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This Section of *Epidemiology and Psychiatric Sciences* appears in each issue of the Journal to stress the role of the epidemiological approach to promote advances in the field of clinical psychopharmacology, with a particular attention to controversial findings. The ultimate aims are to help develop a more critical attitude towards the results of research studies published in the international literature, to promote original research projects with higher methodological standards, and to implement the most relevant results of research in every-day clinical practice. These contributions are written in house by the journal's editorial team or commissioned by the Section Editor (no more than 1000 words, short unstructured abstract, 4 key-words, one Table or Figure and up to ten references).

Corrado Barbui, *Section Editor*

Antipsychotic drug exposure and risk of myocardial infarction

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Patients experiencing psychoses and in need of antipsychotic agents may be exposed to a higher risk of myocardial infarction (MI) than the general population. As there have been no randomised studies investigating this association, a recent systematic review and meta-analysis included all observational studies that compared the incidence of MI among patients receiving antipsychotics *v.* no treatment. It found nine studies and calculated that the odds (risk) for developing MI were 1.88-fold higher in antipsychotic users compared with individuals who had not taken antipsychotic drugs. In this commentary, the results of this systematic review are discussed in view of their clinical implications for everyday clinical practice.

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While it is widely recognised that systematic reviews of randomised controlled trials (RCTs) represent the most reliable and appropriate reference standard to summarise the efficacy of interventions, for safety outcomes individual RCTs and systematic reviews may not provide satisfactory information. This is especially the case when safety outcomes are rare, as RCTs usually enrol too few participants to establish associations, when adverse effects are unexpected, as RCTs may systematically collect information only on pre-defined adverse outcomes, and when adverse effects do not occur immediately after the intervention is provided, as RTCs are usually short in duration.

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For these reasons, observational studies and systematic reviews of these studies are usually considered at the pinnacle of the evidence hierarchy for safety outcomes, to be used to inform future research, clinical practice and policy decisions (Vandenbroucke, 2008). A practical example of synthesis of observational studies for investigating the occurrence of a safety outcome has recently been provided by Yu *et al.* (2016), who carried out a systematic review investigating whether exposure to antipsychotic drugs (AP) increases the risk of myocardial infarction (MI). This association has been investigated by several epidemiological studies, but findings are controversial and therefore difficult to translate into practical recommendations. While an association between cardiovascular events as a group and exposure to AP drugs is well documented (Correll *et al.* 2015), a previous systematic review of five studies found that the risk of MI was increased in one study with a large sample size, but not in other

four studies with small numbers of participants and events (Brauer *et al.* 2011).

In this review the authors included nine observational studies, three case-control, two cohort, two case-crossover and two self-controlled case-series studies. In terms of diagnostic categories, one study evaluated patients with dementia only, four evaluated patients with schizophrenia, mood disorder or dementia and the others included patients with any diagnosis. The association between AP use and MI risk was estimated using odds ratios (ORs) and corresponding 95% confidence intervals (CIs) generated from comparisons between cases and controls. Pooling data was based on the assumption that ORs were good approximations of relative risks, which is a reasonable assumption when the frequency of events is low. The odds (risk) for developing MI were 1.88-fold higher (OR 1.88, 95% CI: 1.39, 2.54) in AP users compared with individuals who had not taken AP drugs. Subgroup analyses found an OR of 2.48 (95% CI: 1.66, 3.69) among patients with schizophrenia and an OR of 2.64 (95% CI: 2.48, 2.81) among short-term (<30 days) AP users. In a subgroup analysis by type of AP drug, a significant association was observed among those using first- (OR 2.19, 95% CI: 1.46, 3.28) but not second-generation AP drugs (OR 1.72, 95% CI: 0.96, 3.07). Only a few studies provided data on individual drugs. In one study, a significantly higher risk of MI was observed with amisulpride (OR 5.65, 95% CI: 2.97, 10.76). Two studies found that AP drug use was associated with a dose-dependent increase in MI risk, but one study did not. On the basis of methodological quality assessment (based on the Newcastle–Ottawa Scale), six studies were of high quality and three were of low quality (Yu *et al.* 2016).

The review authors concluded that, although AP use was associated with a modestly increased risk of MI, the population impact of such a modest risk is likely to be substantial because of the large number of AP users globally. Risk was substantially increased in short-term users, thus suggesting an acute effect of AP drugs, although it remains unclear if AP dose (which could have been higher during short-term acute treatment) or acute medical conditions may have had a role in this finding (Yu *et al.* 2016).

Although it is always difficult to translate research results into clear-cut recommendations useful to inform clinical practice, the considerations reported below may be relevant for those prescribing AP drugs.

- The increased risk of MI associated with AP drugs adds to the existing evidence suggesting that AP drugs increase the risk of a number of medical events, such as venous thromboembolism (Barbui *et al.* 2014; Conti *et al.* 2015), pneumonia (Nose *et al.* 2015*b*), stroke (Hsu *et al.* 2015), hip fracture (Oderda *et al.* 2012) and ventricular arrhythmia (Salvo *et al.* 2016). These risk factors are probably involved in explaining the 15–25 years reduction in life-expectancy observed in psychiatric patients. Clinically, this suggests to prescribe AP drugs only when clinically indicated, following as much as possible the registered indications (labels) of these agents.
- In patients treated with AP drugs, the electrocardiogram (ECG) is a valuable and noninvasive screening tool with a rather high sensitivity for detecting most cardiac conditions, and therefore clinicians should develop with patients and carers a feasible and reasonable ECG monitoring plan, keeping in mind the risk of false-positive and false-negative results. This is in line with most recent guidelines and recommendations for people using AP drugs (Kuipers *et al.* 2014).
- Although current evidence does not undoubtedly indicate clinically relevant differences between individual AP drugs, it is possible to develop cardiovascular risk stratification tables to inform choices in individual patients (Polcwiartek *et al.* 2016). In terms of MI risk, amisulpride, haloperidol, olanzapine, quetiapine and risperidone might be worse than other AP drugs. Obviously, these tables need to be updated using the results of systematic reviews like the one described in this commentary.
- Even though risk of medical events including venous thromboembolism, pneumonia, stroke, MI and ventricular arrhythmia seems to be associated with short-terms AP use, it should be considered that metabolic abnormalities, such as central obesity, dyslipidemia, hypertension and insulin resistance may increase the risk of cardiovascular events and overall mortality in the long-term. In patients with long-term severe mental health problems these metabolic factors add to unhealthy lifestyles (poor diet, vitamin deficiencies, cigarettes smoking) further increasing the overall risk of cardiovascular events.
- As AP dose has been shown to be correlated with cardiovascular risk (Nose *et al.* 2015*a*; Barbui *et al.* 2016; Carra *et al.* 2016) and overall mortality (Ray *et al.* 2009), lowest therapeutic doses should be prescribed. Polypharmacy should be avoided as well, since it is highly correlated with overall AP dose. This recommendation is particularly relevant for clinical practice, as clinicians may not be fully aware that AP polypharmacy is associated with high doses, erroneously arguing that AP polypharmacy reduces the total amount of AP medication (Sernyak & Rosenheck, 2004).
- It is not clear whether and how AP may interact with other drugs bearing a potential cardiovascular risk,

such as, for example, estrogens (Roach *et al.* 2015), tricyclic antidepressant (Tata *et al.* 2005) or chemotherapy agents (Pai & Nahata, 2000). In patients taking these medications, AP drugs should be prescribed at the lowest effective dose under strict monitoring. In general, similar considerations apply to patients with complex therapeutic regimens, such as elderly or cancer patients, and patients with comorbid substance abuse.

In summary, the evidence showing that AP exposure increases the risk of MI suggests careful AP prescribing only when clinically indicated, careful monitoring before and during treatment, and proactive efforts to reduce the negative impact of lifestyle factors and co-morbidities that may further increase the risk.

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Conflict of Interest

None.

Ethical standard

The authors declare that no human or animal experimentation was conducted for this work.

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