

Primumnon Nocere: Supplements as Analgesics, a Neglected Area

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Our analgesic armamentarium is rooted in pharmaceuticals. Drugs initially protected by patent, new chemical entities (NCE), molecules which never existed on earth until medical chemists synthesized them. Within the realm of this type of analgesics there are just a handful of variations: non-steroidal anti-inflammatory drugs (NSAID's such as ibuprofen), opioids (tramadol, oxycontin), antidepressants (amitriptyline, venlafaxin), anti-epileptics (gabapentine, pregabalin), paracetamol/acetaminophen and a waste basket of various old co-analgesics such as baclofen. Cannabinoids are for the courageous pain physicians only, although there are many safety reasons to prefer Cannabinoids over opiates.

Our approach to treatment of pain is very much dictated by efficacy data from RCT's, the meta-analysis based on these trials, and on the Numbers Needed to Treat (NNT), an efficacy derived parameter. How different our approach would be if we selected treatments not based on efficacy plots but on the 'Likelihood to be helped or harmed (LHH)'. This is a number based both on the Numbers Needed to Treat (NNT) as well as on the Numbers Needed to Harm (NNH). Without going into the science of calculus, just as a simple physician, I would propose to redefine the 'Likelihood to be helped or harmed' as the simple quotient of NNH/NNT. The highest quotient would be preferable, in line with one of the medical axiomata: Primumnon nocere, the Latin phrase that means "first, do no harm."

Let us first take amitriptyline. Based on literature amitriptyline has a NNT of 4.6 and a NNH of 4.1. The ratio would be 4.1/4.6 makes 0.89 [1]. For Serotonin noradrenaline reuptake inhibitors the NNT is 5.1, and the NNH 16; the ratio would be 3.1 [2].

If we consider alpha-lipoic acid (ALP), a compound registered in Germany as drug for neuropathic diabetic pain, the NNT for 600 mg ALP/day is 2.7. As the number of adverse events was not significantly different than placebo, let us define the NNH conservatively as 100 [3]. The ratio ALP would then be 37. Let us now take a second supplement with proven efficacy and safety, palmitoylethanolamide (PEA). A natural compound we often use in our clinic for neuropathic pain, either as a standalone therapy, or as part of a multimodal approach [4]. This endogenous lipid has been explored for its analgesic properties since 35 years. Based on a clinical trial in 636 sciatic patients [5], PEA is in the same ball park as ALP, with NNT below 2 and NNH

conservatively defined as 100 [6]. The ration would be approximately 50. Both quotients are far out better compared to the 0.89 and 3.1 of the tricyclic antidepressants.

Palmitoylethanolamide, alpha-lipoic acid and other molecules from the class of dietary supplements are not generally seen as analgesics. There are much more compounds in this forgotten or neglected class, for instance curcumin (diferuloylmethane), a component of turmeric (*Curcuma longa*). This has been referred to as very inexpensive, orally bioavailable and highly safe in humans. The compound is able to block the action and production of TNF- α in vitro model, in animal models and in humans. Curcumin is much cheaper compared to the man-made infliximab's (\$15000-20000 per person per year) and Aggarwal et al. boldly state: "With health-care costs and safety being major issues today, this golden spice (*Curcuma*) may help provide the solution" [7].

Natural compounds, even with higher NNTs, deserve to be considered more often for our patients suffering from pain. We should not focus only on pharmaceuticals and efficacy, but also on analgesic supplements and safety.

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