

Regulatory policies on medicines for psychiatric disorders: is Europe on target?

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Summary The European Medicines Agency (EMA) is the regulatory body that provides the institutions of the European Community with the best possible scientific advice on the quality, safety and efficacy of medicinal products. Drugs approved by the EMA are automatically marketable in all the European member states. Since the beginning of the EMA's activities a number of drugs acting on the central nervous system obtained marketing authorisation. This editorial highlights some aspects of the EMA rules that may negatively affect the evaluation of medicines for psychiatric disorders.

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The recent revision of the European pharmaceutical legislation has given the European Medicines Agency (EMA) new responsibilities. After more than 10 years of existence the EMA has proved useful in ensuring member states shift towards harmonisation of pharmaceutical procedures and simplification of the process by which a central authorisation becomes valid in all the states (Garattini & Bertele, 2001). Any opinion expressed by the EMA on old or new products, relating to changes in therapeutic indications, approval, suspension or withdrawal of a product, has to be accepted by all members of the European Union. The system includes a centralised procedure, through the EMA, and a decentralised procedure, whereby a new drug approved by one member state is accepted by the others after the procedure of mutual recognition. The recent revision of the European legislation (Regulation EC

No. 726/2004 of the European Parliament and of the Council of 31 March 2004; Directive 2004/27/EC of the Parliament and of the Council, 31 March 2004) has extended the list of drugs that must go through the centralised procedure (Garattini *et al*, 2003).

Since its establishment the EMA has issued recommendations, notes for guidance, conceptual papers and other official documents intended to guide the design and reporting of randomised controlled trials conducted for regulatory purposes. These official documents report the EMA rules and criteria for approval of new drugs. So far, nine products acting on the central nervous system have been approved in line with these criteria, and in future years it is expected that the increasing responsibilities of the EMA will progressively increase the number of products for psychiatric disorders submitted for approval (Garattini & Bertele, 2003). In this still-evolving European scenario, at least three technical aspects of the EMA rules may negatively affect the evaluation of medicines for psychiatric disorders.

PROCEDURES FOR DRUG APPROVAL

The centralised procedure is not compulsory for psychotropic drugs. In addition to the fact that the dual system of approval – centralised and decentralised – creates competition between the EMA and the national drug agencies, with financial implications, it generates heterogeneity between countries in terms of approved indications (labels). Olanzapine, for example, has been positively assessed by the EMA through the centralised procedure and released for marketing with the same label in all EU member states. However, a decentralised route has been followed in the case of quetiapine, marketed after 1995, and approved for the treatment of schizophrenia in the UK and for the treatment of 'acute

and chronic psychoses, including schizophrenia', in Italy (Barbui *et al*, 2003). Labels have a key role in regulating the everyday prescribing and consumption of drugs: in Italy quetiapine is the only atypical antipsychotic that can be prescribed in patients without a diagnosis of schizophrenia or bipolar disorder. Off-label prescribing is not forbidden, but implies that doctors take full responsibility for the prescription and that patients give informed consent and pay the full price of the drug, as reimbursement is usually restricted to disorders stated in the label. Theoretically, approved labels should correspond to trial inclusion criteria, and it seems rather contradictory that European regulatory authorities, while strongly supporting the adoption of stringent inclusion criteria in clinical trials, with rigorous and restrictive reference to diagnostic rules, permit drugs to be licensed with generic and unspecific labels for use in clinical practice. Probably, only the abolition of the decentralised procedure will make the licensed indications of new drugs more consistent.

CONTROLLED TRIALS

At the EMA new drugs can still be evaluated with no comparison with active alternative treatments. This means that new drugs can be proved effective and safe on their own, even though they might in fact be potentially less effective or less safe than other drugs currently in use. Although in situations where no (or only a few) active treatments are available this issue may not be relevant, in the field of psychotropic drugs, where many effective agents are available, this issue is crucial. Despite this, the demonstration of a difference against placebo, and not against an active comparator, makes a new psychotropic drug eligible for registration in Europe. If comparisons are made, the industry usually relies on demonstrating therapeutic 'equivalence' or 'non-inferiority', because this is in agreement with current EMA requirements. This results in a high degree of uncertainty about the therapeutic role of new drugs. Even the recent revision of the European pharmaceutical legislation does not include the requirement that, when feasible, clinical studies should be conducted in comparison with reference drugs (in accordance with the Declaration of Helsinki) to establish the relative benefit of a new drug. In terms of public health needs, the concept of added value should be introduced into the legislation. This concept has two

positive consequences. First, it allows determination of whether a drug is active. If comparative trials show that a new drug is more effective than a standard one, it means that the new drug is active. Conversely, if a new drug is not more effective than a standard one, it means that the new drug is inactive or similarly active compared with the reference. In the latter scenario there is no added value. Second, the concept of added value would advance innovation in the development of drugs, because a higher threshold for the entry of new drugs would force investigators towards the development of innovative rather than 'me too' drugs. The current legislation, allowing investigators to demonstrate a difference against placebo, has encouraged the marketing of drugs with little degree of innovation. Investigators should be induced to design and conduct clinical trials aimed at discovering better activity, beneficial effects on different populations, and less or different toxicity.

Methodological considerations also should be taken into account. Recent data have shown that placebo-controlled trials, in comparison with active-controlled trials, tend to overemphasise the occurrence of hard outcomes, such as the rate of participants withdrawing from treatment ('drop-outs'). In antipsychotic drug trials, for example, a systematic review showed that the proportion of participants discontinuing antipsychotics was substantially higher in placebo-controlled trials than in active-control clinical trials (Kemmler *et al*, 2005). In the field of psychotropic drugs, where withdrawal rates approaching or exceeding 50% are not uncommon, this may produce a problem of biased estimation of treatment effect, leading to erroneous conclusions and poor generalisability. Future revisions of the European pharmaceutical legislation should incorporate the requirement of active-control clinical trials in the evaluation of psychotropic drugs, at least in addition to placebo-controlled trials. Active-control clinical trials should be designed and powered to generate evidence of superiority (added value), providing physicians with clear indications on the therapeutic role of new medicines, with respect to older medicines already on the market.

OUTCOMES

A third aspect, particularly relevant to the evaluation of psychotropic drugs, is the choice of the outcome of interest. Whereas

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in other fields of medicine the definition of outcome measures may be a relatively straightforward task, in psychiatric disorders treatment efficacy may often be an elusive concept, typically quantified by means of rating scales. The EMEA guidance on this issue recognises that although improvement in symptoms should be documented as a difference between baseline and post-treatment score, in order to allow an estimate of clinical relevance the proportion of 'responders' or 'remitters' should be presented. Cut-off points should be defined *a priori* in the protocol. From a practical viewpoint this seems reasonable because it allows physicians to make judgements in terms of proportion of patients (and not means and standard deviations), absolute and relative risk differences and number needed to treat (Barbui *et al*, 2001). Unfortunately, this approach systematically magnifies the effect of new medicines against placebo. A situation was hypothesised of a 1-point difference in mean change in scores on the Hamilton Rating Scale for Depression between drug and placebo, and it was shown that by defining response as a minimum 12-point improvement on this scale a response rate of 50% in the drug condition and 32% in the placebo condition could be obtained (Moncrieff & Kirsch, 2005). A small difference in symptom score can thus be translated into a large and clinically relevant difference in proportions.

The EMEA rules should consider scores from rating scales and their categorisation as secondary outcome measures. Randomised controlled trials conducted for regulatory purposes should increasingly use, as primary outcomes, hard and practical measures such as suicide attempts, treatment switching, hospitalisation, school failure or truancy, job loss or even withdrawal from the trial itself (Tansella *et al*, 2006). The example provided by the Clinical Antipsychotic Trials of Intervention Effectiveness is paradigmatic in this regard (Lieberman *et al*, 2005). This study, which randomly assigned a total of 1493 patients

with schizophrenia to receive olanzapine, perphenazine, quetiapine or risperidone for up to 18 months, employed as primary outcome the discontinuation of treatment for any cause. This discrete outcome was selected on the assumption that stopping or changing medication is a frequent occurrence and a major problem in the treatment of schizophrenia. The finding that 74% of patients discontinued the study medication within 18 months is a clear confirmation of the relevance of this outcome (Lieberman *et al*, 2005). A similar approach has been followed by the Bipolar Affective Disorder Lithium Anticonvulsant Evaluation trial, where hospital admission was defined as the primary outcome (Geddes & Goodwin, 2001). In these circumstances, the idea that hard outcome measures are suitable for practical and pragmatic clinical trials, but not for randomised controlled trials conducted for regulatory purposes, appears difficult to reconcile with the principles of evidence-based medicine.

CONCLUSION

In Europe, current policies on medicines for psychiatric disorders need to be further developed in order to fully comply with the EMEA mission statement of promoting 'the protection of human health . . . and of consumers of medicinal products' (Council of the European Communities, 1993).

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REFERENCES

- Barbui, C., Guaiana, G. & Garattini, S. (2001) Regulatory issues in Europe. *Journal of Clinical Psychopharmacology*, **21**, 545–548.

Barbui, C., Tansella, M. & Garattini, S. (2003) Varying and 'atypical' indications for atypical antipsychotics. *Psychopharmacology*, **169**, 205–206.

Council of the European Communities (1993) Council Regulation (EEC) No. 2309/93 of 22 July 1993 laying down community procedures for the authorisation and supervision of medicinal products for the human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. *Official Journal of the European Communities*, **214**, 1–21.

Garattini, S. & Bertele, V. (2001) Adjusting Europe's drug regulation to public health needs. *Lancet*, **358**, 64–67.

Garattini, S. & Bertele, V. (2003) Efficacy, safety and cost of new drugs acting on the central nervous system. *European Journal of Clinical Pharmacology*, **59**, 79–84.

Garattini, S., Bertele, V. & Li, B. L. (2003) Light and shade in proposed revision of EU drug-regulatory legislation. *Lancet*, **361**, 635–636.

Geddes, J. & Goodwin, G. (2001) Bipolar disorder: clinical uncertainty, evidence-based medicine and large-scale randomised trials. *British Journal of Psychiatry*, **178** (suppl. 41), s191–s194.

Kemmler, G., Hummer, M., Widschwendter, C., et al (2005) Dropout rates in placebo-controlled and active-

control clinical trials of antipsychotic drugs: a meta-analysis. *Archives of General Psychiatry*, **62**, 1305–1312.

Lieberman, J. A., Stroup, T. S., McEvoy, J. P., et al (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine*, **353**, 1209–1223.

Moncrieff, J. & Kirsch, I. (2005) Efficacy of antidepressants in adults. *BMJ*, **331**, 155–157.

Tansella, M., Thornicroft, G., Barbui, C., et al (2006) Seven criteria for improving effectiveness trials in psychiatry. *Psychological Medicine*, **36**, 711–720.