palmitoylethanolamide (pea)

a well-tolerated dietary supplement with helpful anti-inflammatory, neuro-protective & anti-depressant properties

(this handout, with links to all mentioned research, was published as a blog post on 16.06.18)

I was intrigued to see the recent paper by Ghazizadeh-Hashemi et al - *"Palmitoylethanolamide as adjunctive therapy in major depressive disorder: A double-blind, randomized and placebo-controlled trial"* – with its abstract reading: *"Experimental studies provide evidence for anti-depressant effects of Palmitoylethanolamide (PEA) in animal models of depression. We aimed to evaluate the efficacy and tolerability of PEA add-on therapy in treatment of patients with major depressive disorder (MDD). Methods In a randomized double-blind, and placebo-controlled study, 58 patients with MDD (DSM-5) and Hamilton Depression Rating Scale (HAM-D) score ≥ 19 were randomized to receive either 600mg twice daily Palmitoylethanolamide or placebo in addition to citalopram for six weeks ... At week 2, patients in the PEA group demonstrated significantly greater reduction in HAM-D scores compared to the placebo group ... The patients in the PEA group experienced more response rate (≥ 50% reduction in the HAM-D score) than the placebo group (100% vs. 74% respectively, P = .01) at the end of the trial. Baseline parameters and frequency of side effects were not significantly different between the two groups ... Conclusions Palmitoylethanolamide adjunctive therapy to citalopram can effectively improve symptoms of patients (predominantly male gender) with major depressive disorder. PEA showed rapid-onset antidepressant effects which need further investigation."*

PEA & depression: Palmitoylethanolamide (PEA) is a well-tolerated dietary supplement first identified as a naturally occuring anti-inflammatory, analgesic & neuro-protective agent isolated from soy, egg yolk & peanut by Kuehl & colleagues over 60 years ago. Back in 2011 Yu et al demonstrated PEA (on its own) compared well to the widely used antidepressant fluoxetine in a mouse model of depression, and this finding was extended further by Crupi et al in 2013. These results led to Coppola & Mondola's 2014 paper *"Is there a role for palmitoylethanolamide in the treatment of depression?"* and then to this year's randomized, controlled trial. I'm always interested in ways of boosting the effectiveness of antidepressants. Remember that less than 60% of depression sufferers respond to initial antidepressant treatment (Papakostas 2016), and these fairly poor outcomes only describe *"response rates"* not *"full cures"*. Recent papers like *"Inflammation in depression and the potential for anti-inflammatory treatment"* and the catchily named *"Inflammation: Depression fans the flames and feasts on the heat"* have highlighted the potential relevance of inflammation for a sub-set of depression sufferers. Poor diet and inadequate exercise contribute to this vulnerability, and so too do early childhood difficulties. Last year's paper *"Hidden wounds? Inflammatory links between childhood trauma and psychopathology"* focuses on this vulnerability, as too does the meta-analysis *"Childhood trauma and adult inflammation".* Although these research findings suggest potential value of anti-inflammatory agents for treating depression, palmitoylethanolamide (PEA) actually has wide-ranging effects involving a series of mechanisms over and above its anti-inflammatory action.

PEA & pain: There has been much more research on the benefits of PEA for pain than for depression. There are two recent review papers - *"Efficacy of palmitoylethanolamide for pain: A meta-analysis"* and *"Palmitoylethanolamide, a special food for medical purposes, in the treatment of chronic pain: A pooled data meta-analysis".* The authors make the usual cautionary statements about needing more high quality studies, but they note the very low rates of side-effects, and they conclude *"Results showed that PEA elicits a progressive reduction of pain intensity signify-cantly higher than control. The magnitude of reduction equals 1.04 points every 2 weeks (on a 0-10 pain scale) ... in contrast, in the control group pain, reduction intensity equals 0.20* ***[Cont.]***

points every 2 weeks ... (results) showed a pain score = 3 in 81% of PEA treated patients compared to only 40.9% in control patients by day 60 of treatment. PEA effects were independent of patient age or gender, and not related to the type of chronic pain." There are studies on back pain & sciatica, for example this year's *"Nonsurgical lumbar radiculopathies treated with ultramicronized palmitoylethanolamide (umPEA): A series of 100 cases",* last year's *"Palmitoylethanolamide in the treatment of failed back surgery syndrome"* and *"Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain".* There are studies on gut pain, for example *"Randomised clinical trial: the analgesic properties of dietary supplementation with palmitoylethanolamide and polydatin in irritable bowel syndrome", "Adelmidrol, a palmitoylethanolamide analogue, as a new pharmacological treatment for the management of inflammatory bowel disease"* and *"Palmitoylethanolamide, a naturally occurring lipid, is an orally effective intestinal anti-inflammatory agent".* There is work too on urogenital pain, for example - *"Micronized palmitoylethanolamide/trans-polydatin treatment of endometriosis-related pain: a meta-analysis", "Effectiveness of the association N-palmitoylethanolamine and transpolydatin in the treatment of primary dysmenorrhea"* and *"Chronic pelvic pain, quality of life and sexual health of women treated with palmitoylethanolamide and alpha-lipoic acid".* Mm ... there is potentially worthwhile pain reduction for a surprisingly wide range of problems here. Further examples include *"Palmitoylethanolamide and polydatin combination reduces inflammation and oxidative stress in vascular injury", "Vulvodynia and proctodynia treated with topical baclofen 5 % and palmitoylethanolamide"* and *"Delay of morphine tolerance by palmitoylethanolamide".*

PEA & neuroprotection (& even flu): And, if all this isn't enough to lead us to pay more attention to PEA studies, there also seem to be benefits from its neuroprotective action. This year's free-full-text paper *"An inflammation-centric view of neurological disease: Beyond the neuron"* gives fascinating, technical scientific background and explains PEA's potentially central role in treating these very common disorders. Amongst other topics, the authors discuss neuropathic pain, fibromyalgia, Alzheimer disease, Parkinson disease, multiple sclerosis, stroke, amyotrophic lateral sclerosis, and autism. There are a series of linked initial research studies, for example - *"Palmitoylethanolamide dampens reactive astrogliosis and improves neuronal trophic support in a triple transgenic model of Alzheimer's disease: In vitro and In vivo evidence","Ultramicronized Palmitoylethanolamide: An efficacious adjuvant therapy for Parkinson's Disease"* and *"Palmitoylethanolamide as adjunctive therapy for autism: Efficacy and safety results from a randomized controlled trial".* And there are interesting results in several other disorders including *eye diseases*, *itch*, and even flu - *"Palmitoylethanolamide: A natural body-own anti-inflammatory agent, effective and safe against influenza and common cold"* ...

PEA type, cost, dose, duration: Some formulations of PEA are more effective than others. An obvious concern for relatively unregulated products like dietary supplements is whether the tablets/capsules actually contain the substance & the quantity that they claim. But to complicate the situation with PEA even a bit further, some ways of preparing PEA seem to be more effective than others, so reducing particle size (through micronization) improves absorption, plasma levels & effectiveness - see, for example *"Oral ultramicronized palmitoylethanolamide: Plasma and tissue levels and spinal anti-hyperalgesic effect".* This however increases cost, so - at today's exchange rates - 30 days of 1,200mg per day of Epitech's ultramicronized PEA preparation Normast would set a UK resident back about £95 for tablet cost & postage. A similar 30-day trial with Russell Science's PEApure (also a micro-particle formulation) sets a UK resident back £77 for cost & postage. Happily buying in bulk reduces prices a good deal (for example, dropping a 30-day PEApure trial to £45), but an individual is unlikely to want to bulk buy until they're clear that PEA is helpful for their particular problem. A fairly standard recommendation is to take a total of 1,200mg daily for a couple of months (typically in two smaller doses split across the day e.g. 600mg & 600mg, or 800mg & 400mg), then (if there is noticeable benefit) try reducing the dose to just 600-800mg daily for a third month. If the improvement is well maintained on this reduced dose, one could try reducing further for the fourth month to 300-400mg daily. If the ***[Cont.]***

improvement continues well maintained one could continue PEA at this level or even try stopping altogether.

These are standard manufacturer recommendations. What's their evidence base? Well, actually improvements may well emerge much more quickly than the two-month manufacturer recommended trial. Successful interventions for flu and for period pain have used short/sharp dosing schedules. In the paper I mentioned at the start of this post - *"Palmitoylethanolamide as adjunctive therapy in major depressive disorder: A double-blind, randomized and placebo-controlled trial"* - active treatment measurably diverged from placebo within two weeks, and in the major pain review - *"Palmitoylethanolamide, a special food for medical purposes, in the treatment of chronic pain: A pooled data meta-analysis"* - better pain relief from PEA than from placebo became evident within a week. However, in both these papers, improvements continued to increase over six to eight weeks. Possibly a good compromise is to give 1,200mg a day a month's trial. Benefits may well emerge within a few days. Hopefully these gains will continue to increase over several weeks. If there is no noticeable benefit after a month, it seems reasonable to terminate the trial. However, if there is clear improvement, it might be sensible to keep taking 1,200mg daily until improvement has plateaued. At this point (possibly a couple of months into the trial), try reducing the dose in steps to see how much PEA is needed to maintain benefits. It might later be possible to stop altogether without loss of the positive changes that have been achieved. One can always restart and/or increase the dose again if needed.

So overall, palmitoylethanolamide (PEA) is an intriguing and well-tolerated dietary supplement that appears to produce encouraging benefits in a wide range of difficult-to-treat disorders. It is fascinating to see the clearer picture that is emerging as research on PEA continues.

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