N-of-1 randomized trials on ultra-micronized palmitoylethanolamide in older patients with chronic pain

First experience of a Geriatric N-of-1 Service

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ABSTRACT

Background: Ultra-micronized palmitoylethanolamide (um-PEA) represents an attractive option for chronic pain control in complex older patients at higher risk of adverse effects with traditional analgesics.

Objective: To determine the effectiveness of um-PEA versus placebo on chronic pain intensity and function in individual geriatric patients.

Design Randomized blinded N-of-1 trials with two 3-week um-PEA versus placebo comparisons, separated by 2-week washout periods.

Participants: Outpatients aged ≥65 with chronic non-cancer non-ischemic pain in the back, joints or limbs.

Intervention: Um-PEA 600 mg or placebo twice daily.

Measurements: Pain intensity using an 11-point visual numeric scale; functional impairment using a Back Pain Functional Scale; impact of each N-of-1 trial on the clinician's intention to treat and confidence.

Results: 10 of 11 eligible patients consented over 7 months (all female, mean age 83.2 years [SD, 4.6]). Three patients interrupted the trial: 1 had diarrhea (under placebo), 1 for low adherence, and 1 for intercurrent pneumonia. A small statistically significant effect in favor of um-PEA was seen at the mixed method analyses in 2 patients (effect size equal to 8% of the baseline pain). A statistically significant impact on function was found in 1 patient. After the trial: um-PEA was prescribed to 4 patients; in 2 patients the

clinician changed her pre-trial intention to treat; the clinician confidence in the treatment plan either increased (5) or remained the same (2).

Conclusions: Our experience confirmed that N-of-1 trials may help make personalized evidence-based decisions in complex older patients, with special feasibility considerations.

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Key points

- We performed randomized controlled trials on single outpatients (N-of-1 trials) referring to our geriatric clinic to assess the effectiveness of palmitoylethanolamide (PEA) on chronic pain in each individual.
- This was a pilot for a Geriatric N-of-1 Service that would help physicians to conduct N-of-1 trials in clinical practice as an instrument for evidence-based and personalized therapeutic decisions in geriatric patients.
- We confirmed that this approach is attractive also in this population, but some specific feasibility aspects need to be taken into account.

1. INTRODUCTION

The reported prevalence of chronic or persistent pain among the elderly is as high as 80%;[1] osteoarthritic back pain is the most frequent noncancer cause.[2] Chronic pain and its inadequate treatment have an important impact on patient function, autonomy, quality of life, and healthcare resource use.[3] Age-related changes in the somatosensory system and in drug pharmacokinetics, together with a higher chance of drug-drug and drug-disease interactions, influence the efficacy and safety of the available analgesic and pain-modulating drugs.[4-9]

In particular, a growing body of evidence suggests that immune cells like microglia and mast cells play a substantial role in the induction, amplification, and maintenance of chronic pain especially with aging.[9-12] After an injury or in the presence of an inflammatory stimulus, immune cells, which are located in proximity to sensory nerve endings and vasculature, release mediators stimulating nociceptors. Physiological activation of microglia generally leads to resolution of neuroinflammation and restoration of tissue homeostasis. With aging, both microglia and mast cells increase their reactivity to stimuli, with a consequent more robust and long-lasting production of pro-inflammatory cytokines. These findings support the hypothesis that non-neuronal cells might be important therapeutic targets for the treatment of chronic pain, especially in older persons. Palmitoylethanolamide (PEA) is an endogenous N-acyl-ethanolamina involved in the modulation of neuroinflammation processes.[13-15] In murine models of chronic inflammation and chronic or neuropathic pain, PEA has been found to reduce the recruitment and activation of mast cells, the production of pro-

inflammatory mediators, and endoneural edema, thus reducing both pain and inflammation while preserving peripheral nerve morphology.[13,14] Several products containing micronized or ultra-micronized PEA (um-PEA) are authorized in Europe as "Food for Special Medical Purposes" (European Commission Directive 1999/21/EC). PEA-based products might represent a safe choice for pain control or modulation in older people. In a systematic review including patient-level data from randomized and non-randomized trials, PEA was found to be effective in reducing chronic pain, independently of sex, age, and type of pain, even if with a smaller effect in people over age 65.[16] No serious product-related adverse events were reported.[16]

Response to many drugs used to treat pain varies across individuals,[16,17] and this is likely true for um-PEA. This likely variability, and the necessity for purchase out-of-pocket, represented the rationale to use N-of-1 trials (within-patient, randomized, multi-period, crossover, blinded studies) to help decide, case by case, whether to prescribe PEA in our geriatric patients. Clinicians have previously used N-of-1 designs to optimize the pharmacological management of chronic conditions including pain, using randomization and blinding as strategies to overcome bias (e.g. natural history of the disease, placebo effect, clinician and patient expectations) that threaten the trustworthiness of the "treat and see" trials routinely used in practice.[18-20] In this report, we present a series of N-of-trials addressing PEA for chronic pain in older patients, conducted in the context of our *Geriatric N-of-1 Service*, i.e. an experimental project we implemented taking inspiration from previous pioneering experiences[21,22] but in the specific setting of the geriatric medicine.

2. METHODS

A previous publication presents the full study protocol with detailed rationale and methods.[23] This study was part of the *Geriatric N-of-1 Service* project, approved by the ethical committee of the Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milan, Italy. The primary objective of the study was to apply the N-of-1 trial approach to test the effectiveness of um-PEA 600 mg (*Normast®)* twice a day for chronic pain in individual patients referred to the geriatric outpatient clinic of our University Hospital. As a secondary methodological objective, the study included a meta-analysis of the N-of-1 trials performed comparing the frequentist and the Bayesian statistical approach.[24,25] The present report focuses on the primary objective, and follows the guidelines of the CONSORT extension for reporting N-of-1 trials (CENT) 2015 Statement.[26]

2.1 Design Overview, Randomization, and Blindness

Figure 1 presents the trials' structure. The expected total length of each trial was 18 weeks, comprising 2 um-PEA and placebo treatment pairs assigned in a random order according to a pairwise randomization scheme. Patients took one tablet containing either Normast® 600 mg or placebo orally twice daily during the treatment periods, with no use of study drug during the washout period. Patients used other pain medication on an as needed basis. The product information sheet for Normast® 600 mg suggests "1-2 tabs a day for 20-30 days", but onset times longer than 1 week might be expected "especially for chronic pain syndromes";[27] a possible carryover effect is also possible. Thus, the uncertain pharmacological characteristics of the product, and the desirability

of avoiding too long trials, dictated two pairs of treatment periods of 3 weeks each with 2-week washout intervals.

Epitech Group SpA provided the active and placebo drugs, with no other involvement in the study. The study drugs were stored at the hospital pharmacy. For each trial, a hospital pharmacist generated the random sequence of treatments using the web site www.randomizer.org, recorded the randomization codes, and provided the study drug at the beginning of each study period, thus allowing the patients, caregivers, treating physicians, and statistician to remain blinded to the sequence of active and placebo treatment.

When the trial was concluded, the clinical investigators and statisticians interpreted the results, and discussed results with the treating physician and, when feasible, with the patient/caregiver at first maintaining the data blinded. Only secondarily the code was broken and the definitive decision upon whether to continue um-PEA was taken.

2.2 Participants

Outpatients 65 years of age or older with a complaint of non-cancer chronic pain in the back, joints or limbs for at least 6 months were invited to participate in the study if the treating physician considered um-PEA as a possible treatment option for the patient but was uncertain about its advisability. We excluded patients with subacute or chronic limb ischemia and those who had recently commenced a new pharmacological or non-pharmacological treatment for pain.

2.3 Outcomes

In each N-of-1 trial patients rated the intensity of their pain daily using an 11-point (from 0 to 10) visual numeric scale[28] in which labels and pictures (modified from the Faces Pain Scale[29]) were included with the numeric horizontal line (**eFigure 1**). In the same daily sheet, the patient was asked to report also every time he/she needed to take analgesic medications, specifying the name and dosage. The impact of pain on daily activities was evaluated at end of each week, using a short questionnaire modified from the Back Pain Functional Scale (BPFS).[30,31] The BPFS consists of 12 items investigating the performance at work, hobbies, home activities, bending or stooping, dressing shoes or socks, lifting, sleeping, standing, walking, climbing stairs, sitting and driving. We modified the BPFS by allowing patients to omit items that did not apply when the patient was not used to perform that activity, regardless of pain (e.g. if she was not used to driving or to have specific hobbies); while items that could potentially apply but were "impossible" to the patient because of the pain, were kept in. Each item was rated using a Likert 5-point scale (1 = no difficulty to perform activity; 2 = little difficulty; 3 = medium difficulty; 4 = great difficulty; 5 = impossibility to perform the activity. The statistical analysis was based on the mean score of the completed items.

The physicians reported their intention whether or not to treat the patient with um-PEA before and after the trial, answering the question "If the patient was not going to participate in the trial, would you treat him/her with um-PEA?", before the trial; and the question "Now the trial has terminated and you know the results, would you continue treating the patient with um-PEA?", after the trial. Both before and after, the physicians

answered also the question “How comfortable do you feel now about your treatment plan?” using a 7 point scale.[22]

2.4 Statistical methods

In accordance with the study primary objective, each trial was analyzed separately. For each patient, the effect on daily pain intensity was represented graphically as the mean scores over each week and over each period. A similar graphical presentation was used for the weekly scores of function impairment. The effect of the active treatment versus placebo in each patient was first statistically evaluated through a paired t-test of the period mean scores within treatment pairs, as previously done in similar studies.[22] Secondarily, to use a more statistically powerful approach, we analyzed the patient’s daily data on pain intensity, or the weekly data on function impairment, without aggregating them into period mean scores, in linear mixed effect models, with the daily data on pain intensity, or the weekly data on function impairment, as dependent variable, and the treatment (active *versus* placebo) as independent variable. We used mixed effect models, at first, to include the treatment pair (first or second pair) as random intercept, in order to account for a possible correlation between data within pair, to be consistent with the trial design, and allow comparison with the paired-t test analyses. However, using the likelihood ratio test, for each trial, we compared the mixed effect model to a linear regression model to verify the pairwise structure of the data. The main analyses were performed assuming that the washout periods were sufficient to overcome the possible carryover effect of PEA. As sensitivity analyses, the models were repeated after excluding the measures made during the first week of each period

in order to account for a slow onset time and/or a residual carryover effect.[32] When the graphical representation suggested a clear trend over time (e.g. a pain or function ratings consistently increased or decreased over the course of the trial regardless of the treatment, with a visual difference between the first two and the last two periods of treatment), we statistically verified this by including in the model an interaction term between treatment and *pair* (e.g. first pair of treatment versus second pair of treatment), and discussed a possible reason with the patient.

Missing data were expected. No imputation method was planned. If more than 3 measures of the daily pain intensity in the same week were missing for at least one week, the period mean score was computed weighting each week mean score according to the inverse-variance method.[33]

Given the heterogeneity in the way they were reported, data on the daily use of pain medications, on a demand base, were not formally analyzed. They were summarized for each week as the weekly mean number of times in a day in which the patient assumed a medication (any type, any dosage), and included in the graphical representation that was shown to the patient and the treating physician as an additional element for the discussion (**eFigure2**).

Each trial was eventually classified according to its *completeness* and the *statistically significance* of its results (threshold p value ≤ 0.1).

3. RESULTS

In the period between September 2015 and March 2016, we suggested participation to 11 patients referred to the outpatient geriatric clinic and complaining for chronic pain who met the eligibility criteria. The study flow diagram is reported in **eFigure 3**. **Table 1** presents the baseline characteristics of the 10 patients who initially consented to participate and started the trial. All patients were female, with a mean age of 83.2 years (SD 4.6 years). Only 3 patients were on chronic analgesic therapy at the time of enrolment (patient 2, 5, 10), with a history of multiple pharmacological failures, and different pain etiologies additional to osteoarthritis. All patients used to take painkillers on demand.

Table 2 synthesizes the methods and completeness of individual N-of-1 trial. Three patients did not complete the trial. Patient 1 interrupted the trial because of diarrhea in the first 4 days during which she was taking placebo. Patient 4 withdrew before the last period, but since her adherence was suspected to be low since the beginning because of behavioral issues (eventually found to be related to an initial dementia), we did not further consider her data. In one case (patient 10) the trial was interrupted due to intercurrent illness. Among the 7 patients in which the trial was conducted through the last period, outcome questionnaires were returned with no missing data in one case (patient 5); in the case of patient 3, the questionnaires for periods 3 and 4 were lost and never returned; in all the other cases, questionnaires were returned with few missing data.

Table 3 presents results on pain intensity of individual trials according to different statistical approaches. **Figure 2** shows the corresponding graphical results as presented

to the treating physicians, patients, and caregivers. **eTable 1** in the supplement presents individual results of functional impairment. **eTable 2** presents a more detailed synthesis of outcome data of the N-of-1 trial of patient 5. **Table 3** shows the impact on physician's therapeutic choice and confidence, and follow-up data.

Overall, both daily pain intensity scores (**table3, figure 2**) and weekly function impairment scores (**eTable 1**) generally showed small variations over the trial. None of the studies showed a statistically significant difference in pain intensity between um-PEA and placebo using the paired-t test of mean period pain intensities (**table 3**). A statistically significant effect was seen at the mixed method analyses either in favor of um-PEA for patients 2 and 9 (with an effect size that corresponded in both case to about 8% of the baseline pain), or in favor of placebo for patients 3 and 5. The sensitivity analyses accounting for a possible carryover effect and slow onset not sufficiently overcome by the scheduled washout, supported a probable favorable effect of um-PEA in patients 2 and 9, and suggested a possible favorable effect in patient 5 and 6. In patient 5, the graphical representation (**figure 2**) suggested a slow onset, the need for drug titration and a delayed carryover effect. A pair effect was statistically significant in patients 8 and 9. In the former case, it was mainly attributed to the onset of stomachache in the second part of the trial; in the latter, a clear reason for a sharp pain improvement in the second part of the trial could not be found. The reported daily need for on-demand pain medication was consistent with the intensity of pain. A statistically significant favorable effect on function impairment was seen only in patient 7 (**eTable 2**), who on average reported a relatively low impact on functional impairment during

the trial according to the questionnaire, and eventually placed a low value on the effect on function against the lack of effect on pain intensity.

After the discussion of the results and experience of the trial with the treating physicians, patients, and caregivers, 4 patients continued with um-PEA (**table 3**). In all 4, the physician's intention before the trial was to treat with um-PEA; in 2 patients the level of confidence in the decision increased after the trial; in 2 cases it remained the same (Table 3). Three of these 4 patients were still using um-PEA at the first clinical follow-up (**table 3**). Three patients were not prescribed um-PEA; in 1 case this coincided with the physician's pre-trial intention, while in 2 cases the physician's intention before the trial was to treat the patient. In all 3 cases, the confidence in the decision increased after the trial.

5. DISCUSSION

We report the results of a series of N-of-1 trials to test the efficacy of um-PEA in reducing chronic non-cancer pain and its impact on function performed in older outpatients referred to the geriatric clinic of our University hospital in Milan. We found a statistically significant favorable impact on either pain intensity or function impairment in 3 of 7 patients that completed the trial; in the other 4 completed trials, the results did not reach a statistical significance or were in favor of placebo. After the trial, um-PEA was prescribed to 4 patients. In 2 patients, the physician changed her pre-trial intention to treat the patient with um-PEA based on trial results. In 5 patients, the clinician expressed greater confidence in the decision after the trial; in 2 patients the

pre-trial level of confidence (i.e. “Quite comfortable, likely that the treatment plan is best for the patient”) was unaffected by the trial.

Our study has several strengths. It was the first time a series of N-of-1 trials was implemented with the aim of optimizing pain medication, through an empirical, objective and personalized approach, specifically in geriatric patients. These N-of-1 trials represent a pilot of a wider project aiming to create a *Geriatric N-of-1 Service*, based on the rationale that older complex patients are underrepresented in the current paradigms of the evidence based medicine,[34,35] extremely heterogeneous, and are often exposed to therapeutic failures and adverse events. Such patients therefore stand to benefit from use of a method that would establish or refute benefit with greater certainty than conventional multiple “try and see” trials,[19] and from an approach that would put patient characteristics, needs and preferences at the center.[36,37] The specific context of chronic pain management, often associated with long term use of multiple medications and abuse of nutraceuticals despite unclear benefit,[38,39] and the specific case of um-PEA, with the need for the patient to pay cover the product cost, contributed to our motivation. Our experience has commonalities with previous experiences with N-of-1 trials not specifically conducted in a geriatric setting.[22,23,40] First, the approach helped to strengthen the confidence in the therapeutic decisions, whether the decision was a confirmation of a pre-trial intention or not, and, often, independently of the statistical significance of the results. Second, the graphical representation of the results, more than statistics, played a role in the decision making process involving patients, caregivers and treating physicians, as did in similar experiences.[22] The lack of

power of statistical tests, and the potentially compelling impact of visual presentation of results, has made practitioners of single-subject studies question the necessity of statistical tests.[41] The analysis of N-of-1 trials based on a paired-t test is consistent with treatment periods being the unit of randomization, and with the pairwise structure, but it is known to have a limited statistical power.[42] Visual presentation of results mitigates this limitation in practice. However, we were aware that patients, caregivers and, above all, physicians, even when able to appreciate the visual presentation, would sometimes rely on us for advice on the trial results from a more analytical perspective. Thus, we decided to use also mixed methods, which, still accounting for the trial structure, would allow using all the daily (or weekly) outcome measurements, yielding a greater power. Therefore, the difference in the statistical significance of the results between the two tests, for the same trial, in some of the patients, was someway expected.

We also learned lessons regarding the feasibility of this approach with the oldest patients. Compliance and reliability of the patients represented the main anticipated threats to the trials, which we tried to reduce through enrolling patients whom we had already evaluated based on a comprehensive geriatric assessment, who appeared to be keen to undertake such a type of trial that would help them with their pain, and who, in a screening visit, when instructed on how to complete the questionnaire, demonstrated their ability to do so. In fact, in only one of 10 patients did the trial fail because of patient's noncompliance, which corresponds to a similar noncompliance rate (10%) as what a previous report of a 3-year experience with N-of-1 trials and a case mix that included also younger patients.[22]

In terms of adherence to the drug protocol, in their proof-of-concept series of N-of-1 trials on statin-related myalgia in patients with a relatively lower mean age than ours (66 years, female in 7 of 8 cases),[40] Joy and colleagues reported a 92 to 100% adherence based on pill counts. We decided not to formally assess adherence in this way because it would not definitely prove a correct daily dose regimen. Similarly, previous reports of N-of-1 trials have also described instances in which patients forgot to complete the questionnaires for a certain period, or lost the questionnaires, or did not adhere temporarily to the trial design.[40] In some cases, we suspected, on the basis of clinical contact and the way they patients completed the questionnaires, that their reliability was lower than expected from their MMSE score at the screening visit. In some patients, especially in those with no etiologies other than osteoarthritis, we suspected that the patient's inurement to pain, together with reduced discernment abilities, explained average moderate outcome scores with small variation. Indeed, the fact that most of these patients, despite complaining about pain, were not on chronic analgesic therapy, was already a clue for their tendency to resist pain. In particular, it has been our own experience that older patients tend to underestimate the medical importance of pain, compared with other medical conditions they are affected by, which might be a fact related to age but also to our own cultural background, therefore not necessarily generalizable. However, we cannot exclude that our patients were not on any chronic analgesics because of (patient's or physician's) low confidence in their efficacy and/or safety, or because pain had been previously underestimated or overlooked by other physicians. Finally, we encountered social barriers that we tried to address. For instance,

in one patient, because she lived alone and had mobility limitations, we delivered the study drugs and questionnaires to her home. In another patient, because there were no close relatives, we engaged a patient's friend who, eventually, withdrew from her caregiving role.

Lastly, we experienced some feasibility issues previously described as obstacles to the adoption of N-of-1 trials in practice: difficulties in educating, involving and keeping engaged the medical staff.[43] Conversely, we easily succeeded in involving the hospital pharmacy to store and deliver the study drugs, generate the randomization schemes, and ensure blindness.

5.1 Limitations

In designing the study, we needed to compromise to take into account the expected pharmacological characteristics of um-PEA. Hence, we conducted trials of about 4 months each, with the awareness that we were at the limit beyond which important criteria for an N-of-1 trial to succeed, including patient compliance and clinical stability, are jeopardized.[41,44] Second, we designed the study based on evidence about the product pharmacokinetics and pharmacodynamics that are not definitive, with a possible inter-individual variability that could not be anticipated. Our trials could be an opportunity to explore the product characteristics further; yet, the trial structure might have been not completely appropriate to study the product efficacy in every case. Third, even though chosen after a careful review of the relevant literature, we could not exclude that the instruments we used were not fully appropriate; in particular, we could

not exclude that the instruments' limitations contributed to the small variations that the patients overall reported.

5.2 Conclusions

In conclusion, our series of N-of-1 trials on um-PEA to reduce the intensity and the impact on function on chronic non-cancer pain in a geriatric outpatient setting represented the opportunity to test the feasibility of this approach to make personalized evidence based decisions in complex older patients. We can confirm that the approach remains attractive in this population, but requires special considerations beyond those suggested in the users' guide proposed by the pioneers of the method.[41,44] Our experience demonstrates that the final objective of creating "a real clinical learning community"[45] was achieved, and that the approach facilitates older patients' desire to participate in decision making and research.[46]

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7. COMPLIANCE WITH ETHICAL STANDARDS

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Figures' captions

Figure 1. N-of-1 trial design

Figure 2. Effect on pain intensity based on treatment period in individual N-of-1 trials

Table 1. Baseline characteristics

Characteristics	All patients (n=10)
Mean age (SD, range), y	83.2 (4.6, 74-89)
Female, n (%)	10 (100)
Living condition, n (%)	
Alone	4 (40)
With partner	5 (50)
With other relatives	0 (0)
With a formal caregiver	1 (10)
Nursing home resident	0 (0)
Mean, median ADL (SD, range)	4.8, 5 (1.2, 3-6)
Mean, median IADL (SD, range)	6.1, 7.5 (2.4, 2-8)
Mean, median MMSE (SD, range)	28.4, 29 (1.6, 26-30)
Mean, median Charlson Comorbidity Index (SD, range)	1.5, 2 (1.3, 0-3)
Mean, median number of drugs (SD, range)	7.2, 7.5 (3.4, 1-13)
Mean eGFR (SD)	56.5 (17.9)
Pain: location, n (%)	
Back (alone)	2 (20)
Back and joints	4 (40)
Back and limbs	2 (20)
Joints (alone)	0 (0)
Joints and limbs	0 (0)
Limbs (alone)	1 (10)
Back, joints and limbs	1 (10)
Pain: etiology, n (%)[a]	
Degenerative (osteoarthritis /osteoarthrosis /spondylosis /radiculopathy)	10 (100)
Diabetic neuropathy	1 (10)
Post-herpetic neuralgia	1 (10)
Restless leg syndrome	1 (10)
Post-trauma	1 (10)
Patients on chronic analgesic therapy, n (%)	3 (30)[b]
Baseline pain assessment	
Mean, median pain intensity score[c] (SD, range)	5.4, 5.7 (1.3, 3-7)
Mean, median impact on function score[c] (SD)	2.8, 2.4 (0.8, 1.9-4.2)

Abbreviations: SD, standard deviation; ADL, basic Activity of Daily Living (Katz scale); IADL, Instrumental Activity of Daily Living (Lawton scale); MMSE, Mini Mental State Examination; eGFR, estimated glomerular filtration rate (Cockcroft-Gault formula)

[a] The table lists non exclusive etiologies. All patients had a degenerative cause of persistent pain; some have also additional causes.

[b] At the time of the enrollment, 1 patient was taking gabapentin and clonazepam, 1 only gabapentin, and 1 duloxetine

[c] The baseline pain intensity and function impairment for each patient has been defined as the mean between the value given the day in which the patient consented to the trial and the value given the first day of the trial, to take into account the daily fluctuations of chronic pain. Indeed, these two values were substantially different in some patients.

Table 2. Methods and completeness of individual N-of-1 trials

ID	Randomization sequence	Person in charge of filling outcome questionnaires	Trial completeness	Completed periods[a]	Reasons for incompleteness	Notes
1	PA - PA	Patient	Incomplete	None	Acute incoercible diarrhea after 4 days from the beginning of the trial without clear alternative explanations	The sequence was open and the patient was showed she was taking the placebo drug. She recovered from diarrhea in few days; the diarrhea was judged to be of unclear origin, and the patient was offered to restart the trial. The patient refused.
2	AP - PA	Patient	Complete	1, 2, 3, 4, 5, 6, 7	-	-
3	AP - PA	Patient with daughter's help	Complete	1, 2, 3, 4, 5, 6, 7	-	The patient completed each trial's period but did not return the questionnaires for period 3 and 4
4	AP - PA	Patient with a friend's help	Incomplete	1, 2, 3, 4, 5, 6	Withdrawal, low compliance	The patient was suspected to have low compliance to the trial protocol; hence, even data for completed periods were judged unreliable and not analyzed
5	AP - AP	Patient with husband's help	Complete	1, 2, 3, 4, 5, 6, 7	-	-
6	PA - AP	Patient	Complete	1, 2, 3, 4, 5, 6, 7	-	-
7	PA - AP	Patient	Complete	1, 2, 3, 4, 5, 6, 7	-	-
8	PA - AP	Patient with formal caregiver's help	Complete	1, 2, 3, 4, 5, 6, 7	-	In the second part of the trial the patient complained for stomachache for which she started assuming antacid and antispasmodic drugs (Mg hydroxide and hyoscine butylbromide) almost daily. Also, patient cognition deteriorated during the trial. The trial was however continued.
9	AP - PA	Patient with	Complete	1, 2, 3, 4, 5, 6, 7	-	The patient discontinued the trial at the end

		daughter's help				of period 2 (i.e. first washout) for 16 days, for unclear reasons; then the trial was restarted from period 3 and completed.
10	AP - AP	Patient	Incomplete	1, 2	The patient was hospitalized for pneumonia	

Abbreviations: ID, patient number; A, active drug (um-PEA); P, placebo

[a]Periods were considered completed when the patient followed the trial design and took the active drug or placebo or nothing, according to the schedule, regardless of the presence and number of missing outcome data. See Figure 1 for each trial structure and period numbering.

Table 3. Results of completed N-of-1 trials: effect on pain intensity, physician's treating plan and confidence, and follow-up data

ID	Pain Intensity					Physician's treating plan and confidence		First clinical follow-up	
	Mean daily score (SD) during the trial	Weeks with at least 3 days with missing data, n	Mean difference (95% CI)[a], p value			Intention to treat with um-PEA BEFORE the trial (confidence[d])	Decision to treat with um-PEA AFTER the trial (confidence[d])	Patient treated with um-PEA (months since N-of-1 trial completion)	Clinical notes
			Paired t test	Mixed effect model[b]	Mixed effect model, sensitivity analysis[c]				
2	6.6 (0.5)	2	-0.50 (-0.56, 0.46)[e] p=0.443	-0.40 (-0.66, -0.14) p=0.003	-0.67 (-0.87, -0.46) p<0.001	To treat (5)	To treat (5)	Yes (3)	After a month of open therapy, the patient opted to continue with um-PEA even if "it had only a small effect on her pain"
3	5.6 (1.1)	5[f]	0.53 (-1.12, 2.19)[g] p=0.300	0.90 (0.36, 1.44) p=0.001	1.21 (0.49, 1.94) p=0.002	Not to treat (3)	Not to treat (7)	No (12)	The patient had started pregabalin some months before with partial pain relief
5	5.2 (1.6)	0	1.00 (-12.31, 14.31) p=0.515	1.00 (0.33, 1.67) p=0.003	0.32 (-0.49, 1.13) p=0.436	To treat (5)	To treat (5)	No (6)	After 10 days of open therapy with um-PEA, the patient presented fluid retention and withdrew the drug (with no symptom improvement). She never resumed um-PEA afterwards.
6	5.2 (0.8)	0	-0.05 (-5.77, 5.67) p=0.930	0.01 (-0.31, 0.32) p=0.969	-0.33 (-0.66, 0.01) p=0.056	To treat (5)	To treat (6)	Yes (4)	The patient referred a mild effect on pain after the first month of open therapy and was prescribed with continuing um-PEA every other

									month.
7	4.3 (1.3)	3[h]	-0.25 (-5.97, 5.47) p=0.677	-0.29 (-0.83, 0.26) p=0.306	0.25 (-0.31, 0.81) p=0.306	To treat (4)	Not to treat (6)	No (10)	The patient never showed up at the scheduled follow-up visits at the geriatric clinic in the 8 months after the completion of the trial. She was contacted by phone.
8	4.9 (2.1)	1	0.55 (-20.41, 21.51) p=0.795	0.53 (-0.35, 1.42) p=0.238	0.91 (-0.22, 2.04) p=0.114	To treat (4)	Not to treat (6)	No (9)	The patient referred a spontaneous attenuation of her back pain. The stomachache she had referred during the trial occurred intermittently also later.
9	4.1 (1.4)	0	-0.65 (-20.34, 19.04) p=0.747	-0.67 (-1.21, -0.13) p=0.015	-0.86 (-1.51, -0.20) p=0.010	To treat (4)	To treat (6)	Yes (5)	The patient referred a satisfactory control of her pain with um-PEA and on-demand acetaminophen.

Abbreviations: ID, patient number; SD, standard deviation; CI, confidence interval; A, active drug (um-PEA); P, placebo; um-PEA, ultra-micronized palmitoylethanolamide

[a] Calculated as active-minus-placebo difference (i.e. a positive mean indicates greater pain while receiving um-PEA versus placebo, whereas a negative mean indicates greater pain intensity while receiving placebo)

[b] Linear mixed effect model with the daily pain intensity as dependent variable, and pair included as random effect (random intercept).

[c] Calculated using the same linear mixed effect model as in note b but after excluding the outcome assessments made in the first week of each treatment period to reduce the effect of possible drug's slow onset and/or carryover effect.

[d] 1=Extremely uncomfortable, uncertain about the treatment plan and, if wrong, the patient may suffer. 2=Moderately uncomfortable, feeling that the treatment plan may not be the best for the patient. 3=Mildly uncomfortable, some uncertainty whether the treatment plan is best for the patient. 4=Not totally comfortable, but treatment plan is very likely to be as good as alternatives. 5=Quite comfortable, likely that the treatment plan is best for the patient. 6=Almost totally comfortable, very likely it's the right thing for the patient. 7=Totally comfortable, certain it's the right thing for the patient.

[e] Pain intensity data were missing for the entire week for 2 weeks of the same period (period 5, while the patient was taking placebo). The results shown in the table were obtained computing the mean period score ignoring the missing data. Secondarily, the mean difference was also computed

weighting each period mean score based on data missingness using the inverse-variance method. Even if only 7 out of 21 assessments were available, they all corresponded to a score of 7. Thus the analysis based on the inverse-variance method (taking into account the number of assessments but also the data variance) provided a larger statistically significant effect size favoring the active drug (with high data heterogeneity according to the I-squared test).

[f]Data missing for every week of period 3 and every week of period 4 (washout) because outcome assessments were lost and not returned

[g]Paired t test on period means could not be performed because data for the entire period 3 were missing. For this patient, the table shown the results for the paired t test on week means of the second pair of treatment

[h]All weeks with missing data were in washout periods

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