Pilot Efficacy and Tolerability: A Randomized, Placebo-Controlled Trial of Levetiracetam for Essential Tremor

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Abstract: **The purpose of this pilot single-site study was to assess efficacy and safety of levetiracetam for essential tremor, using a placebo-controlled, double-blind, randomized crossover design with an interim analysis planned after completion of the first 10 to 15 subjects. The study was designed to detect a mean 30% reduction in composite tremor score, comparable to that of primidone or propranolol, which can be demonstrated with 30 or fewer subjects. Each treatment arm included baseline tremor assessments, a 4-week medication titration, 2 weeks of stable dose, and treatment tremor assessments. Levetiracetam was titrated to 3,000 mg/day or to a lower maximal tolerated dose. The median age was 72 years, with 28 years median tremor duration. There was no statistically significant difference in response between placebo and levetiracetam on any tremor rating scale or accelerometry measure. The 95% confidence interval for the true mean difference between placebo and levetiracetam treatments was +18.5 to −22.5%, which excludes the minimum 30% drop required to consider levetiracetam clinically effective to a degree comparable to primidone or propranolol. Whether levetiracetam has lesser-degree antitremor efficacy was not addressed in this pilot study.**

Key words: essential tremor; levetiracetam; clinical trial

Levetiracetam is a recently introduced antiepileptic medication shown in animal models to have a unique antiseizure profile with a high safety margin.[1] Early studies established that it has a unique central nervous system binding site[2] but appears not to affect brain levels of GABA or excitatory amino acids.[3,4] Recently, levetiracetam has been reported to block high-voltage–activated calcium channels.[5–7]

Levetiracetam antagonizes the increase in the CA3 field potential population spike amplitude that normally occurs in vitro in a high-potassium, low-calcium medium, indicating that it inhibits neuronal hypersynchrony.[8] This property may underlie the observation that levetiracetam reduces high-stimulation transcranial magnetic stimulation-induced potentials.[9] Levetiracetam has been reported to be effective in the treatment of chronic myoclonus, including post-hypoxic forms, and in progressive myoclonic epilepsies.[10–12] It has also been reported to suppress dystonia in a hamster model.[13] Given levetiracetam's interesting properties, the ability of several antiepileptic drugs to suppress essential tremor, and preliminary patient reports of levetiracetam antitremor efficacy, an examination of potential efficacy for essential tremor (ET) was warranted.

SUBJECTS AND METHODS

Subjects

Subjects were eligible if they had ET for at least 1 year in both upper extremities and had a Tremor Rating Scale[14] score of at least 3 in at least one upper extremity in the Location/Severity subscale. Subjects had to have tried either primidone or propranolol without adequate control and could be taking either no medication for ET or a stable dose that was started at least 30 days before study entry. Subjects had to abstain from caffeine for 8 hours and from alcohol for 12 hours before each visit, be 18 years of age or older, and use adequate contraception if female of child-bearing potential.

Subjects were excluded for taking medications known to exacerbate tremor, progressive neurological condition other than ET, medical condition likely to result in hospitalization, hepatic disease, abnormal creatinine level, inability to give proper consent or to comply with study procedures, treatment with botulinum toxin within the past 6 months, current use of an investigational device, history of alcohol or drug abuse in the past year, drinking more than two glasses of wine or equivalent per day in past 30 days, history of blood dyscrasia, or significant psychiatric history within the past year.

The protocol was approved by the Institutional Review Board, and informed consent was obtained from all subjects. Subjects were recruited by the principal investigator and started Visit 1 between March 17, 2001, and June 16, 2001, with the last subject completing the controlled study on September 28, 2001. The study visits were conducted at the Clinical Research Center of the

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Protocol

This was a crossover treatment design, in which subjects received either levetiracetam or placebo in the first treatment arm, and the opposite treatment in the second treatment arm. At baseline Visit 1, medical and tremor history was obtained and a neurological and medical examination was performed by the treating physician in a blinded manner. Baseline tremor measures were obtained by a separate blinded examiner. Study medication was dispensed at the end of Visit 1, with the first dose taken the same evening. Levetiracetam, 500 mg, and placebo were supplied as scored tablets. Subjects started at 250 mg/day for 2 days, then 500 mg a day for 4 days, raising the dose by 500 mg at 4-day intervals, to a maximum of 3,000 mg per day, divided into twice-a-day dosing. The treating physician could stabilize or reduce the dose if symptoms were reported. The dose endpoint was, thus, 3,000 mg/day or a lower tolerated dose.

Subjects were seen by the treating physician and coordinator at 2-week intervals during the 4-week titration (Visits 2 and 3). At each visit, medication bottles dispensed at the previous visit were returned by subjects, and pill counts were performed to assess compliance. By Visit 3, titration was completed and subjects remained on a stable dose for 2 weeks prior to the treatment tremor assessment by the blinded examiner on Visit 4.

A 4-week washout period elapsed before initiation of the second treatment arm, including a 6-day taper off the first treatment. Baseline (Visit 5) and all other procedures (Visit 6–8) were performed as with the first arm, except that the opposite blinded treatment was administered. At the end of Visit 8, subjects were eligible to enter long-term follow-up and receive openly labeled levetiracetam, with assessments at 1, 3, 6, and 12 months.

Randomization and Blinding

Identically matched placebo and levetiracetam tablets were supplied by UCB Pharma in numbered bottles. Randomization of the order of study treatment assignment was performed by UCB Pharma, in groups of 4 subjects, by using a previously randomized sequence of numbers. The coded study drug was dispensed by the institutional research pharmacist in sequential order. The code was partly broken to "Treatment A" and "Treatment B" by the UCB pharmacist to the external statistician for the interim analysis. The identity of the treatments was not revealed until all data had been collected and the decision made to terminate the study. No study team member or subject was unblinded during the study.

Subjects and members of the study team were blinded to the identity of the treatments. Dosages and adverse events were monitored by the treating physician and the study coordinator. Data for efficacy analysis were obtained by the blinded examiner, who was not only blinded to study treatments but also to experimental medication dosages and adverse symptoms. Subjects were instructed not to provide this information to the blinded examiner who, thus, was not exposed to information that might lead to guessing the identity of treatments. Data forms filled by the blinded examiner were not accessible to other study team members during study conduct, nor did the blinded examiner have access to study files.

Procedures

Tremor severity was assessed with published ordinal scales in which tremor was rated 0 to 4, with 0 representing normal and 4 severely abnormal. In the Tremor Location/Severity scale, part of the Tremor Rating Scale (TRS) battery,[14] tremor in various body parts was rated at rest, posture, and kinesis. In the Specific Motor Task/Functions evaluation, used in both TRS and Unified Tremor Rating Assessment[15] (UTRA), subjects used the dominant hand to write, and each hand to draw a spiral, straight lines, sine waves, and to pour water. The UTRA Tremor Functional Rating scale rated disability from tremor in everyday tasks such as feeding, drinking, hygiene, dressing, writing, working, and fine movements.

These tremor evaluations were performed at baseline and after 2 weeks of stable medication in each treatment arm. In addition, the effect of study medication was evaluated in the Tremor Treatment Response (UTRA) scale. The examiner and subject independently rated the overall level of disability and extent of change from baseline. A visual analog scale was also used for global assessment of treatment effect.

Accelerometry was performed by attaching a small accelerometer to the hand over the dorsal third metacarpal head, and connecting this device to a digital display unit (Model MM1, Axon Instruments). Tremor was measured for 15 seconds while each upper extremity was at rest and during outstretched and wing-beating positions. The frequency of the dominant movement, movement Maximum Power (MP), and Total Power (TP) were recorded. The MP measures the maximum acceleration in a 0.2 Hz bandwidth centered around the dominant movement frequency. The TP provides the amplitude measurement of the total acceleration in the 0.2 to 20 Hz

bandwidth. Functional Accelerometry, a test battery currently being developed by the authors, assessed tremor in positions used in everyday life, including holding a pen, holding a glass, and holding a spoon with bent elbow at specific heights and the spoon or glass near the mouth.

Safety Monitoring and Adverse Events

Information was collected at each visit after baseline visit on adverse symptoms, and judged whether the symptom was not, possibly, probably, or definitely related to the study medication. General physical and neurological examinations and Mini-Mental State Examinations were conducted at baseline and at the concluding visit for each treatment arm.

Statistical Analysis

The primary measure was the summated tremor score from the TRS Location/Severity, UTRA Specific Motor Task/Functions, and UTRA Tremor Functional Rating subscales. The summated score at baseline was subtracted from the summated score at the end of the corresponding treatment arm; this difference was the primary measure of analysis. A negative difference connoted improved tremor scores. The hypothesis was tested that levetiracetam reduced tremor compared to baseline more than did placebo. Secondary endpoints were changes in upper extremity TRS Location/Severity, tremor treatment response, and global assessment, as rated by examiner and subject, and accelerometry measures.

The Shapiro-Wilks test was used to test the assumption of normality of error distribution. Mean changes were compared in this crossover design using repeated-measures analysis of variance. Formal tests for period and order effects were performed for each outcome variable.

Estimates of the treatment effect, possible period effect, and possible order/carryover effect were computed using the method of maximum likelihood. This method allowed inclusion of those subjects who had only partial data in the second treatment arm by taking advantage of the known correlations in the observed data between periods to adjust the treatment, period, and order effect estimates. The method also adjusted the corresponding standard errors (made them larger) to account for greater uncertainty in these estimates when there is partially missing data. The method assumes that the probability that a value is missing is not correlated with the unobserved value. For example, the method assumes that high values are no more likely to be missing than low values.

A clinically meaningful reduction in tremor was defined as 30%. Based on ET trials with first-line propranolol and primidone[16–18] that demonstrated a mean percent change in tremor of approximately 30% and a standard deviation of 30%, power analysis indicates that a crossover study with 30 subjects has a 98% chance of detecting a mean difference of 30%. We thus chose a total sample size of 30 subjects, sufficient to demonstrate efficacy for a treatment with efficacy comparable to that of first-line ET treatments primidone and propranolol.

In addition, we used an interim analysis, using the methodology described by O'Brien, Fleming, and Emerson.[19–21] A single interim analysis was incorporated into the study plan, to be performed by an external statistician when data were collected for 10 to 15 subjects. This strategy would lead to a decision to stop or continue the study according to established criteria.[20] If the interim analysis indicated a positive result with $P < 0.01$ (two-tailed), the study was to be terminated. If the upper boundary of the 95% confidence interval of the difference in the treatment means did not exceed 30% improvement, then the chance of subsequently detecting a difference with more subjects was less than 5%, and the study was to be terminated. In addition, if interim analysis indicated that a significant result with 30 subjects was less than 5%, the study was to be terminated early, as the requirement for more subjects would signify that the efficacy of levetiracetam was less than that of currently available propranolol and primidone. If, however, the upper boundary did exceed 30%, and the probability of a significant outcome with 30 subjects was greater than 5%, the study was to recruit additional subjects to a total sample size of 30. The final P value for significance was set at 0.045.[20]

RESULTS

Subjects

Subject flow is depicted in Figure 1. One subject was discontinued before randomization due to noncompliance with study procedures. Of 12 randomly assigned subjects, 2 withdrew during the first treatment arm; therefore, efficacy data are available from the remaining 10 subjects. Three subjects withdrew early during the second treatment arm.

Of the 12 randomly assigned subjects, 7 were men, 5 were women, all Caucasian. The median age was 72.5 years (range, 67–81 years), with median age of tremor onset at 42.5 years (range, 2–63 years) and median tremor duration of 28.5 years (range, 11–65 years). A positive family history of tremor was reported by 10 of

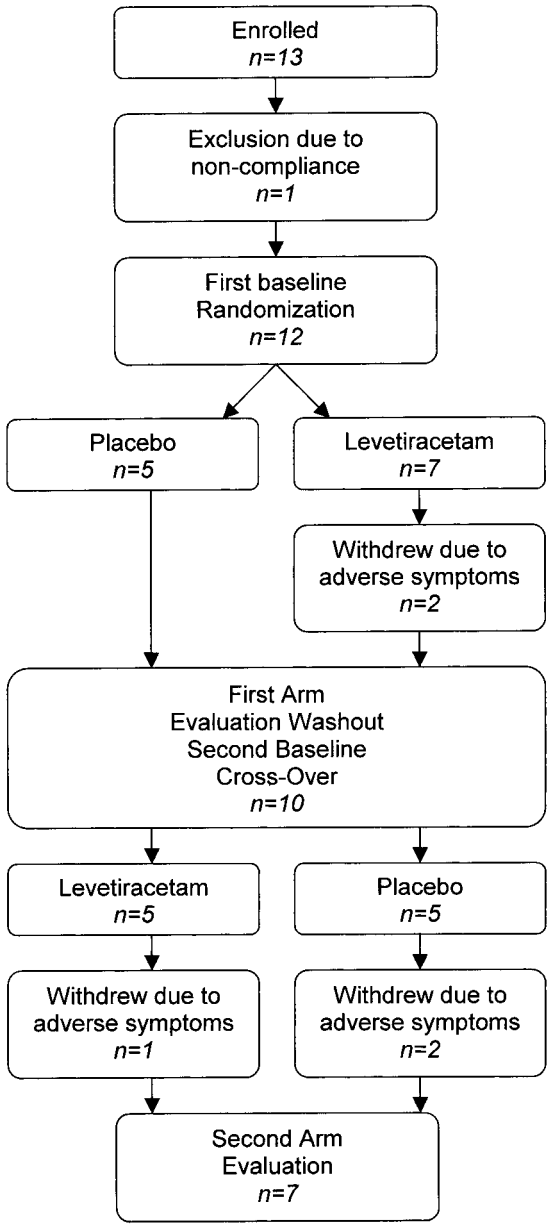

FIG. 1. Subject flow.

12, and tremor suppression by alcohol by 10 of 12 subjects. In addition to bilateral upper extremity tremor, 2 had head tremor and 1 had voice tremor. The median number of medications previously tried for tremor and discontinued was two (range, 0 to 5). During the study, no antitremor medication was taken by 2 subjects, one medication by 7 subjects, two medications by 2 subjects, and 1 subject took four concurrent medications for tremor.

Efficacy

Analysis indicated no significant period or order effect for any outcome variable. For the period and order effects of the primary endpoint (the summated score from the TRS Location/Severity, UTRA Specific Motor Task/Functions, and UTRA Tremor Functional Rating scales), P values were 0.90 and 0.88, respectively. For the primary endpoint and most of the secondary endpoints, the Shapiro–Wilks test was compatible with a normal data distribution.

Primary efficacy endpoint analysis revealed that the baseline summated tremor scores were 41.7 ± 3.7 and 41.9 ± 2.2 for placebo and levetiracetam treatments, respectively. These treatments reduced the tremor score compared to baseline by 4.7 ± 3.1 points with placebo and by 1.0 ± 3.1 points (mean ± SEM) with levetiracetam (Table 1), an effect that was not statistically significant ($P = 0.42$). No subject attained a clinically meaningful reduction in tremor severity of 30%. Examination of secondary efficacy endpoints revealed no statistical significance between placebo and levetiracetam treatments in TRS Location/Severity, upper extremity TRS Location/Severity, UTRA Specific Motor Task/Functions, or UTRA Tremor Functional Rating scores (Table 1).

Tremor Treatment Response scores revealed a trend by the blinded examiner and subject to associate levetiracetam with worse tremor relative to baseline (Table 2)

TABLE 1. *Treatment effect on tremor efficacy endpoints*

Variable	Placebo mean difference	Levetiracetam mean difference	P
Primary endpoint	−4.73 ± 3.1	−1.03 ± 3.1	0.42
TRS Location/Severity	−1.25 ± 1.71	0.36 ± 1.74	0.43
TRS Location/Severity, upper extremities	−0.77 ± 0.86	−1.57 ± 0.79	0.50
Functional Disability Scale	0.13 ± 1.12	1.16 ± 1.04	0.51
UTRA Tremor Functional Rating	−0.80 ± 1.10	−0.75 ± 0.96	0.97
Specific Motor Task/Functions	−1.91 ± 1.95	0.21 ± 1.79	−0.44
Accelerometry, MP	−73 ± 153	179 ± 140	0.25
Accelerometry, TP	293 ± 283	274 ± 260	0.96
Functional Accelerometry, MP	−194 ± 456	805 ± 385	0.13
Functional Accelerometry, TP	−255 ± 611	1063 ± 517	0.13

Mean differences between treatment and baseline tremor measures are shown. A negative difference indicates tremor reduction, positive change connote increased tremor from baseline to treatment. Primary endpoint tremor measure was summated score from Location/Severity, Specific Motor Task/Functions, and Tremor Functional Rating scales. Means ± SEM are shown. TRS, Tremor Rating Scale; UTRA, Unified Tremor Rating Assessment; MP, Maximum Power; TP, Total Power.

TABLE 2. *Treatment effect on treatment response and global measures*

Variable	Placebo	Levetiracetam	*P*
UTRA Treatment Response, by subject	0.47 ± 0.32	−0.43 ± 0.29	0.06
UTRA Treatment Response, by examiner	0.05 ± 0.34	−0.88 ± 0.33	0.07
Global Evaluation, by subject	13 ± 2.23	8.0 ± 2.1	0.08
Global Evaluation, by examiner	9.0 ± 5.15	−2.0 ± 4.7	0.19

These measures were obtained only at the treatment tremor evaluation. Negative numbers connote more tremor; positive numbers connote improvement. Means ± SEM are shown. UTRA, Unified Tremor Rating Assessment.

and placebo with slightly improved tremor ($P = 0.06$, 0.07, respectively). Similarly, the blinded examiner tended to rate with the global evaluation scale the response to placebo better than to levetiracetam ($P = 0.08$). Compliance, expressed as a percentage of medication taken versus medication prescribed, was 97.5% ± 9.1% (mean ± standard deviation) for the levetiracetam arm and 97.0% ± 7.2% for the placebo arm.

Interim Analysis

The levetiracetam arm had a mean drop of the primary endpoint of 2.5%, whereas the placebo arm had a mean drop of 11.3%. To be considered clinically effective, the levetiracetam group would have needed a drop of at least 30% above that of the placebo group, i.e., 41.3%. The 95% interval for the true mean change in the levetiracetam arm was +14.3% to −19.3%. Because the demonstration of clinical efficacy required that the composite tremor score fall by 41.3% or more, a value outside the bounds of this 95% confidence interval, the addition of more subjects was very unlikely to produce a positive result. This outcome met one of the criteria for early study termination, with no further subject recruitment.

Accelerometry

Standard accelerometry of upper extremity posture revealed no difference in MP and TP measures between placebo and levetiracetam conditions (Table 1). Functional accelerometry, which involved postures relevant to everyday tasks (holding a pen, cup, or spoon), yielded MP and TP measures that were not statistically different between the two conditions.

Safety Monitoring and Adverse Events

No changes from baseline occurred in vital signs or the neurological or Mini-Mental State Examination. Among 12 randomly assigned subjects, 7 subjects attained the levetiracetam top dose of 3,000 mg/day, whereas other subjects did not exceed 2,000 mg (1), 1,500 mg (1), 500 mg (2), or 250 mg (1).

The most common adverse symptom, rated as possibly, probably, or definitely related by the treating physician, was worse tremor, reported by 7 subjects taking levetiracetam and by 2 taking placebo. Other adverse symptoms included fatigue (5 vs. 1), drowsiness (4 vs. 2), impaired balance (2 vs. 0), dizziness (1 vs. 0), poor concentration (1 vs. 0), nausea (1 vs. 1), forgetfulness (1 vs. 1), diarrhea (0 vs. 1), and vivid dreams (0 vs. 1).

Three subjects withdrew during the levetiracetam treatment arm due to fatigue, dizziness, nausea (1), fatigue and lack of efficacy (1), and worse tremor, balance and concentration (1). A total of 2 subjects withdrew during the placebo arm: 1 with reported forgetfulness and worse tremor, and the other with acute drowsiness, diarrhea, and nausea.

Follow-Up

Only 2 of 12 subjects elected to enter the extension follow-up phase and receive openly labelled levetiracetam. One withdrew in the first 2 months due to lack of efficacy. The remaining subject reported subjective tremor reduction on a regimen of 500 mg twice a day; at 3 to 12 months of follow-up, the primary endpoint score was unchanged from baseline.

DISCUSSION

The dominant medications used to treat ET remain primidone and propranolol. Early crossover studies demonstrating clinical efficacy used 15 to 25 subjects[22–24] and indicated a mean percent change in tremor of approximately 30%.[16–18] We chose a trial design that could detect efficacy of a new therapy, provided that its efficacy was comparable or better to that of primidone or propranolol. Power analysis indicated that such efficacy had a high chance of detection with 30 or fewer subjects in a crossover design. A negative result with such a design does not exclude a lower level of efficacy.

The crossover design has been popular in ET drug trials[16,22,23,25] as it economizes on sample size. An adequate washout time between treatments is required, and assumptions of lack of period effect, order/carryover effect, and normal distribution of error need to be met. In this study, a 4-week washout was used and formal analyses indicated that requirements for repeated measures analysis were satisfied.

Interim analysis procedures[19–21] provide a useful method to terminate studies early when sufficient data

have accrued to indicate that the study endpoint has already been met or will not be met with the planned recruitment target. To be used appropriately, an interim analysis must be part of the study design with specified *P* values, so that the final alpha takes the interim analysis into account. The interim analysis must also be performed without unblinding the study team. These requirements were met in this study. Interim analysis of the composite tremor score revealed no significant difference between the placebo- and levetiracetam-treatment arms. Interim analysis indicated that the true difference between placebo- and levetiracetam-treated arms is considerably smaller than the 30% fall in tremor scores that was required. Thus, the interim analysis indicated that levetiracetam was very unlikely to exert efficacy comparable to that of propranolol or primidone. Whether levetiracetam has a lesser degree of antitremor potency was not assessed in this study.

Although the sample size may be regarded as small, the study outcome may be considered as part of a Gehan procedure.[26] In this procedure, one recruits enough subjects in the first part to assess whether the observed responder rate is compatible with the desired responder rate. If the first part is affirmative, one recruits additional subjects in the second part to estimate the actual responder rate. In this study, the desired responder rate was 0.5 (with normally distributed data, half the subjects would achieve a 30% tremor reduction). Only 5 subjects are needed in a part 1 Gehan procedure to reject the hypothesis with $P < 0.05$, because if all 5 fail to respond, the chance of this occurring, if the true responder rate is 0.5, is only $P = (0.5)^5 = 0.03$. In fact, all 12 subjects failed to respond, sufficient to rule out a true responder rate of 0.25 with a rejection error of $P < 0.05$.

A potential limitation of this study is that published inter-rater and test–retest reliability data for the Tremor Rating Scale are not available, despite its routine use in ET studies. In addition, the subjects may have been more refractory to antitremor medications than many ET patients, as they had usually tried other medications without success and had marked tremor. The titration of levetiracetam was rapid, raising the possibility that some subjects might have attained a higher dose with a slower titration. However, 7 of 12 subjects did attain the top dose of 3,000 mg/day. Three did not tolerate 250 or 500 mg/day and would not have benefited from a slower titration. Two subjects attained 1,500 and 2,000 mg/day, respectively; had they responded to higher doses, the study result would still have been negative.

The effect of antiepileptic medications on ET tremor is mixed. Primidone, benzodiazepines, topiramate, and gabapentin[27] reduce tremor, whereas carbamazepine, phenytoin,[28] lamotrigine,[29] valproate, and tiagabine may exacerbate or induce tremor. Their mechanisms of action on tremor are unknown or speculative, reflecting the finding that drug discovery for ET remains predominantly empirical.

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In Vivo Imaging of Microglial Activation With [^{11}C](*R*)-PK11195 PET in Corticobasal Degeneration

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Abstract: **Corticobasal degeneration (CBD) is a neurodegenerative parkinsonian disorder of unknown cause that shows considerable clinical heterogeneity. In CBD, activated microglia have been shown to be associated closely with the extensive tau pathology found in the affected basal ganglia, brainstem nuclei, and cortical regions. We report on the use of [^{11}C](*R*)-(1-[2-chlorophenyl]-*N*-methyl-*N*-[1-methylpropyl]-3-isoquinoline carboxamide) (PK11195) positron emission tomography (PET), a marker of peripheral benzodiazepine binding sites (PBBS) that are expressed by activated microglia, to demonstrate in vivo the degree and distribution of glial response to the degenerative process in 4 patients with CBD. Compared with normal age-matched controls, the CBD patient group showed significantly increased mean [^{11}C](*R*)-PK11195 binding in the caudate nucleus, putamen, substantia nigra, pons, pre- and postcentral gyrus, and the frontal lobe. [^{11}C](*R*)-PK11195 PET reveals a pattern of increased microglial activation in CBD patients involving cortical regions and the basal ganglia that corresponds well with the known distribution of neuropathological changes, which may therefore help to characterize in vivo the underlying disease activity in CBD.**

Key words: corticobasal degeneration; [^{11}C](*R*)-PK11195 PET; activated microglia

Corticobasal degeneration (CBD) is an adult onset progressive neurodegenerative disease of unknown cause. Clinically, patients present with an asymmetrical akinetic-rigid syndrome in combination with limb dystonia, apraxia, myoclonus, and cortical sensory deficit. Bulbar dysfunction, dysphasia, and supranuclear gaze

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