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Medicine-based evidence: the case of antidepressants in patients with coronary artery disease

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Abstract

In individuals with coronary artery disease and concurrent depressive symptomatology, the evidence on the beneficial and harmful effects of antidepressants is very limited. Recently, a study was carried out to describe depressive symptoms and the treatments provided under real-world circumstances to cardiac patients who entered the Mayo Clinic cardiac rehabilitation program. Antidepressant use was associated with reductions in depressive symptoms, but also with poorer cardiovascular outcomes. In this commentary, the results of this study are discussed in view of their clinical implications for everyday clinical practice and for the production of knowledge.

Although randomised controlled trials (RCTs), and systematic reviews of data extracted from RCTs, are at the pinnacle of the evidence-based hierarchy, aiming to assist health care professionals in making decisions, in clinical practice making decisions in the absence of evidence, or in the presence of incomplete evidence, is a common problem (Barbui, 2017). In such situations of clinical uncertainty, health care professionals have increased responsibility, as the provision of care would need to be as much in line as possible with the limited evidence available and would also require strict monitoring (Barbui *et al.*, 2002).

An interesting example of a clinical situation with imperfect evidence is represented by patients with coronary artery disease and concurrent depressive symptomatology. This comorbidity is epidemiologically and clinically relevant (Zuidersma *et al.*, 2013). Up to 30% of patients who have been hospitalised for a myocardial infarction experience increased depressive symptoms, and 15–20% suffer from major depression (Thombs *et al.*, 2006). Clinically, the presence of depressive symptoms has a negative impact on treatment adherence, quality of life and, interestingly, on major adverse cardiovascular events, including death (Wu and Kling, 2016). For these reasons, existing guidelines suggest to routinely screen cardiac patients for depressive symptoms, and to provide cognitive-behavioural treatments and/or antidepressants for those with a formal diagnosis (Lichtman *et al.*, 2009). One of the selective-serotonin reuptake inhibitors (SSRIs) is generally recommended, as it is the case for patients with medical comorbidities (NICE, 2009). However, very few experimental studies have been conducted, and the credibility of evidence is low (Lichtman *et al.*, 2009).

Against this scenario, a recent study was carried out to describe the treatments provided under real-world circumstances to cardiac patients with depression in the area of Rochester and Olmsted, USA and the long-term depressive and cardiovascular outcomes (Grace *et al.*, 2018). The investigators collected data on patients with coronary artery disease who entered the Mayo Clinic cardiac rehabilitation program between 2002 and 2012. Patients were administered the patient health questionnaire (PHQ-9) before and after the program. Information on medicine use and major adverse cardiovascular events were extracted from a population-based record linkage system that electronically stores a variety of clinical information. The cardiac rehabilitation program included group stress management sessions, a video describing how stress affects the body, as well as techniques such as relaxation, exercise and deep breathing. Patients were also provided videos to take home demonstrating relaxation, tai chi/qigong and mindfulness-based approaches to stress management.

During the study period, 1694 patients initiated the cardiac rehabilitation program and 1266 (74.7%) of these completed the follow-up PHQ-9 and were included in the analysis. Interestingly, in this unselected sample of patients, depressive symptoms were moderate or severe in less than 10% of patients only, while the majority of cases scored in the minimal range of severity. A total of 446 (35.2%) participants were taking one or more psychopharmacological medications at any point during the period of this study; 433 (34.2%) of them were on antidepressants and 118 (9.3%) were taking more than one antidepressant, with a median of two drugs per patient. Most participants were on one of the SSRIs, in particular, citalopram, sertraline and paroxetine. Depressive symptoms decreased significantly from pre- to post-program. Use of antidepressants was associated with lower depressive symptoms

after cardiac rehabilitation; however, after propensity matching based on pre-cardiac rehabilitation depressive symptoms, participants taking tricyclics had significantly more cardiovascular events than those not taking tricyclics (hazard ratio (HR) = 2.46; 95% confidence interval (CI) 1.37–4.42), as well as those taking atypical antidepressants *v.* not (HR = 1.59; 95% CI 1.05–2.41) and those on SSRI (HR = 1.45; 95% CI 1.07–1.97). There was no increased risk with the use of selective serotonin reuptake inhibitors (SNRI) (HR = 0.89; 95% CI 0.43–1.82). The study's main conclusion was that antidepressant use was associated with reductions in depressive symptoms, but also with poorer cardiovascular outcomes (Grace *et al*., 2018).

These results raise interesting questions, as depression in cardiac patients has been associated with poorer cardiovascular outcomes in a number of studies, possibly because the presence of depression in this population is associated with less treatment adherence, deregulation of systemic inflammatory mediators (Empana *et al*., 2005), higher risk of smoking and sedentary lifestyle (Lichtman *et al*., 2014), and, ultimately, poorer quality of life and higher rates of cardiovascular events, including death (Thombs *et al*., 2006). Therefore, it could be expected that improving depressive symptoms would lead to better cardiovascular outcomes. By contrast, in the present study, only depressive symptoms improved, but not cardiovascular outcomes. The reasons for this apparent paradox are still unknown. One possibility is that the beneficial effects that improving depression had on cardiovascular outcomes were counterbalanced by the negative effects of antidepressants on the same cardiovascular outcomes. For example, the SSRIs may have some safety problems in this population. In particular, SSRIs may be associated with hypotension in the elderly (Press *et al*., 2016) and with abnormal bleeding (Ceylan and Alpsan-Omay, 2005), while citalopram and escitalopram may cause abnormal changes in the electrical activity of the heart (Nose and Barbui, 2014; Nose *et al*., 2016), and there are also some reports of adverse cardiac effects in geriatric samples taking venlafaxine (Johnson *et al*., 2006), a SNRI, although this antidepressant class was not associated with increased risk in this study. Based on these considerations, current guidelines suggesting one of the SSRIs in this population would need to be corroborated by new clinical and epidemiological studies describing the long-term consequences of antidepressant exposure. Additionally, randomised evidence and systematic reviews should attempt to ascertain the safety profile of individual SSRIs and SNRIs. This would represent an invaluable step ahead in the treatment of this comorbidity. Additionally, given the unwanted side-effects of antidepressants, current guidelines might consider to offer non-pharmacological interventions as initial treatment.

Methodologically, this study is an important example of how clinical practice may be used to produce knowledge (Barbui *et al*., 2018). Collecting clinical data under real-world circumstances should be considered an essential component of the evidence-based medicine process: while the evidence produced under experimental conditions should be implemented in clinical practice, the evidence collected in clinical practice should be used to (a) support audits of medical practice checking the degree of coherence between what evidence would suggest and what is actually provided in practice, and, if the degree of coherence is low, to ascertain which factors, besides scientific evidence, might play a role in determining clinician's attitudes and patient's preferences (e.g. costs, ethical and cultural elements, stigma associated with particular medications, etc.); (b) facilitate comparisons of outcome indicators between practices and investigate possible differences, which is important for accountability reasons, as patients, families, other interested stakeholders and the healthcare professionals themselves are interested to know what types of treatments are provided and the outcomes associated with their provision; (c) encourage a research attitude among professionals, thus helping produce 'real world' knowledge, or 'medicine-based' evidence, to be used to guide the design of pragmatic trials in such areas (Knottnerus and Dinant, 1997). This approach would ultimately lead to the development of permanent infrastructures for experimental and non-experimental studies in typical patients and settings.

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