Methodology and Therapeutic Trials

Stability of Cataplexy Over Several Months—Information for the Design of Therapeutic Trials


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Summary: Twenty-seven narcoleptic patients severely affected with cataplexy completed four symptom diaries over a 4-month period in order to clarify some of the controversies surrounding assessment of anticataplectic medications. The home diary method was found to be a viable model for the assessment of anticataplectic activity. Assessment of reliability in 1-, 2-, 3-, 4-, 5- and 10-day intervals indicated that reliability increases with the number of days included. A 10-day design was found to be optimal. Reliability decreased, however, with each successive diary over the 4-month period. Power analysis indicates that two groups of 30-40 subjects in a parallel design, or one group of 30-40 subjects in a crossover design, would be sufficient to demonstrate a significant therapeutic anticataplectic effect in most cases. A “first diary effect” was observed, suggesting that a training period prior to the actual trial might improve reliability. Whether the patient was treated or untreated with stimulant medications did not affect severity or fluctuation of cataplexy, suggesting that both groups of patients could be included in therapeutic trials. No time-of-day fluctuation was observed in the daily distribution of cataplexy attacks. Sudden increases in cataplexy were often, although not always, caused by unusual emotional events or sleepiness. The finding of a long-lasting “precataplectic” feeling or “aura” pointed to the need to carefully clarify the symptom prior to beginning a therapeutic trial. Key Words: Cataplexy—Narcolepsy—Anticataplectic medications—Therapeutic trials.

Despite the fact that cataplexy, a sudden loss of muscle tone usually triggered by an emotion, is among the most disabling symptoms of narcolepsy (1–8), its pharmacological treatment remains poorly codified. Experimentally, the most effective anticataplectic agents have been tricyclic antidepressants such as imipramine, protriptyline and chlorimipramine (3–15). These agents combine anticholinergic and monoaminergic uptake inhibition activities (16–20), two properties that may contribute to their therapeutic effects (4,19–21). These compounds, however, produce significant side effects that limit their long-term usage (7,8,14,15,17,18). Clinical experience also reveals significant individual differences between patients in their response to a specific drug. A compound that effectively controls cataplexy in one patient for many years may produce no effect or cause undesirable side effects in another. Furthermore, none of the tricyclic medications currently prescribed for cataplexy was developed specifically for its treatment, and the mode of action or mechanisms through which they suppress cataplexy remain largely unknown (19–21). Finally, due to the comparatively small commercial market for cataplexy medication, most drug companies have shown little interest in either investigating new compounds for this disabling symptom or testing existing compounds developed for other indications (especially depression) in narcoleptic patients.

One of the major obstacles to better pharmacological control of cataplexy has been the difficulty of performing appropriate double-blind studies on new, potentially active compounds. Four factors are responsible for this difficulty. First, though previous reports have
pointed to the day-to-day variability in cataplexy, no clear data exist on the fluctuation of the symptom over the short and long term in the absence of anticataplectic medication. This in turn impedes assessment of the therapeutic effect of new compounds. Second, it is extremely difficult to observe cataplexy directly in an experimental setting (4,10,22,23). Cataplexy is usually triggered by an “emotional” event (1–8), but simulating the particular situation or emotion that strikes the proper emotional “chord” has proven extremely difficult in the laboratory. Indeed, many patients have reported in clinical interviews that their cataplectic attacks are typically triggered by a family member (1–3). Because therapeutic effect cannot be accurately observed in the laboratory, patient self-monitoring in their natural environment is necessary. Third, the relationship between cataplexy and sleepiness is poorly understood, which has led to controversy over whether patients treated with stimulant medications should be included in cataplexy trials. This issue also bears directly on the important practical and ethical considerations raised whenever narcoleptic patients are removed from medication for the purpose of research. Finally, assessment of anticataplectics has been hampered by the absence of a standardized, universal protocol. Specifically, sample size, duration of trial, inclusion criteria, efficacy criteria and stimulant-medication status of patients have differed from study to study. All these factors have worked against improved control of cataplexy for narcoleptic patients.

In the current study, 27 narcoleptic patients completed detailed “cataplexy diaries” over a 4-month period. The goals of the study were twofold. First, we sought to document the fluctuation of cataplexy over time in order to suggest an appropriate design for clinical trials of anticataplectic medications. Specifically, we sought to address the following questions. Is the home diary method a viable model for assessing the symptom of cataplexy? If so, how large must the sample be, for how long should the diary be kept, and how many diaries should be completed in order to achieve an acceptable degree of reliability? Should patients treated with stimulants be excluded from cataplexy trials? In addition to recording the number of attacks experienced, subjects were asked to note the time of day and the circumstances surrounding the attack. This was done in accordance with the other goal of the study, which was to examine other issues relevant to the self-monitoring of cataplexy.

METHODS

Population

Thirty-five patients complaining of inappropriate control of their cataplexy were recruited through advertisements from the Stanford University Sleep Disorders Clinic Database or the American Narcolepsy Association and its patient support groups. Inclusion criteria were i) narcolepsy with unambiguous cataplexy, with diagnosis confirmed by an accredited sleep disorders center and reconfirmation of the clinical symptomatology by phone interview; ii) absence of anticataplectic treatment with tricyclic antidepressant medications; and iii) report of at least one cataplectic attack per week. Patients cited four reasons for not taking anticataplectic medication despite the severity of the symptom: anticataplectics were contraindicated because of another medical problem, usually a heart condition; anticataplectics were tried but found to be ineffective; anticataplectics were tried and were found to cause severe side effects, such as nausea, dizziness and rapid heart beat; and subjects were unaware of the existence of anticataplectic medications. Additionally, none of the subjects included was taking fluoxetine (Prozac®) or any other kind of antidepressant.

The 35 subjects included 26 women and nine men with a mean age of 56.6 ± 1.89 (mean ± SEM) years. There were three Black, one Asian and one Asian-Hispanic subjects; all other subjects were Caucasian (86%). Seven were retired, 10 were unemployed and 18 were employed. Investigation of previously conducted Multiple Sleep Latency Tests (MSLTs) indicated that one subject had a mean sleep latency of 11.4 minutes without any sleep onset rapid eye movement period (SOREMP), but with severe cataplexy (mean daily cataplectic attacks = 0.96), and another had a mean sleep latency of 2 minutes but no SOREMPs, with a mean daily cataplectic attack score of 3.85. All other subjects had a short sleep latency (<8 minutes) and at least two SOREMPs. HLA typing was conducted on a subset of the sample who consented to the test to substantiate the quality of our sample, particularly the specificity of our diagnostic assessment of cataplexy. Nineteen subjects were HLA typed (24) and were found to be DR2, DQ1 and/or DQB1*0602. Thirty-three subjects (91%) reported the presence of hypnagogic hallucinations and sleep paralysis.

Design

An initial questionnaire containing 104 questions evaluated syndrome history: a) onset of symptoms and associated problems; b) cataplexy: frequency of attacks, duration, triggering factors, life-long evaluation, response to treatment, etc.; c) family history of narcolepsy; d) sleep history and nocturnal sleep; e) past medical history and current health status; f) drug history; and g) demographic information including ethnic background. This initial questionnaire was used to review the patients’ narcolepsy history and to evaluate...
FLUCTUATION OF CATAPLEXY OVER TIME

1. Did you have cataplexy today? If so, how many times?
2. What form did it take?
3. What parts of the body were affected?
4. What triggered it?
5. When did it happen?
6. How long did it last?
7. Did the cataplexy blend directly into a sleep period? If so, how long did the sleep period last?
8. Where were you when the attack(s) occurred?
9. Did you experience any warning signs—emotions or physical sensations—that indicated you were about to have cataplexy?
10. Did you resist the attack(s) just before it began, and if so, how?
11. Did stress, heat, or food play a role in causing the attack(s) of cataplexy?
12. What sensations did you experience during the attack(s)?
13. Once the attack(s) started, what strategies did you use to stop it?
14. What did you experience immediately following the attack(s) and the circumstances surrounding sudden surges in cataplexy?
15. Were there any accidents or injuries as a result of the cataplexy attack(s)?
16. Did you experience any of these other symptoms today: hypnagogic hallucinations, sleep paralysis, automatic behavior, blackout, sleep attack?
17. Rate your sleepiness/sleerness today (Very Sleepy, Somewhat Sleepy, Fairly Alert, Quite Alert).
18. Evaluate your night-time sleep for last night (Very Good, Good, Fair, Poor).
19. How hard was it to wake up and get out of bed this morning? (Very Hard, Hard, Not Hard)?
20. Did you nap during the day today? From when to when?
21. Rate your overall mood today (Excellent, Good, Fair, Poor).
22. How physically active were you today? (Very Active, Fairly Active, Not Very Active, Not at all Active)?
23. How emotionally active were you today? (Very Active, Fairly Active, Not Very Active, Not at all Active)?

FIG. 1. The cataplexy symptom diary. Each month for 4 months each subject received a book composed of 10 forms identical to the one shown. In addition to these questions, two blank "notes" pages were provided for the subject to recount any other relevant information. Subject comments on these notes pages identified the phenomenon of a warning sensation prior to cataplexy, which was experienced by many subjects (see Results). Comments from this section also allowed us to examine the circumstances surrounding sudden surges in cataplexy.

in detail the symptom of cataplexy and its impact on the patients' daily lives.

After review of the initial questionnaire, subjects received the first cataplexy diary, which included 10 successive forms, each containing 1 day (Fig. 1). In addition to the objective questions, two blank "notes" pages were provided, on which the subject was encouraged to provide more detailed descriptions of the cataplectic attack and the circumstances surrounding it. The diary was designed to document how many cataplectic attacks occurred each day and how they manifested themselves. Subjects were instructed to try to keep track of the day's events with notes and to fill out the diary every evening just before going to bed.

Each subject participating in the study was asked to complete four cataplexy diaries, mailing each one back at the end of each 10-day period. The diaries were to be spaced exactly 1 month apart so that a total of 4 months could be examined. When all diaries had been received, a brief questionnaire, administered by phone to all patients, was used to clarify unclear cataplexy diary data.

Statistical analysis

Reliability. The test-retest reliability of the frequency of attacks was estimated using intraclass correlation coefficients (25). This was done for single, 2-, 3-, 4-, 5- and 10-day (one diary) intervals to determine the optimal length for a diary in this design.

Power analysis. Based on the reliability measure and the estimates of the standard deviation of each sample, the number of subjects needed to detect a statistical effect at a 5% level of significance with a one-tailed test and 80% power was also calculated, as described in Kraemer and Thiemann (25). Estimates are given for both a parallel and a crossover design. All calculations were done using all subjects or stimulant-treated/un­treated only.

RESULTS

Patients' compliance with the protocol

Of the 35 subjects initially included, one filled out 3/4 diaries, one filled out 2/4 diaries, two filled out 1/4 diaries, and four subjects did not finish a diary. Twenty-seven subjects sent back all four cataplexy diaries. For the analysis of fluctuation of cataplexy over time, reliability measures and power analysis only the 27 subjects who completed all four diaries were used. Table 1 shows that the eight subjects who were dropped from the reliability analyses did not differ significantly from the 27 subjects who completed all four diaries. For all other analyses, the diaries received from all 31 subjects were used.

A total of 1,150 daily reports were received in which 1,766 cataplectic attacks were described. Three subjects averaged less than one attack per week, but overall, subjects were severely affected (1.53 ± 0.14 (mean ± SEM) attacks/day) and 45% of the population reported more than one attack per day. The less affected subjects were included in the analysis.

Fluctuation of cataplexy over time and reliability measures

The fluctuation of cataplexy over the 4-month period was analyzed in the 27 subjects who completed
TABLE 1. Comparative profile of the subjects who completed all diaries versus those who did not complete the study

<table>
<thead>
<tr>
<th></th>
<th>Subjects who completed four diaries</th>
<th>Subjects who completed less than four complete diaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of subjects</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>Mean age</td>
<td>56.00 ± 2.05</td>
<td>49.38 ± 4.78</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>29.63</td>
<td>12.50</td>
</tr>
<tr>
<td>Stimulant treated (% of subjects)</td>
<td>7.037</td>
<td>75.00</td>
</tr>
<tr>
<td>Subjects with employment (%)</td>
<td>55.56</td>
<td>37.50</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>88.89</td>
<td>75.00</td>
</tr>
<tr>
<td>DR2 or DQB1-0602 positive (%)</td>
<td>(n = 11)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>Mean age of onset of cataplexy</td>
<td>27.31 ± 2.07</td>
<td>26.25 ± 4.49</td>
</tr>
<tr>
<td>Mean age at first diagnosis at sleep clinic</td>
<td>41.91 ± 1.92</td>
<td>38.75 ± 2.58</td>
</tr>
<tr>
<td>Estimate of mean number of cataplectic attacks per week, given by subject</td>
<td>11.70 ± 4.58</td>
<td>19.21 ± 8.56</td>
</tr>
</tbody>
</table>

Data are means ± SEM where given. n indicates the number of subjects when different from the total number of subjects in both groups. The information contained in the table was compiled from answers to the initial survey of 104 questions (see Design in the Methods section).

all four diaries (Fig. 2). Reliability measures calculated for 1-, 2-, 3-, 4-, 5- and 10-day intervals for these 27 subjects are reported in Fig. 3 and Table 2. As expected, reliability increased as the time interval analyzed increased (Fig. 3). The mean reliability for 10-day diaries (0.67 ± 0.10) was considered acceptable. Reliability for shorter intervals of time (1–5 days) was generally below 0.50, suggesting that at least 5 days of recording are needed to reliably evaluate the frequency of cataplexy over time.

Further analysis of the reliabilities also showed that the reliability of the fourth diary was consistently poor (Fig. 3 and Table 2). This was evident both in the 1–5-day analyses (Fig. 3) and in the diary-to-diary analysis (Table 2; compare reliabilities of diaries 2–3 and 3–4). The diary-to-diary analysis of reliability also showed that the best comparison was obtained between diaries 2 and 3, rather than between 1 and 2 (Table 2). This was apparently due to an overreporting of cataplexy in the first few days of recording (see Fig. 1), which accounted for a large portion of the variability. The comparison of the mean number of cataplectic attacks reported per day was also statistically different in diaries 1 and 2 (Table 2).

Power analysis

Reliability coefficients were also used to approximate the number of subjects that would be needed in the estimation of the number of attacks per day for each diary.

TABLE 2. Number of cataplectic attacks and reliability estimates calculated for each diary

<table>
<thead>
<tr>
<th>Diary no.</th>
<th>No. of attacks per day</th>
<th>Reliabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.215 ± 0.375</td>
<td>0.572</td>
</tr>
<tr>
<td>2</td>
<td>1.272 ± 0.182</td>
<td>0.882</td>
</tr>
<tr>
<td>3</td>
<td>1.070 ± 0.217</td>
<td>0.620</td>
</tr>
<tr>
<td>4</td>
<td>1.413 ± 0.329</td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SEM of 270 days of recording in each group (one diary of 10 days for 27 subjects). Reliabilities between successive diaries are calculated as indicated in the Methods section. Note that the best reliability was obtained between diaries 2 and 3. ∗ p < 0.01 using a paired t test.
TABLE 3. Estimation of the sample size needed to demonstrate a significant anticataplectic effect in a randomized double-blind parallel study design

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Reliabilities</th>
<th>SD of the corresponding sample</th>
<th>No. of subjects needed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>Untreated</td>
<td>Overall</td>
</tr>
<tr>
<td>1 day</td>
<td>0.409</td>
<td>0.163</td>
<td>0.350</td>
</tr>
<tr>
<td></td>
<td>(n = 760)</td>
<td>(n = 320)</td>
<td>(n = 1,080)</td>
</tr>
<tr>
<td>3 days</td>
<td>0.580</td>
<td>0.467</td>
<td>0.540</td>
</tr>
<tr>
<td></td>
<td>(n = 228)</td>
<td>(n = 96)</td>
<td>(n = 324)</td>
</tr>
<tr>
<td>10 days</td>
<td>0.781</td>
<td>0.303</td>
<td>0.690</td>
</tr>
<tr>
<td>(all diaries)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 days</td>
<td>0.959</td>
<td>0.379</td>
<td>0.882</td>
</tr>
<tr>
<td>(diaries 2 and 3 only)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The number of subjects needed was calculated for an effect size corresponding to a final therapeutic goal of one cataplectic attack per month, with the conservative assumption of obtaining a similar variance in both the treated and untreated groups. The inclusion criteria for the study required that patients report one cataplectic attack per week on average, which was confirmed by their reports during the study (for the 27 subjects, 1.493 attacks per day). Calculations were performed as described in Kraemer and Thiemann (25), using a 5% significance level and 80% power. In both the stimulant-treated and untreated groups, it was found that 61 subjects (31 in each randomized group) would be needed to demonstrate a statistically significant effect at a 5% level of significance with an 80% power using a parallel design. Alternatively, 31 subjects, or fewer, might be sufficient to demonstrate a therapeutic effect using a crossover design (25).

Fluctuation of cataplexy over time

A therapeutic trial of an anticataplectic compound (25). The therapeutic goal was a mean of one cataplectic attack per month after treatment (Table 3), a goal in line with the efficacy of currently available anticataplectic compounds (3-15,26-28). At least 61 subjects are required for a parallel design and 31 for a crossover design. The analysis was performed both for subjects treated with stimulants (n = 19) and untreated (n = 8), and the results are shown in Table 3.

Treatment status

Whether or not patients took stimulant medications did not seem to impact on the report of cataplexy (mean daily attacks of treated group = 1.56 ± 0.17 vs. 1.46 ± 0.22 for untreated group). The treated and untreated groups were compared for every test run for reliability (across days and across diaries) and no differences were found. Stimulant treatment status did not make a significant difference in the overall severity of cataplexy, its fluctuation over time or across the day, or in any other factor analyzed. The only exceptions to this were the days of extreme increases in cataplexy that were attributed by a few subjects to missing a dosage of stimulant medication.

Fluctuation of cataplexy across the day

Investigation of the distribution of cataplectic attacks over the 24-hour day indicates that few cataplectic attacks were reported between 10:00 p.m. and 9:00 a.m. (i.e. nocturnal sleep period). Between 10:00 a.m. and 9:00 p.m., however, cataplexy appeared stable (Fig. 4). This result was the same in stimulant-treated and untreated subjects, and in employed and unemployed subjects (data not shown).

Sudden increases in cataplexy

In therapeutic trials, it would be necessary to know which patients, if any, would be subject to sudden increases in cataplexy, so we looked closely at the days of greatest individual variability. Seven subjects (23%) reported days with extremely frequent cataplexy (38 days with >10 daily attacks). These subjects were more severely affected overall, and they typically reported several attacks even on days without these sudden "surges" in cataplexy (mean daily attacks = 4.31 ± 1.49). One such patient reported 21 days of >10 attacks, but for the entire 40 days sampled, this subject had a mean of 13 attacks/day; therefore, for this subject days of >10 attacks could not be considered an extreme fluctuation. Excluding this patient, we examined the subjects’ descriptions of days with a surge (>10
attacks) in cataplexy (six subjects, 17 days). For 12 of these 17 days, there were clear changes in the daily routine in the form of social interactions, more “emotional” involvement and clear disturbances of daily nap schedules. For example, patients described attending an emotional reunion, attending parties or entertaining guests, unusual anxiety over the prediction of an earthquake in the Bay Area, and missing sleepiness medication and naps as circumstances associated with the sudden increases in cataplexy. Investigation of the subjective reports of increased sleepiness (see Fig. 1, question 17) in these cases, however, was not supportive of that variable playing an important role. Only 6% of days with these surges in attacks were scored as “very sleepy”, whereas 41% were scored as “very” or “quite” alert. Also, it must be emphasized that in 5 of the 19 days with more than 10 attacks, there was no clear change in emotional or physical status.

**Triggering factors**

The highly individual, personal nature of the cataplectic attack, which has been described in several reports (1-8,10,22,23) and which prevents direct experimental observation of the symptom, was confirmed. Although emotions commonly trigger attacks [e.g. laughter (cited by 65% of subjects), anger/frustration/annoyance (40%), nervousness (19%), embarrassment (13%), sadness (13%), fear (6%)], the precipitant can also be physical in nature [e.g. feeling hot (23%), getting pets, public speaking, trying to rise from a chair who suddenly became ill) temporarily suppressed the symptom. Indeed, there were nearly as many stimulating situations reported (e.g. being teased by children, disciplining pets, public speaking, trying to rise from a chair after a long rest, sexual fantasies, receiving flattery, playing racquetball, hearing religious music) as there were patients. Sleepiness was also commonly reported as the immediate trigger of an attack (48%). As has been reported (1,3,5), abrupt stressful demands (including subject reports of being involved in a boating accident, having one’s son involved in a serious motorcycle accident and having to take care of a friend who suddenly became ill) temporarily suppressed the symptom.

**Patient description of cataplexy**

The individual nature of the symptom was seen in the form of the attack as well. Though the two classic manifestations of cataplexy were well represented [collapse, cited by 68% of subjects; and a combination of i) twitching, contortion, tingling or paralysis in the face (52%), ii) dropping of the head (35%) and/or,jaw (13%) and iii) buckling of the knees (32%)], patients also reported attacks that took the form of spasmodic weakness with a warm sensation in the upper body or torso (42%), or a generalized weakness of the entire body (35%), which did not escalate into actual paralysis. Also reported by four subjects were attacks described as “sudden jolts or interruptions in consciousness”, “waves of dizziness” or “like ongoing storms in the brain”, that is, attacks not localizable to a specific muscle group. Patients also reported that they were occasionally able to fight off the attack by talking through it (cited by 35% of patients), changing the subject or thinking of other things (29%), mentally fighting against it by concentrating on the attack (26%), tensing muscles or moving vigorously (e.g. swinging arms or walking fast) (13%), or applying a damp, cool cloth or a soda can to the face (10%).

**Reports of “warning” sensations prior to cataplexy**

Patient report of the previously reported phenomenon (1,3) of a warning sensation prior to an attack of cataplexy was found to bear directly on the assessment of the symptom. Sixteen subjects (52%) reported some kind of warning sensation before the attack. The reports of warnings can be divided into two different types of events. The first, which was reported to occur a few seconds before the actual muscle weakness, consisted of a feeling of a warmness, nervousness, fear or fright, or a sense that time was somehow suspended (and, therefore, may have been part of the trigger phenomenon). The other type of warning was of greater interest as it tends to indicate that cataplexy may occur against a background of greater vulnerability than usual. Seven patients (23% of all subjects) described a long-term warning lasting hours or days, during which time the subject felt physically fragile, constantly on the verge of an attack, or “precataplectic”. This feeling was often referred to by subjects as an “aura” or a sense that cataplexy was imminent without obvious physiological symptoms. A few subjects reported that this feeling eventually led to a barrage of actual attacks. In other cases, no cataplexy ever developed. It must be pointed out that a few subjects defined this precataplectic feeling not as a type of warning, but as an actual long-lasting, low-grade attack. Both the 16 subjects who reported some kind of warning sensation and the subgroup of seven patients who reported this long-term precataplectic feeling were more severely affected than other subjects (mean daily attacks 2.03 ± 0.76 and 3.10 ± 1.68, respectively).
DISCUSSION

Certain aspects of cataplexy—its unknown variability over time, its poorly understood relationship to sleepiness, how it is affected by stimulant medication and the difficulty of inducing it in the laboratory—have made it difficult to assess the efficacy of compounds that could be used to treat it. Indeed, protocols assessing anticataplectics have varied greatly in their sample size (most studies have used fewer than 10 subjects), duration, stimulant-medication status of subjects, severity of cataplexy required of subjects upon entry, degree of symptom reduction sought and manner of assessing therapeutic effect (8-15, 26-28). The need for a standardized human protocol is emphasized by our recent identification of several compounds found to completely suppress cataplexy in the narcoleptic dog without discernible side effects (20,29). The absence of a standardized protocol will slow the application of these findings in human patients. Although the current study has not attempted to resolve all the controversies surrounding the assessment of anticataplectic effect, it has attempted to clarify some of them by gathering detailed information on a large number of cataplectic events in a group of stimulant-treated and untreated subjects.

The highly individual nature of cataplexy in terms of triggering factors and muscle groups affected strongly supports assessing anticataplectic activity in the subject’s natural environment. The viability of a home diary design was confirmed in our study, because even those narcoleptic subjects severely affected with cataplexy were able to complete detailed symptom diaries over a long period of time. However, subject reports demonstrated the need to carefully clarify the symptom prior to the outset of the trial. Cataplexy often does not present as an unmistakable collapse or buckling of the knees triggered by laughter or anger. Instead, a long lasting warning or precataplectic feeling associated with enhanced vulnerability to attacks is often seen, especially in severely affected subjects. Whether the subject defines this phenomenon as a kind of warning or as a kind of low-grade attack (or series of low-grade attacks) directly determines the amount of cataplexy reported. Therefore, it is essential to carefully define cataplexy at the outset of therapeutic trials. We rec-
ommend that for an event to qualify as cataplexy, it must be of sudden onset, localizable to a specific muscle group(s) or part of the body, and the subject must be lucid during the experience. The long-lasting pre-cataplectic feelings or auras, although interesting, are difficult to quantify and thus tend to obscure long-term monitoring. Requiring that the subject be lucid is important for subjects who report attacks in the form of sudden interruptions in consciousness. These events sometimes seem more reminiscent of sleep attacks or microsleeps than cataplexy, and requiring lucidity would help subjects distinguish between these different symptoms of narcolepsy.

Another advantage of the diary model is that it enables the investigator to test the success of the compound against the unpredictable surge of cataplectic attacks reported by many of our subjects. We found that these surges were often, but not always, caused by sleepiness or unusual emotional events. Ideally, an ant-cataplectic compound would suppress even days of severe cataplexy, so it would be important to try to include them in a diary study. This is another reason for having subjects complete two or three diaries over a significant time period rather than a single diary. The fact that these days are not always linked to emotional changes or unusual sleepiness makes their appearance unpredictable, and further reinforces the value of assessing cataplexy by symptom diary in the subject's natural environment as opposed to the laboratory.

Our results indicate that a 10-day diary would be the most reliable, but that the overall study should not consist of more than three diaries, because reliability decreases at that point. We attribute this result to simple fatigue and boredom with completing the diaries. To this end, we recommend that the diary itself be briefer and simpler than the one used in this study (Fig. 1). The subject should be provided with a space to indicate the number of attacks experienced on the given day, another space to describe the form of the attack (to ensure a consistent definition is being applied throughout the sample) and perhaps a single page for additional comments. Additionally, the first diary should be used as a training period to acclimate subjects to the procedure and reduce the early overreporting (first diary effect) we observed and which we attribute to an exaggerated vigilance caused by the subjects' excitement and eagerness to comply with the protocol. Thirty-one and 31 patients are required for a parallel and crossover design, respectively, and subjects should average at least one cataplectic attack per week.

Both stimulant-treated and untreated subjects can be included in the sample. This would have the dual advantage of assessing the symptom as it actually manifests itself in the subject's normal environment and freeing the subject and the investigator from the risks involved (in terms of potential driving and industrial accidents and loss of work time) when narcoleptic patients are withdrawn from medication for research protocols. This design is described in greater detail in Fig. 5, in which we propose a 10-day washout period (which includes a diary training period), followed by a placebo/treatment randomization and an optional period to reach stability of therapeutic effect. This optional period could also be used to adjust dosage if called for by the protocol. Comparison between treatment and placebo will then be performed using a 10-day diary.

In conclusion, narcoleptic subjects severely affected with cataplexy were found to be able to complete detailed "cataplexy diaries" over a long period of time. Reliability of subject report was found to increase from 1 to 10 days but decrease by the fourth diary. Sixty-one subjects (parallel design) or 31 subjects (crossover) are necessary for a 5% level of significance and 80% power, and a training period should be included in the protocol. More severely affected subjects will show sudden increases in cataplexy and the trial should be long enough to assess therapeutic effect on these kinds of days. Both stimulant-treated and untreated subjects can be included in therapeutic trials because treatment status does not seem to affect severity or fluctuation of cataplexy. Finally, two opposite manifestations of cataplexy—a long-lasting precataplectic state which can be interpreted as a warning or part of an actual attack, and very brief and minor jolt-like interruptions in consciousness—both serve to emphasize the need to carefully define the symptom to all subjects at the outset of the trial.

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