propranolol during prolonged administration in patients with essential tremor. J Neurol Neurosurg Psychiatry. 1982; 45(10):893–897. [PubMed: 6815306]
18. Mera T, Vitek JL, Alberts JL, Giuffrida JP. Kinematic optimization of deep brain stimulation across multiple motor symptoms in Parkinson's disease. J Neurosci Methods. 2011; 198(2):280–286. [PubMed: 21459111]
19. Handforth A, Martin FC. Pilot efficacy and tolerability: a randomized, placebo-controlled trial of levetiracetam for essential tremor. Mov Disord. 2004; 19(10):1215–1221. [PubMed: 15390011]
20. Haubenberger D, McCrossin G, Lungu C, et al. Octanoic acid in alcohol-responsive essential tremor: a randomized controlled study. Neurology. 2013; 80(10):933–940. [PubMed: 23408867]
21. Gorman WP, Cooper R, Pocock P, Campbell MJ. A comparison of primidone, propranolol, and placebo in essential tremor, using quantitative analysis. J Neurol Neurosurg Psychiatry. 1986; 49(1):64–68. [PubMed: 3514797]
22. Schwingenschuh P, Katschnig P, Seiler S, et al. Moving toward "laboratory-supported" criteria for psychogenic tremor. Mov Disord. 2011; 26(14):2509–2515. [PubMed: 21956485]
23. Wastensson G, Holmberg B, Johnels B, Barregard L. Quantitative Methods for Evaluating the Efficacy of Thalamic Deep Brain Stimulation in Patients with Essential Tremor. Tremor and Other Hyperkinetic Movements. 2013:3.
24. Elble RJ, Pullman SL, Matsumoto JY, Raethjen J, Deuschl G, Tintner R. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. Brain. 2006; 129(Pt 10):2660–2666. [PubMed: 16891320]
25. Voller B, Lines E, McCrossin G, et al. Alcohol challenge and sensitivity to change of the essential tremor rating assessment scale. Mov Disord. 2014; 29(4):555–558. [PubMed: 24123358]
26. Jeon H, Kim SK, Jeon B, Park KS. Distance estimation from acceleration for quantitative evaluation of Parkinson tremor. IEEE Engineering in Medicine and Biology Society Conference. 2011; 2011:393–396.
27. Mostile G, Fekete R, Giuffrida JP, et al. Amplitude fluctuations in essential tremor. Parkinsonism Relat Disord. 2012; 18(7):859–863. [PubMed: 22591578]
28. Cleeves L, Findley LJ. Variability in amplitude of untreated essential tremor. J Neurol Neurosurg Psychiatry. 1987; 50:704–708. [PubMed: 3612150]
29. Heldman DA, Espay AJ, LeWitt PA, Giuffrida JP. Clinician versus machine: Reliability and responsiveness of motor endpoints in Parkinson's disease. Parkinsonism Relat Disord. 2014; 20(6):590–595. [PubMed: 24661464]
30. Bushara KO, Malik T, Exconde RE. The effect of levetiracetam on essential tremor. Neurology. 2005; 64(6):1078–1080. [PubMed: 15781835]
31. Gironell A, Kulisevsky J, Barbanoj M, Lopez-Villegas D, Hernandez G, Pascual-Sedano B. A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor. Arch Neurol. 1999; 56(4):475–480. [PubMed: 10199338]
32. Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. Neurology. 1989; 39(12):1587–1588. [PubMed: 2586774]

33. Koller WC. Dose-response relationship of propranolol in the treatment of essential tremor. Arch Neurol. 1986; 43(1):42–43. [PubMed: 3942513]
34. Koller W, Herbster G, Cone S. Clonidine in the treatment of essential tremor. Mov Disord. 1986; 1(4):235–237. [PubMed: 3332805]
35. Koller WC, Royse VL. Time course of a single oral dose of propranolol in essential tremor. Neurology. 1985; 35(10):1494–1498. [PubMed: 4033931]
36. Koller WC. Propranolol therapy for essential tremor of the head. Neurology. 1984; 34(8):1077–1079. [PubMed: 6379505]
37. Baruzzi A, Procaccianti G, Martinelli P, et al. Phenobarbital and propranolol in essential tremor: a double-blind controlled clinical trial. Neurology. 1983; 33(3):296–300. [PubMed: 6338416]
38. Kuroda Y, Kakigi R, Shibasaki H. Treatment of essential tremor with arotinolol. Neurology. 1988; 38(4):650–652. [PubMed: 2451192]
39. Papapetropoulos S, Gallo BV, Guevara A, et al. Objective tremor registration during DBS surgery for essential tremor. Clin Neurol Neurosurg. 2009; 111(4):376–379. [PubMed: 19121890]
40. Jankovic J, Schwartz K, Clemence W, Aswad A, Mordaunt J. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. Mov Disord. 1996; 11(3):250–256. [PubMed: 8723140]
41. Ushe M, Mink JW, Revilla FJ, et al. Effect of stimulation frequency on tremor suppression in essential tremor. Mov Disord. 2004; 19(10):1163–1168. [PubMed: 15390071]
42. Fox P, Bain PG, Glickman S, Carroll C, Zajicek J. The effect of cannabis on tremor in patients with multiple sclerosis. Neurology. 2004; 62(7):1105–1109. [PubMed: 15079008]
43. Koller WC, Herbster G. Adjuvant therapy of parkinsonian tremor. Arch Neurol. 1987; 44(9):921–923. [PubMed: 3619710]
44. Obwegeser AA, Uitti RJ, Witte RJ, Lucas JA, Turk MF, Wharen RE Jr. Quantitative and qualitative outcome measures after thalamic deep brain stimulation to treat disabling tremors. Neurosurgery. 2001; 48(2):274–281. discussion 281–274. [PubMed: 11220369]
45. Papapetropoulos S, Jagid JR, Sengun C, Singer C, Gallo BV. Objective monitoring of tremor and bradykinesia during DBS surgery for Parkinson disease. Neurology. 2008; 70:1244–1249. [PubMed: 18391156]
46. Sturman MM, Vaillancourt DE, Metman LV, Bakay RA, Corcos DM. Effects of subthalamic nucleus stimulation and medication on resting and postural tremor in Parkinson's disease. Brain. 2004; 127(Pt 9):2131–2143. [PubMed: 15240437]
47. Popa T, Russo M, Vidailhet M, et al. Cerebellar rTMS stimulation may induce prolonged clinical benefits in essential tremor, and subjacent changes in functional connectivity: an open label trial. Brain stimulation. 2013; 6(2):175–179. [PubMed: 22609238]
48. Shill HA, Bushara KO, Mari Z, Reich M, Hallett M. Open-label dose-escalation study of oral 1-octanol in patients with essential tremor. Neurology. 2004; 62(12):2320–2322. [PubMed: 15210907]
49. Lorenz D, Hagen K, Ufer M, Cascorbi I, Deuschl G, Volkmann J. No benefit of 3,4-diaminopyridine in essential tremor: a placebo-controlled crossover study. Neurology. 2006; 66(11):1753–1755. [PubMed: 16769957]
50. Zesiewicz TA, Ward CL, Hauser RA, Sanchez-Ramos J, Staffetti JF, Sullivan KL. A double-blind placebo-controlled trial of zonisamide (zonegran) in the treatment of essential tremor. Mov Disord. 2006; 22:279–282. [PubMed: 17149715]
51. Akano E, Zesiewicz T, Elble R. Fahn-Tolosa-Marin scale, digitizing tablet and accelerometry have comparable minimum detectable change. Mov Disord. 2015; 30(Suppl 1):S556.
52. Milner-Brown HS, Stein RB. The relation between the surface electromyogram and muscular force. J Physiol. 1975; 246(3):549–569. [PubMed: 1133787]
53. Boose A, Spieker S, Jentgens C, Dichgans J. Wrist tremor: investigation of agonist-antagonist interaction by means of long-term EMG recording and cross-spectral analysis. Electroencephalogr Clin Neurophysiol. 1996; 101:355–363. [PubMed: 8761046]
54. Scholz E, Bacher M, Diener HC, Dichgans J. Twenty-four-hour tremor recordings in the evaluation of the treatment of Parkinson's disease. J Neurol. 1988; 235(8):475–484. [PubMed: 3210053]

55. Spieker S, Boose A, Breit S, Dichgans J. Long-term measurement of tremor. Mov Disord. 1998; (13 Suppl 3):81–84. [PubMed: 9827600]
56. Spieker S, Ströle V, Sailer A, Boose A, Dichgans J. Validity of long-term electromyography in the quantification of tremor. Mov Disord. 1997; 12(6):985–991. [PubMed: 9399225]
57. Pogarell O, Gasser T, van Hilten JJ, et al. Pramipexole in patients with Parkinson's disease and marked drug resistant tremor: a randomised, double blind, placebo controlled multicentre study. J Neurol Neurosurg Psychiatry. 2002; 72(6):713–720. [PubMed: 12023411]
58. Spieker S, Jentgens C, Boose A, Dichgans J. Reliability, specificity and sensitivity of long-term tremor recordings. Electroencephalogr Clin Neurophysiol. 1995; 97:326–331. [PubMed: 8536582]
59. Heldman DA, Jankovic J, Vaillancourt DE, Prodoehl J, Elble RJ, Giuffrida JP. Essential tremor quantification during activities of daily living. Parkinsonism Relat Disord. 2011; 17(7):537–542. [PubMed: 21570891]
60. Mostile G, Giuffrida JP, Adam OR, Davidson A, Jankovic J. Correlation between Kinesia system assessments and clinical tremor scores in patients with essential tremor. Mov Disord. 2010; 25(12):1938–1943. [PubMed: 20623687]
61. Pulliam CL, Eichenseer SR, Goetz CG, et al. Continuous in-home monitoring of essential tremor. Parkinsonism Relat Disord. 2014; 20(1):37–40. [PubMed: 24126021]
62. Lambrecht S, Gallego JA, Rocon E, Pons JL. Automatic real-time monitoring and assessment of tremor parameters in the upper limb from orientation data. Front Neurosci. 2014; 8:221. [PubMed: 25120424]
63. Gallego JA, Rocon E, Roa JO, Moreno JC, Pons JL. Real-time estimation of pathological tremor parameters from gyroscope data. Sensors. 2010; 10(3):2129–2149. [PubMed: 22294919]
64. Chow R. Evaluating inertial measurement units. Test & Measurement World. 2011:34–37.
65. Giuffrida JP, Riley DE, Maddux BN, Heldman DA. Clinically deployable Kinesia technology for automated tremor assessment. Mov Disord. 2009; 24(5):723–730. [PubMed: 19133661]
66. van Someren EJW, Vonk BFM, Thijssen WA, et al. A new actigraph for long-term registration of the duration and intensity of tremor and movement. IEEE Trans Biomed Eng. 1998; 45(3):386–395. [PubMed: 9509754]
67. Parees I, Saifee TA, Kassavetis P, et al. Believing is perceiving: mismatch between self-report and actigraphy in psychogenic tremor. Brain. 2012; 135(Pt 1):117–123. [PubMed: 22075068]
68. Salarian A, Russmann H, Wider C, Burkhard PR, Vingerhoets FJ, Aminian K. Quantification of tremor and bradykinesia in Parkinson's disease using a novel ambulatory monitoring system. IEEE Trans Biomed Eng. 2007; 54(2):313–322. [PubMed: 17278588]
69. van Someren EJ, Pticek MD, Speelman JD, Schuurman PR, Esselink R, Swaab DF. New actigraph for long-term tremor recording. Mov Disord. 2006; 21(8):1136–1143. [PubMed: 16639727]
70. Hoff JI, Wagemans EA, van Hilten BJ. Ambulatory objective assessment of tremor in Parkinson's disease. Clin Neuropharmacol. 2001; 24(5):280–283. [PubMed: 11586112]
71. Binder S, Deuschl G, Volkmann J. Effect of cabergoline on parkinsonian tremor assessed by long-term actigraphy. Eur Neurol. 2009; 61(3):149–153. [PubMed: 19092251]
72. Goetz CG, Stebbins GT, Wolff D, et al. Testing objective measures of motor impairment in early Parkinson's disease: Feasibility study of an at-home testing device. Mov Disord. 2009; 24(4):551–556. [PubMed: 19086085]
73. Picillo M, Moro E, Edwards M, Di Lazzaro V, Lozano AM, Fasano A. Subdural Continuous Theta Burst Stimulation of the Motor Cortex in Essential Tremor. Brain Stimul. 2015; 8(4):840–842. [PubMed: 26038179]
74. Nahab FB, Wittevrongel L, Ippolito D, et al. An open-label, single-dose, crossover study of the pharmacokinetics and metabolism of two oral formulations of 1-octanol in patients with essential tremor. Neurotherapeutics. 2011; 8(4):753–762. [PubMed: 21594724]
75. Elble RJ, Brilliant M, Leffler K, Higgins C. Quantification of essential tremor in writing and drawing. Mov Disord. 1996; 11:70–78. [PubMed: 8771070]
76. Elble RJ, Sinha R, Higgins C. Quantification of tremor with a digitizing tablet. J Neurosci Methods. 1990; 32:193–198. [PubMed: 2385136]

77. Rudzinska M, Izworski A, Banaszkiewicz K, Bukowczan S, Marona M, Szczudlik A. Quantitative tremor measurement with the computerized analysis of spiral drawing. Neurol Neurochir Pol. 2007; 41(6):510–516. [PubMed: 18224573]

78. Zesiewicz TA, Sullivan KL, Hinson V, et al. Multisite, double-blind, randomized, controlled study of pregabalin for essential tremor. Mov Disord. 2013; 28(2):249–250. [PubMed: 23238907]

79. Elble RJ, Lyons KE, Pahwa R. Levetiracetam is not effective for essential tremor. Clin Neuropharmacol. 2007; 30(6):350–356. [PubMed: 18090460]

80. Haubenberger D, Kalowitz D, Nahab FB, et al. Validation of digital spiral analysis as outcome parameter for clinical trials in essential tremor. Mov Disord. 2011; 26(11):2073–2080. [PubMed: 21714004]

81. Shatunov A, Sambuughin N, Jankovic J, et al. Genomewide scans in North American families reveal genetic linkage of essential tremor to a region on chromosome 6p23. Brain. 2006; 129:2318–2331. [PubMed: 16702189]

82. Hsu AW, Piboolnurak PA, Floyd AG, et al. Spiral analysis in Niemann-Pick disease type C. Mov Disord. 2009; 24(13):1984–1990. [PubMed: 19672994]

83. Rudzinska M, Krawczyk M, Wojcik-Pedziwiatr M, Szczudlik A, Tomaszewski T. Tremor in neurodegenerative ataxias, Huntington disease and tic disorder. Neurol Neurochir Pol. 2013; 47(3): 232–240. [PubMed: 23821420]

84. Hess CW, Hsu AW, Yu Q, Ortega R, Pullman SL. Increased variability in spiral drawing in patients with functional (psychogenic) tremor. Human movement science. 2014; 38:15–22. [PubMed: 25240176]

85. Bain, PG.; Findley, LJ. Assessing Tremor Severity: A Clinical Handbook. London: Smith-Gordon; 1993.

86. Feys P, Helsen W, Prinsmel A, Ilsbroukx S, Wang S, Liu X. Digitised spirography as an evaluation tool for intention tremor in multiple sclerosis. J Neurosci Methods. 2007; 160(2):309–316. [PubMed: 17113154]

87. Elble R, Zesiewicz T. Fahn-Tolosa-Marin tremor scale and digitizing tablet have comparable minimum detectable change. Mov Disord. 2015; 30(Suppl 1):S558.

88. Adler CH, Bansberg SF, Hentz JG, et al. Botulinum toxin type A for treating voice tremor. Arch Neurol. 2004; 61(9):1416–1420. [PubMed: 15364688]

89. Bové M, Daamen N, Rosen C, Wang CC, Sulica L, Gartner-Schmidt J. Development and validation of the vocal tremor scoring system. Laryngoscope. 2006; 116(9):1662–1667. [PubMed: 16955000]

90. Busenbark K, Ramig L, Dromey C, Koller WC. Methazolamide for essential voice tremor. Neurology. 1996; 47(5):1331–1332. [PubMed: 8909454]

91. Gamboa J, Jimenez-Jimenez FJ, Nieto A, et al. Acoustic voice analysis in patients with essential tremor. J Voice. 1998; 12(4):444–452. [PubMed: 9988031]

92. Chenausky K, Macauslan J, Goldhor R. Acoustic Analysis of PD Speech. Parkinsons Dis. 2011; 2011:435232. [PubMed: 21977333]

93. Schoentgen J. Modulation frequency and modulation level owing to vocal microtremor. The Journal of the Acoustical Society of America. 2002; 112(2):690–700. [PubMed: 12186048]

94. Buder EH, Strand EA. Quantitative and graphic acoustic analysis of phonatory modulations: the modulogram. J Speech Lang Hear Res. 2003; 46(2):475–490. [PubMed: 14700387]

95. Lester RA, Barkmeier-Kraemer J, Story BH. Physiologic and acoustic patterns of essential vocal tremor. J Voice. 2013; 27(4):422–432. [PubMed: 23490130]

96. Shao J, MacCallum JK, Zhang Y, Sprecher A, Jiang JJ. Acoustic analysis of the tremulous voice: assessing the utility of the correlation dimension and perturbation parameters. J Commun Disord. 2010; 43(1):35–44. [PubMed: 19909966]

97. Anand S, Shrivastav R, Wingate JM, Chheda NN. An acoustic-perceptual study of vocal tremor. J Voice. 2012; 26(6):811. e811–817. [PubMed: 22921293]

98. Hertegard S, Granqvist S, Lindestad PA. Botulinum toxin injections for essential voice tremor. Ann Otol Rhinol Laryngol. 2000; 109(2):204–209. [PubMed: 10685574]

99. Warrick P, Dromey C, Irish JC, Durkin L, Pakiam A, Lang A. Botulinum toxin for essential tremor of the voice with multiple anatomical sites of tremor: a crossover design study of unilateral versus bilateral injection. Laryngoscope. 2000; 110(8):1366–1374. [PubMed: 10942143]

100. Cook CE. Clinimetrics corner. The minimal clinically important change score (MCID): a necessary pretense. J Man Manip Ther. 2008; 16(4):E82–E83. [PubMed: 19771185]

101. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. Lancet Neurol. 2011; 10(2):148–161. [PubMed: 21256454]