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Meta-Analyses and the Janus Effect

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The editorial warning against the limitations of systematic reviews and meta-analyses (SRMA) is welcome [1].

The tsunami of meta-analyses (12,631 hits in 2018 vs. 2,481 in 2010; PubMed) indicates the shipwreck of evidence-based medicine as it is currently implemented. While clinicians, policy makers, and ultimately patients should base decisions on a limited number of reproducible and well-designed studies, they are confused by a flow of SRMA that precludes wiseness. The problem is endemic, firstly with head-to-head meta-analyses [2] and now network meta-analyses [3]. The latter appeared in a title in 2007 (148 hits in 2017 vs. 223 in 2018; PubMed).

Of course, although commercial endeavors may use flawed meta-analyses for marketing authorization to fool naïve, at best, regulatory agencies [4] and prescribers or to promote off-label use, the problem is deeper [5]. Why so many healthcare professionals are torturing data rather than being at the bedside or performing pragmatic trials?

First, SRMA are easier to run than randomized controlled trials and can be published in high-impact journals, being naïvely considered as a response to weak evidence from poorly designed trials, despite the motto "garbage in, garbage out." SRMA may be used by academics as easily published outputs because careers are based on productivity metrics. Further, SRMA may be commissioned by the industry through contract research organizations [6] with ghost-writers and key opinions leaders.

Accordingly, investigators of FOCUS deserved commendations: this independent randomized clinical trial, which recruited 3,127 patients from 103 hospitals in the UK with a follow-up of 6–12 months, failed to demonstrate any benefit of fluoxetine after acute stroke [7]. Will FOCUS end the flow of meta-analyses nurtured by short-term trials in short series of patients as the 2011 FLAME trial (3 months follow-up, 118 highly selected patients not representative of the real-life setting) which naïvely and prematurely claimed for benefits and promoted early prescription of fluoxetine? [8].

While overlapping meta-analyses on antidepressants after stroke univocally but unduly promote this treatment [9], sometimes overlapping meta-analyses are deeply contradictory, making a synthesis impossible. For instance, an indirect SRMA of two very similar opioid antagonists, nalmefene and naltrexone, for alcohol use disorders illustrated that the choices of inclusion/exclusion criteria and analytical models for meta-analysis can result in such vibration of effects (VoE, i.e., the range of different results of any given SRMA) that a Janus effect can develop, i.e., entirely opposite results arise from various SRMAs on the same topic [10].

As a scientific community, we have to adopt a research agenda to better understand and treat the causes and consequences of VoE in meta-analyses without, of course, throwing the baby in the tsunami of bathwater.

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