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SPOTLIGHT

New migraine prophylaxis compounds from serendipity: gambling or wisdom?

The modern physician has a feeling of being one-armed when dealing with a headache patient. In fact, his therapeutic armamentarium allows concrete control opportunities over migraine attacks, by choosing the best option among the various triptans according to their rapidity, sustained response and minor incidence of side-effects. Up to this point, the perception of the patient's satisfaction appears tangible.

However, in high frequency migraine, which requires a therapeutic prophylactic strategy to contrast its natural tendency to become more chronic, the physician's virtual handicap becomes entirely evident. His ghost hand traces insecure therapeutic hints, often out of date and with an occasionally low efficacy index. The natural reluctance of *primum non nocere* leads him towards failure already in the patient's reassurance phase, even before the beginning of the chosen prophylaxis therapy.

These patterns, which can be observed daily all over the world, induced both researchers and clinicians to convey the use of substances applied to the headache field on the basis of pure serendipity, or both therapeutic and borrowed by different pathologies, into the field itself, with alternate chance.

This is not necessarily a criticism of the easy off-label custom, due to the absence of new available molecules for headache prophylaxis for decades. Yet enumerating ancient molecules belonging to the pharmacologic classes of β-blockers, Ca^{2+}-channel blockers, 5-HT antagonists, tricyclic antidepressants and, recently, antiepileptic topiramate, among high evidence molecules in headache prevention, gives us an idea of the current stalemate. Besides, only a few of these molecules received an official therapeutic indication by the various national health organisations [1].

Why does the headache field suffer compared with other branches of medicine, where new and more efficacious molecules always proliferate? Both the relative youth of this therapeutic area, which again became, after the appearance of the first triptan less than 15 years ago, the object of drug companies' attention, and the actual economic trend that imposes caution, are the main reasons. We researchers do not have to debate upon the lack of investment in new headache drugs, but it is our duty to test new ways and opportunities for our patients. Therefore, one need not be surprised at the frenetic pursuit of new therapies rather than refinement of already existing ones. Cyclic discussions about the therapeutic efficacy of botulinum toxin type-A, endocannabinoids, riboflavin, niacin and capsaicin applied in migraine preventative thera-

py [2], just to cite a few, originate precisely from this innovation anxiety. How do these compounds behave? In fact, they behave by locally influencing the autacoids' response, eliciting the synthesis, release, transduction system or blockade of several substances presumably involved in headache mechanics. In view of these reflections, we can consider autacoids as biological agents, which have been recently tested as innovative headache therapies, like the TNF-α infliximab inhibitor for cervicogenic headache [3]. Would a spurt in basic research on innovative substances for headache prophylaxis be based on these unconventional efforts?

We must remain free of scepticism in reading these speculations, that duly necessitate rigorous scientific examination, through controlled trials involving great numbers of patients to minimise placebo effects and to climb the steps of evidence based medicine. Only in this way will headache prophylaxis be able to redeem itself from the unavoidable initial serendipity and reach official recognition.

If we want to end the war on headache, we should ask ourselves if all the scientific possibilities, also the most improbable, have been explored. This is the crucial issue: given a desolate pharmacologic landscape, is it wisdom or gambling to place our hope in new escape routes?

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