

SELF-REPORTED PAIN ASSESSMENTS IN CLINICAL TRIALS USING ELECTRONIC PATIENT DIARIES: RELATIONSHIP BETWEEN COMPLETION COMPLIANCE AND AGE, GENDER, PAIN SEVERITY

D Manning,¹ L Mesenbrink,¹ P Mesenbrink,¹ B Marino,² S Hendrix,² S Raymond²

¹Clinical Research & Development, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; ²PHT Corp, Charlestown, MA, USA

ABSTRACT

Assessing pain in humans has traditionally relied on paper self-reports. Recently a direct test by Stone and colleagues has confirmed anecdotal evidence that paper diaries are not completed at scheduled times. Electronic diaries (EPDs) can track and control time of data entry, thus ensuring currency of ratings of present pain. While subjects generally prefer EPDs compared to paper, no studies have tested the hypothesis that older people, people in pain or males would have problems complying with a schedule for diary completion. This paper reports on demographics of such compliance for 2 studies measuring efficacy and safety of Trileptol® (n=140) for treatment of chronic pain of diabetic neuropathy and another agent (n=123) investigated for neuropathic pain. Study subjects were outpatients with diabetic mellitus (type 1 or 2) from ages 32-93 diagnosed with a history of neuropathic pain for at least 6 months prior to study entry. Subjects were asked to complete and transmit daily self-assessments of symptom severity during the entire period of participation (17 weeks for Trileptol, 8 weeks for agent A). Each EPD report was signed and time stamped, and could not be retrospectively entered after the appropriate day. Compliance (percentage of the total number of daily diary reports scheduled that were actually completed) was evaluated for subjects grouped by gender, age category and mean pain score category. Overall compliance for all patients has exceeded 88%. There were no statistically significant differences in compliance between females and males or patients above or below 60 years old. Regression analysis of compliance versus age and versus mean pain score demonstrated slopes not significantly different from zero. We conclude that collection and transmission of daily EPD pain data is a feasible method that can be adopted with high compliance rates across a range of patient demographic subgroups.

BACKGROUND AND SIGNIFICANCE

- With the increased use of electronic patient diaries (EPDs), there has been growth in the number of published studies on the feasibility and value of this method of data collection. Electronic diaries have been used successfully in studies of asthma, lung transplantation, heartburn, headache, irritable bowel syndrome, diabetes, cancer, women's health, alcoholism, chronic pain, and incontinence.¹⁻¹²
- Several investigators have tested the feasibility of various forms of EPD using single-group designs. These studies demonstrate high patient acceptance and data quality with tele-monitoring,^{1,5} electronic spirometers,^{2,7} and hand-held touch screen devices.^{3,4,6}
- Other studies have been designed to compare accuracy, convenience, patient preference and data quality of EPD to that of paper diaries. Comparisons of electronic spirometry results to paper diaries in subjects with asthma have shown that subjects, both adult and children, report more peak flow entries in the paper diaries than the electronic spirometer recorded.¹³⁻¹⁵

- These results support the conclusion that subjects invent measurements when reporting such data on paper forms. A similar study compared inhaled medication use as recorded by an inhaler equipped with a clandestine timer/counter to self-reporting on paper. Findings again indicated that self-reported medication use on paper forms was higher than the use as recorded by the inhaler device.¹⁶
- A recent study on timely compliance of diary completion has shown that paper diary data intended to be entered at a specific time is often recorded retrospectively and invented prospectively.¹⁷ Comparisons of hand-held electronic diaries to paper diaries consistently report higher data quality, higher overall completion rates, more efficient data management, and patient preference for the EPD.^{8,9,11,12,17,18}
- One study examined the relationship between subject characteristics and preference for the EPD, and found no difference in preference attributable to age, gender, or experience.¹⁸ No studies specifically addressed the relationship of subject age or gender to compliance with the completion of an EPD. Factors such as age, gender, race, and disease severity could influence a patient's ability or willingness to comply with an EPD protocol.
- Any systematic variation in compliance with scheduled completion of self-reporting among patient subgroups could induce bias within randomized clinical trials that use an EPD for pain assessment.
- Therefore, we tested the null hypotheses that none of these demographic characteristics influenced the compliance in a multi-center, placebo-controlled study of patients with neuropathic pain due to diabetic neuropathy who had agreed to provide daily pain assessments.

METHODS

- After obtaining informed consent and screening for the presence of painful diabetic neuropathy, 123 diabetics (64 males, 59 females) were randomized in a multi-center, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of an investigational drug (Novartis Pharmaceuticals Corp) for treating neuropathic pain due to diabetic neuropathy.
- The oxcarbazepine (Trileptol®, Novartis Pharma AG) data examined, did not differ in conclusion, but were not part of the data analysis reported in this poster.
- Patients were asked to complete and transmit daily self-assessments of pain severity during their 6 weeks of study participation (1-week baseline, 4 weeks double-blind, 1-week follow-up). Pain severity was assessed on a previously validated 5-cm electronic visual analogue scale¹⁹ implemented on a LogPad™ handheld EPD (PHT Corp, Boston, MA).
- Patients were consistently instructed to collect EPD pain assessments daily and to transmit the data trans-telephonically to a secure, central database. Internet-based review of EPD entries allowed real-time access to patient randomization and diary compliance by the project team. Daily EPD entries were signed and time stamped, and could not be retrospectively entered after the appropriate day.

- Compliance was measured as the percentage of the total number of daily diary reports scheduled that were actually completed. EPD data were merged with the demographic data after the study was unblinded.

ANALYSIS

- All statistical testing was performed using an alpha level of 0.05 for main effects and 0.10 for interactions. No adjustments of significance levels were made for the multiple hypotheses that were tested.
- All statistical analyses were performed using SAS version 8.02 statistical software.
- Compliance was evaluated for subjects grouped by gender, race, treatment, age category, and mean pain score category. Analyses were also performed using age and mean pain score as quantitative variables.
- A general linear model was fit to assess the relationship between study variables and overall compliance.
- The following study variables were included in the model: gender, age (linear), race category (Caucasian or other), treatment group (placebo or investigational drug), and mean pain score (linear). All two-way interactions with treatment group were also included.
- The model was then reduced to exclude non-significant interactions at the 0.10 level and main effects at the 0.05 level with a backward selection process.
- Because no interactions were significant, p values were reported for each variable included as the only term in a t-test or regression model. If the assumption of equal variances was not met for a two-sample t-test, then a Satterthwaite t-test was used.

RESULTS

- Overall compliance for all patients (aged 32-93 years) was 88% ± 14% (mean ± SD).
- There were no statistically significant differences in compliance between females and males (88 ± 13% vs 88 ± 16%; p=0.97) (Figure 1), between patients aged above or below 60 years (90 ± 15% vs 85 ± 13%; p=0.07), or between Caucasians and other races (89 ± 11% vs 81 ± 23%; p=0.12 from Satterthwaite t-test).
- The linear relationship between age and compliance was also non-significant (p=0.09).
- Regression analysis of compliance versus age and versus mean pain score demonstrated slopes not significantly different from zero for either relationship (p=0.09 for age, see Figure 2; p=0.99 for mean pain score, see Figure 3).
- Finally, there were no differences between the compliance observed for patients treated with placebo and the investigational drug (87 ± 15 vs 88 ± 14%; p=0.67).
- Because no differences were found, post-hoc power analysis was performed. From this analysis, it was determined that the sample size was sufficient to detect a difference in compliance between the gender groups of 5.6% with 95% confidence, and a difference in compliance between age groups (<60 vs ≥60 years) of 5.6% with 95% confidence.

Figure 1. Compliance by gender (p=0.97)

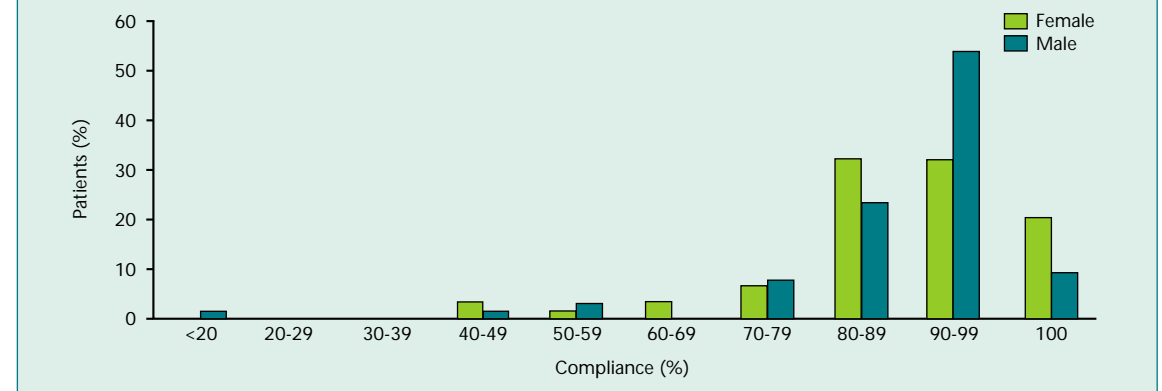


Figure 2. Compliance by age (p=0.09)

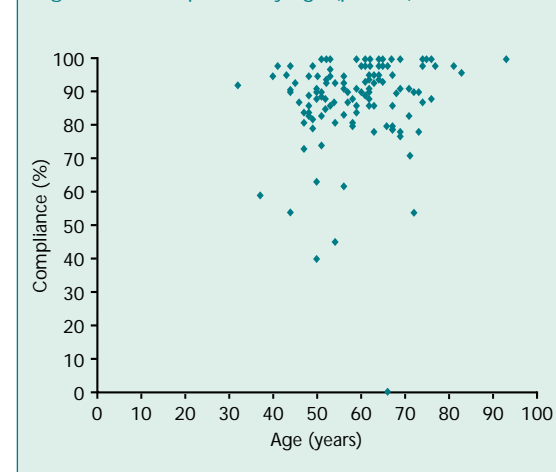
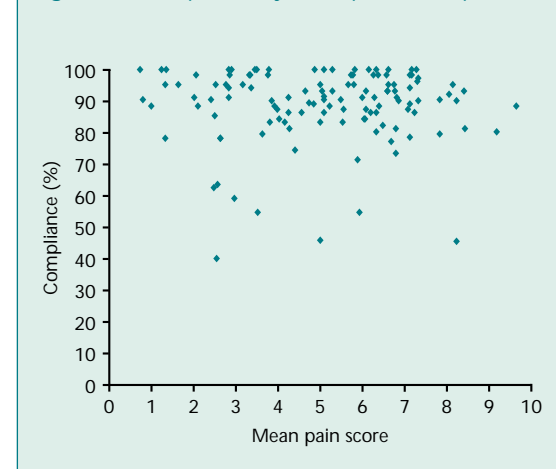


Figure 3. Compliance by mean pain score (p=0.99)



- Because the race groups differed in size and had differing standard deviations, the power for detecting a difference in compliance between race groups of 5.6% was only 64%. This comparison had a 95% power for detecting a difference between race groups of 10.6% or more.

CONCLUSIONS

- Compliance for EPD entry and transmission was excellent overall and in all patient subgroups.
- There was no evidence that age, gender, treatment group, race, or mean pain score influenced compliance with EPD use for chronic pain assessments in patients with diabetic neuropathy.
- We conclude that collection and transmission of daily EPD pain data is a feasible method that can be adopted with high compliance rates across a range of patient demographic subgroups, and allow study managers immediate data access after trans-telephonic data transmission.
- Additional studies are required to ensure that these results are widely applicable to a broader range of demographics and clinical syndromes.

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