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Corrado Barbui, *Section Editor*

Adherence to generic *v.* brand antidepressant treatment and the key role of health system factors

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One of the major challenges with antidepressant (AD) use is poor adherence and early treatment discontinuation. In addition to socio-demographic and clinical variables, treatment discontinuation may also be related to the capacity of the health system to assure and maintain continuity and intensity of care. Among health system factors that may interfere with adherence to pharmacological treatment, use of generic drugs may play a key role. It has been argued that, although the lower cost of generics may favour persistence on treatment, a widespread *a priori* scepticism about their effectiveness and safety by doctors and patients may have an opposite effect. This compelling research question has recently been addressed by an observational cohort study that involved 16 778 Medicare fee-for-service beneficiaries who received a new depression diagnosis and initiated generic *v.* brand AD therapy. The study found that generic initiation was associated with improved adherence. The benefits resulted from the lower out-of-pocket cost associated with generic ADs. In this commentary, we discuss the main findings of this study in view of its methodological strengths and limitations, and we suggest implications for policy.

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Antidepressants (ADs) are one of the most prescribed drug classes, with a reported increasing trend in use (McCarthy, 2013). In the USA, for example, the overall prevalence of use increased from 6.5% in 1999–2000 to 10.4% in 2009–2010 (Mojtabai & Olfson, 2014). In Europe, a recent overview of AD prescribing in seven different databases from five European countries showed the highest prevalence of prescribing in the UK and the lowest in the Netherlands, with Spain, Denmark and Germany in between (Abbing-

Karahagopian *et al.* 2014). In Italy, AD use increased from 27.5 to 39.1% defined daily doses per 1000 inhabitants/day in the period 2005–2013 (OSMED, 2014).

One of the major challenges with AD use is poor adherence and early treatment discontinuation, which may have negative consequences in terms of treatment effectiveness and patient outcomes. Adherence can be as low as 20–30% over the treatment period, ranging from 6 months to several years (Vlahiotis *et al.* 2011). In a recent study carried out in Italy, more than 70% of the population of patients with severe mental disorders discontinued AD treatment over 12 months after initial prescription (and almost 60% over 6 months; Conti *et al.* 2012). Socio-demographic variables, clinical features of

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depression, comorbidities, pharmacological factors, attitude towards ADs, previous experiences of AD treatment, patient-professional relationship and genes were found to be factors associated with poor adherence (Hung, 2014).

However, treatment discontinuation may also be a factor related to the capacity of the health system to assure and maintain continuity and intensity of care. Among health system factors that may interfere with adherence to pharmacological treatment, use of originator (brand-name) drugs, strongly supported by healthcare systems which recommend physicians to prefer them rather than brand-name drugs, may play a key role. It has been argued that, although the lower cost of generics may favour persistence on treatment (Shrank *et al.* 2006), a widespread *a priori* scepticism about their effectiveness and safety by doctors and patients may have an opposite effect (Himmel *et al.* 2005). A recent study by Bao *et al.*, who conducted a longitudinal survey of an epidemiologically representative sample of Medicare fee-for-service beneficiaries in the USA, expended current knowledge on this compelling issue (Bao *et al.* 2013).

In the USA, generic use might be associated with increased adherence because patient out-of-pocket costs for generics are nearly always much lower than they are for brands. Choice of generic or brand name is partly a function of provider preferences, and when a branded drug is prescribed in absence of a 'dispense as written' request by the prescriber or the patient, patients often receive a generic equivalent because of state mandates of generic substitution (Bao *et al.* 2013). Bao *et al.* enrolled a 5% random sample of Medicare fee-for-service beneficiaries who received a new depression diagnosis in the first half of 2007 and initiated generic or brand AD therapy within 60 days ($n=16\,778$). Adherence to AD therapy was measured by (a lack of) disruption in medication use defined by a gap of 30 days or more in AD possession and monthly days of possession, both measured over 180 days since the AD initiation. More than half of participants received a low-income subsidy (LIS) which means that they were not subject to any out-of-pocket expenditure. Therefore, in this subgroup, the impact of generic *v.* brand AD prescribing was expected to be lower as compared with those who were not eligible for an LIS (Bao *et al.* 2013).

The study found that generic AD initiation was associated with improved adherence, with a stronger effect among the non-LIS patients. Among the LIS patients, the rate of AD disruption ranged from 29 to 31% in aged and disabled patients, whereas among the non-LIS patients, the rates were significantly higher, ranging from 35 to 39% in aged and disabled patients. Cox model showed that generic initiation

was associated with a lower hazard of AD treatment disruption across all four subgroups. The authors concluded that, in this system of health care, initiating the therapy with a generic AD was consistently associated with increased medication adherence. The benefits resulted from the lower out-of-pocket cost associated with generic ADs. This finding is in line with the current evidence linking out-of-pocket cost differentials between generic and branded medications to substantially increased adherence among patients starting with a generic medication for several chronic medical conditions. Another interesting finding was that, around half of the disruption in AD therapy occurred during 30 days after initiation (early discontinuation; Bao *et al.* 2013).

As with all studies that use claims data, there are limitations that should be recognised. First, the study was unable to adjust for clinical variables that may influence the choice of branded *v.* generic AD. It might be a hypothesis, for example, that patients who were prescribed a brand AD were at higher risk of treatment non-adherence, as doctors might have been reluctant to prescribe generics to patients whom they perceived as having a high risk of non-adherence. Second, the lack of data on whether patients eventually took the prescribed agents should be highlighted, since a relevant proportion of the medicines prescribed for people with chronic conditions are not taken (Jones, 2003). Additionally, AD dose, combinations of different AD agents and switches have not been taken into consideration. Finally, according to the definition of discontinuation, during the last 30 days of the 180 days of follow-up, patients could not discontinue AD therapy. The consequences of this short window (30 days) of 'immortal-time' (Rothman *et al.* 2008) are expected to be the following: (i) the disruption rate among groups (29, 31, 35 and 39%) may be slightly underestimated; (ii) the association estimated by the Cox model might be stronger, thus suggesting an even greater impact of the results originally reported by the authors.

Strengths of this study include adjustment for confounders that should always be considered in persistence analyses: age, sex, race/ethnicity, an indicator of comorbidity status and prescriber status (primary care doctor, mental health/other medical specialty).

In terms of implications for policy, a reason for concern is whether these findings may apply to healthcare systems which have implemented drug policies that are radically different as compared with this Medicare fee-for-service scheme (Corrao *et al.* 2014). It may be argued, however, that what may be generalised is the finding that lower out-of-pocket costs are associated with increased adherence. Prescribing generics, which are associated with lower costs in most

healthcare systems, may therefore be considered as a tool for increasing adherence to AD treatment. What still remains to be investigated is whether this beneficial effect might be counterbalanced by potential concerns of doctors and patients on the effectiveness and safety of generic drugs. The quality of generics might be another concern in countries that do not have strict regulations similar to the Food and Drug Administration in the USA and European Medicine Agency in Europe. As these concerns are expected to be widely heterogeneous and heavily connected with local variables and cultures, the need for more epidemiological studies linking clinically relevant variables, such as treatment adherence, with drug policy and healthcare system factors, should be strongly emphasised (Minas & Cohen, 2007; Eaton, 2008).

Indirectly, these findings would also suggest that, in countries where there is a little or no co-pay for drugs, increased use of generics v. originators as well as v. patented products can save considerable resources (Godman *et al.* 2014). Therefore, the implementation of measures aimed at increasing the prescribing of generics, such as for example high voluntary International Non-proprietary Name prescribing rates in the UK, compulsory generic substitution in Sweden as well as switching targets among pharmacists in France, should be considered by health systems both as a cost-containment strategy, and as a clinically reasonable strategy to increase treatment adherence (Abuelkhair *et al.* 2012).

We need to know how to plan and organise services and improve the use of scarce financial and human resources in order to provide effective treatments to those who need care (Saraceno, 2007), including pharmacological treatments. More generally, we need to expand current knowledge and experience on all those system factors that may play a crucial role in improving access to, and rational use of, psychotropic medicines.

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Conflict of Interest

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