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LETTER TO THE EDITOR

The underestimation of antidepressants role in risk of fractures: clinical and public health implications

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The Authors [1] confirmed that depression, affecting 18% of men and 26% of women in the USA, is significantly associated with increased risks of osteoporotic fractures and bone loss, and invoke "prevention and treatment of depression" to substantially decrease these risks.

A causal association is plausible, for many reported poor health behaviors, linked to depression and impacting with bone metabolism [1]: smoking, increased alcohol drinking, decreased physical activity. However, antidepressant therapies are not mentioned among the risk factors, despite a rich scientific literature reporting them for many years. Indeed, selective serotonin reuptake inhibitors (SSRIs), first-line agents in the pharmacologic treatment of mood disorders, have also showed to negatively affect bone metabolism [2] and fractures. Also tricyclic antidepressants (TCAs) may convey an increased risk of fracture, independent of depression and BMD [3], possibly due to increased falls in the first months of treatment, while the risk of SSRIs lasts longer.

The Authors indirectly admit it, since controlling for antidepressant the HR halves, though reaching statistical significance only in this way (Table 2 of [1]), in nine studies with 309,862 participants. We recognize that stratified analyses of risk ratio for fracture risk associated with depression shows the reverse (Table 3 of [1]): the risk is strengthened, becoming significant, only in the subgroup controlled for antidepressants.

Nevertheless, in our view, this is not enough to dismiss the possible additional contribution of antidepressants to fractures, also for their hypothesized mechanisms of action and biological plausibility, for the suggestions of a dose-response effect, and for the precautionary principle.

In fact, if antidepressants add an autonomous contribution to fractures, the consequences could be serious if their use was extended also in moderate or medium-mild depressions, where their effectiveness is barely distinguished from placebo. Moreover, their use is associated with many other adverse effects: e.g., gastrointestinal symptoms (nausea, diarrhea, gastric bleeding, dyspepsia), hepatotoxicity, weight gain, metabolic abnormalities, cardiovascular disturbances (heart rate, QT interval prolongation, hypertension, orthostatic hypotension), genitourinary symptoms (urinary retention, incontinence), sexual dysfunction, hyponatremia, bleeding, central nervous system disturbances (lowering of seizure threshold, extrapyramidal side effects, cognitive disturbances), sweating, sleep disturbances, affective disturbances (apathy, switches, paradoxical effects), glaucoma, cataract, and hyperprolactinemia. Not surprisingly, a meta-analysis [4] found antidepressants also associated with an excess of mortality and myocardial effects, although moderated by pre-existing cardiovascular disease (for their anti-clotting properties?).

Therefore, the prevention and treatment of depression should be primarily directed towards public health interventions, like more adherence to a Mediterranean diet or an Alternative-Healthy-Eating-Index-2010 (AHEI-2010) [5, 6], proven effective also with depressed patients [7, 8]; the promotion and prescription of physical activity and exercise [9, 10]; psychotherapeutic interventions with robust efficacy (e.g., cognitive-behavioral, interpersonal, and problem-solving therapies) [11]. A healthy diet and exercise are useful also for preventing fractures and promoting general health.

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The tendency to almost exclusively rely on pharmacological therapies and to prolong them without real necessity [12] should be opposed. Indeed, one in eight Americans aged 12 and over (NHANES 2011–2014) reported taking antidepressants in the previous month, and one fourth of them have taken antidepressants for ≥ 10 years.

Compliance with ethical standards

Conflicts of interest None.

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