A natural fix for knee pain?

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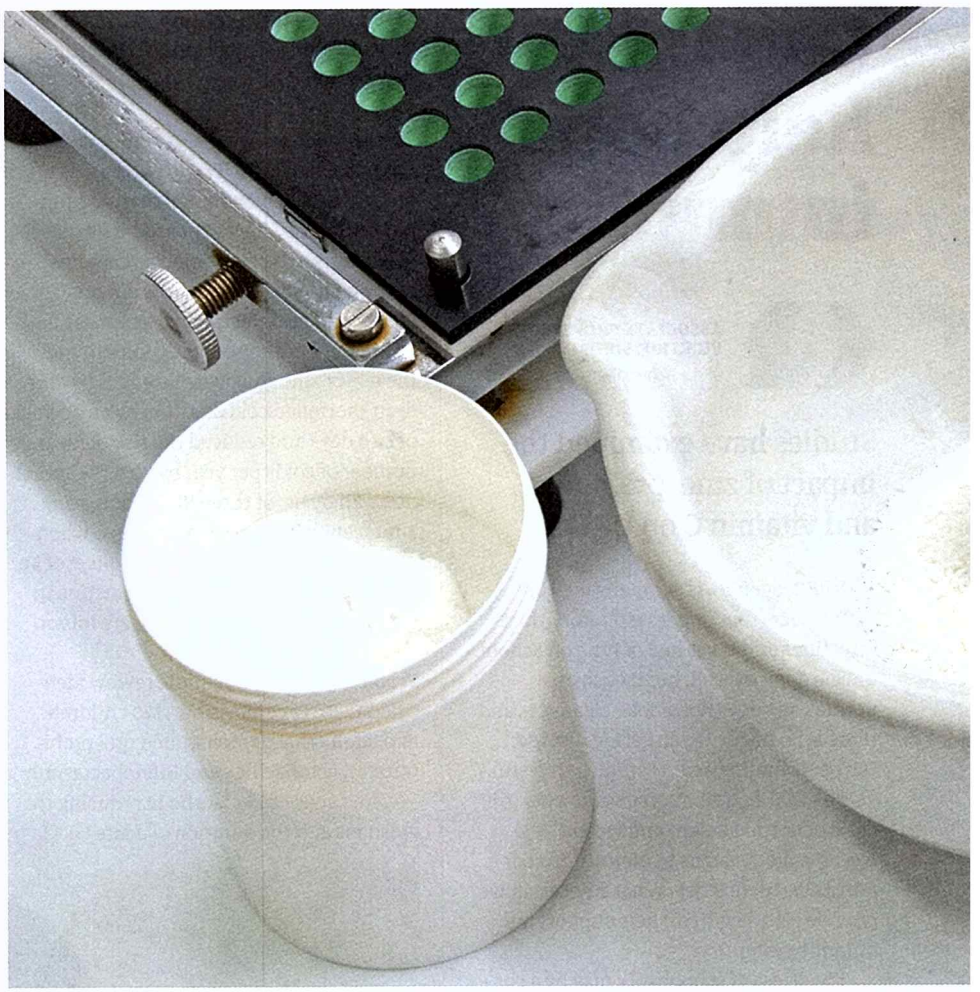


While PEA might be plausible for osteoarthritis, more research is needed.

CLINICAL SCENARIO

FATIMA, 59, a woman living with painful knee osteoarthritis whose case was described in Examining the Evidence in the July 2019 issue of *Medical Observer*, was brought in again by her daughter, a pharmacy assistant.

In this consultation she raised a new 'natural' treatment, palmitoylethanolamide (PEA), for osteoarthritis.

I recognised this substance from discussion on an online GP forum, with several members having had patients prescribed it by a pain physician. So, what is the evidence?

CLINICAL QUESTION

Does oral PEA improve knee osteoarthritis pain and function?

WHAT DOES THE RESEARCH EVIDENCE SAY?

Step 1: The Cochrane Library

The Cochrane Library does not have a systematic review on PEA. However, the Cochrane Central Register of Controlled Trials does identify a very relevant and recently published Australian trial.[1]

Step 2: TripDatabase

I conducted a search using the TripDatabase PICO search tool initially with the following search terms: Participant: "knee osteoarthritis"; Intervention: "palmitoylethanolamide"; Comparator: blank; Outcomes: blank.

This did not find anything useful. I broadened the search by changing the participant field to simply "pain". This identified a systematic review and meta-analysis of PEA for pain, but it was for a heterogenous range of conditions.[2]

Let's look at the paper, by Steels et al. 2019 published in the journal *Inflammopharmacology*, in detail.[1]

CRITICAL APPRAISAL

I will use the randomised controlled trial appraisal sheet from the Centre for Evidence-Based Medicine.[3]

PICO

Participants: who was studied?

Some 111 adults, recruited through local published media in Brisbane, Australia, from 2016 to 2018, with a diagnosis of osteoarthritis in at least one knee, and a minimum pain level of four out of 10 on a numerical rating score. The mean age was 57 years, roughly equal numbers of males and females, and mean BMI of 27.

Important exclusions: People with other forms of arthritis, significant joint injury in the past six months, use of analgesics (eg, NSAIDs) or natural therapies (eg, glucosamine) in the past 30 days, BMI over 35, "uncontrolled" other chronic disease (diabetes, hypercholesterolaemia, hypertension), anticoagulant use, history of stroke, substance use, or major depressive disorder.

Intervention: what was the exposure?

PEA 300mg: palmitoylethanolamide 150mg, one cap twice daily

PEA 600mg: palmitoylethanolamide 300mg, one cap twice daily

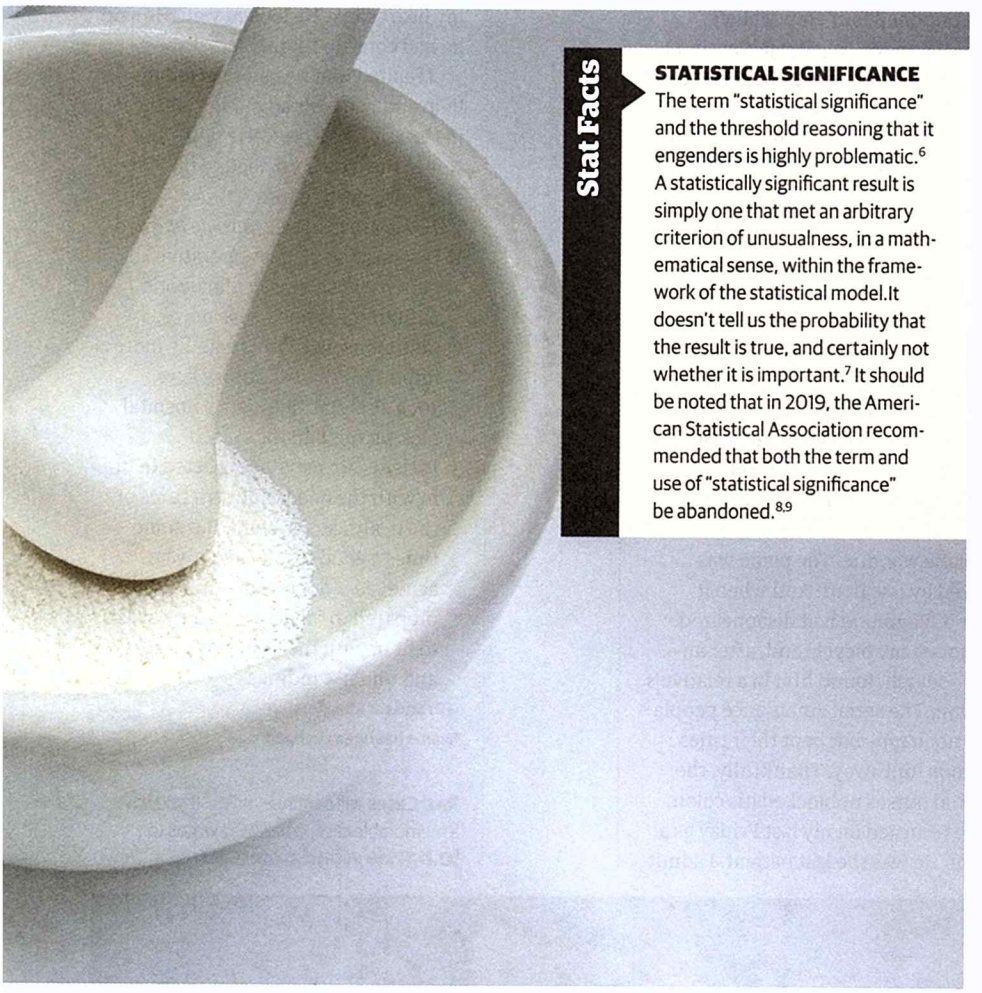
No other osteoarthritis medication could be used, except for paracetamol as rescue medication.

Comparator: what was the control/ alternative?

Placebo group: matched placebo capsules, one cap twice daily

Outcomes: what was measured?

Primary outcome: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which includes pain, stiffness,



Stat Facts

STATISTICAL SIGNIFICANCE

The term "statistical significance" and the threshold reasoning that it engenders is highly problematic.[6] A statistically significant result is simply one that met an arbitrary criterion of unusualness, in a mathematical sense, within the framework of the statistical model.It doesn't tell us the probability that the result is true, and certainly not whether it is important.[7] It should be noted that in 2019, the American Statistical Association recommended that both the term and use of "statistical significance" be abandoned.[8,9]

and function sub-scores, at week four and week eight.

THE RESULTS

Primary outcomes - WOMAC pain scores, baseline and week eight:

- PEA 300mg group: 8.9 to 4.5
- PEA 600mg group: 9.2 to 3.9
- Placebo group: 9.0 to 6.8

Interpretation: the point estimate differences at eight weeks were statistically significant (see: StatFacts) between both doses of PEA and placebo. However, it is likely the difference between PEA and placebo is not clinically important. The minimum clinically important difference (MCID) for improvement of knee osteoarthritis on the WOMAC pain score is 7.09.[4]

WOMAC function scores: baseline and week eight:

- PEA 300mg group: 28.1 to 17.7
- PEA 600mg group: 30.2 to 14.2
- Placebo group: 29.1 to 22.2

Interpretation: the point estimate difference at eight weeks was statistically significant between PEA 600mg and placebo. However, like the pain sub-score, this difference might not be important as the MCID for improvement of knee osteoarthritis on the WOMAC function score is 11.25.[4]

DISCUSSION AND CONCLUSION

PEA is a compound that is thought to have effects on the endocannabinoid system.[5] Prior reviews of the limited evidence supports the notion that it may have analgesic properties, and seems to have been well tolerated by participants in short-term research settings.[2,5]

This study supports the belief that PEA might have some effect on knee osteoarthritis pain compared with placebo.[1] However, the effect sizes were not impressive and, on average, did not appear to be larger than the minimum clinically important differences for knee osteoarthritis.[4]

It is always important to be sceptical of more enthusiastic researcher statements, for instance, "PEA was effective for attenuating pain ... of knee OA"[1] and to consider what is clinically meaningful.

This study recruited people with no substantial comorbidities, who were not obese, and were taking no analgesia other than paracetamol, and were without a major depressive or substance use disorder. That is, the participants were largely well, other than living with mild-to-moderate knee osteoarthritis. It is unknown what effect that PEA may have when used with other common osteoarthritis therapies, or in the setting of multimorbidity, or for people living with more severe disease.

My interpretation is that this study does demonstrate that PEA, or substances like PEA, are plausible potential treatments that deserve further research and investigation. However, given the limited nature of the current evidence-base, the lack of clarity regarding dosage and formulation, and that it isn't available in Australia without special order and compounding, PEA cannot be recommended as a routine therapy for knee osteoarthritis in primary care.

References on request

Internal validity
Are the results valid?

Randomised patient assignment?
Yes. The randomisation was generated by computer by an "independent" person. The PEA and placebo capsules were delivered to the investigators in identical containers, numbered from 001 to 120. On enrolment, participants were allocated to the next available number.

Groups similar at the start?
Yes. There did not appear to be any important differences between the three groups.

Groups treated equally apart from assigned treatment?
Yes.

All patients accounted for?
Yes. Of the 111 patients randomised, 10% withdrew. An intention to treat approach was used, with 110 participants included in the analysis.

Measures objective? Or patients and clinicians kept blinded?
Probably, yes. Self-reported pain is a subjective measure. Nonetheless, it is likely that both the investigators and patients were kept blinded even though adequacy of blinding was not measured in this study.