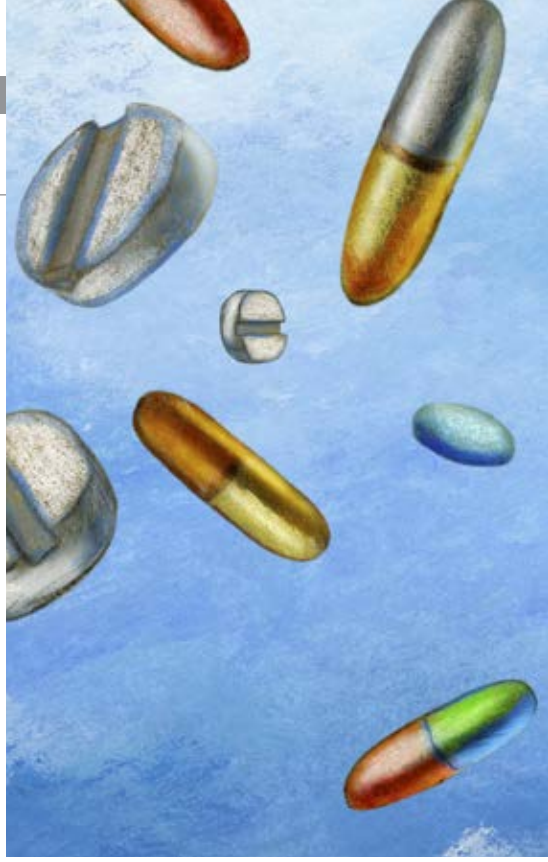

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Decisions on WHO's essential medicines need more scrutiny

Global endorsement as a WHO essential medicine is a big step. But **Corrado Barbui** and **Marianna Purgato** find that the quality of applications for antidepressants and antipsychotics is poor and call on applicants and WHO to raise standards

The World Health Organization produced its first essential medicines list in 1977 in response to a request from member states to help them select and procure medicines for priority healthcare needs.[1 2] The list included 208 drugs selected on the basis of their efficacy, safety, availability, ease of use in various settings, comparative cost effectiveness, and public health needs.[1] It has been updated every two years since by a WHO expert committee.

The list does not include all effective medicines, the latest medicines, or even all medicines needed in a country; rather, it helps define the minimum needs for a basic health system. Essential medicines include, for example, amoxicillin, diazepam, and haloperidol. WHO suggests that essential medicines should be available within functioning health systems at all times, in adequate amounts, in the appropriate doses, with assured quality, and at a price the individual and the community can afford.[2]

The effect of the essential medicines list has been remarkable. Conceptually, it has led to global acceptance of essential medicines as a powerful means to promote health equity. Countries are not bound by the list, but it has provided a guide for the development of national, provincial, or state lists and helped promote the development of medicine policies and access initiatives.[1] However, our review of medicines for mental disorders in the list raises questions about how decisions are made on what is included.

KEY MESSAGES

- Applications for inclusion of medicines in the WHO list of essential medicines are often not based on a systematic review of the evidence
- WHO should require applicants to use a tool such as GRADE to ensure they search the best evidence and critically appraise its quality in a more transparent way
- WHO should require applicants to produce summary of findings tables with absolute and relative estimates of treatment effects for each outcome of interest and for the populations for which the drug is intended

Getting onto the list

The rules governing the process for inclusion on the list have changed substantially over time. Originally, the expert committee largely decided what should be included. But in 2002, in response to growing methodological concerns,[3] a more systematic assessment of the evidence base was implemented.[4] Changes to the list are made on the basis of applications from WHO departments or external organisations, including academic centres and public or private institutions. WHO sets out the information to be included in the application, which includes basic details of the drug, its availability, licensing status, use, details of the applicant, and summary of the comparative effectiveness, safety, and cost effectiveness including a search strategy (box 1). An expert committee appointed by the WHO director general meets every two years to review applications with expert assessors and decide which medicines are added or deleted.[1] Reports of the WHO expert committee meetings are then published in the *WHO Technical Report Series*.

Decisions on which medicine should be included are difficult and might be prone to vested interests trumping need or evidence. We examined whether applications for inclusion of antipsychotic or antidepressant medicines from 1977 onwards met WHO requirements (box 2, thebmj.com). Medicines for mental disorders make an interesting case study because several treatments have been marketed in the past 35 years and randomised trials and systematic reviews have been produced, but the overall quality of evidence remains a major concern.

Applications for mental disorders

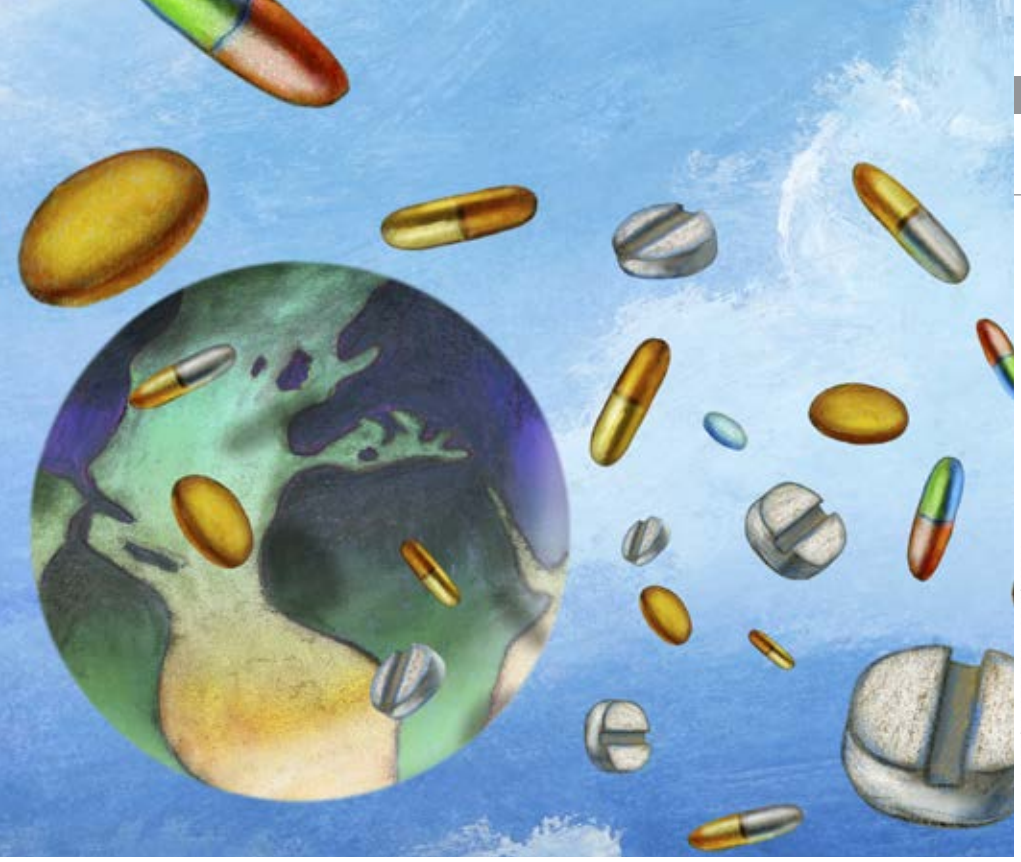
Nineteen applications for antipsychotic or antidepressant medicines were submitted to WHO between 1977 and 2013. Details of five applications submitted before 2002 were unavailable. We therefore reviewed 14 applications (table 1). The medicines considered were the antipsychotics clozapine, aripiprazole, risperidone, and ziprasidone and the antidepressants clomipramine, imipramine, fluoxetine, paroxetine, sertraline, and the whole class of serotonin reuptake inhibitors. Some medicines have been considered more than once.

Only one application was drafted and submitted by a WHO department (the department of mental health and substance use). Three were commissioned or supported by WHO but drafted by external institutions. All other applications were unsolicited submissions from outside WHO.

Quality of evidence

Four applications included a systematic review of the evidence, although only one reported the strategy used. Only one application evaluated data with specific reference to the target population for which the medicine was intended (table 1; thebmj.com).

Data on the comparison between the submitted medicine and placebo or active medicines were reported in 10 applications. A quantitative



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summary of treatment effect and cost effectiveness data was reported in four of 14 applications and one (the application on clozapine submitted in 2013) systematically incorporated feasibility or other considerations not related to the evidence. Only two applications included an assessment of quality of the data presented in the application.

There were three applications for risperidone. All considered short term outcomes, although in clinical practice treatment is usually long term and concern exists about whether the initial effect is maintained. Also there were no data presented on satisfaction with care, quality of life, or other functional outcomes, which should be a priority interest for WHO.

The risperidone applications provided a narrative overview of how risperidone compares with placebo and with first and second generation antipsychotics, but its potential advantage over comparators is vaguely reported. One application suggests that risperidone may be less effective than olanzapine, another second generation antipsychotic. The reasons why this drug rather than other (or all) second generation antipsychotics was selected for inclusion in the essential medicines list are not clear. Uncertainty about the inclusion of risperidone is reinforced by recent scientific findings that other second generation antipsychotics may be similarly or even more effective than risperidone, including olanzapine and amisulpride.[5]

Further context can be gathered on the state of the evidence presented from the reviewers' reports. One of the two applications submitted in 2013 to support the inclusion of risperidone, for example, was criticised by one referee for the omission of more than one pertinent recent systematic review. Another referee noted lack of consideration of one of the most influential pragmatic, independent studies conducted so far on second generation antipsychotics.[6]

Questions raised about applications and decisions

Our review of applications for antipsychotic and antidepressant drugs cannot be used to draw a general conclusion about the quality of all applications submitted to WHO. However, we believe it highlights some important questions. The standard of applications was low, with applicants interpreting the WHO requirements loosely. Most of the information needed to make an evidence based decision was lacking. It is unclear why such low quality information is being accepted and taken into consideration. WHO could reject the applications if basic information is missing. Not only is consideration of poor applicants a waste of time and resource, but it undermines the relevance of the list for patients, doctors, policy makers, drug companies, and healthcare systems. If poor applications are considered, there is a possibility that medicines with limited value are prioritised and that those with a real added value are overlooked.

The list has led to global acceptance of essential medicines as a powerful means to promote health equity

It is unclear whether the high proportion of rejections is related to the low quality of applications. In three cases the expert committee disagreed with the recommendation of the WHO department of mental health, but again it is unclear whether this is related to poor reporting.

Box 1 | Information to be included with an application for inclusion, change, or deletion of a medicine in WHO list of essential medicines

1. Summary statement of the proposal for inclusion, change, or deletion
2. Name of the focal point in WHO submitting or supporting the application (where relevant)
3. Name of the organisation(s) consulted or supporting the application
4. International Nonproprietary Name (INN, generic name) of the medicine
5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)
6. International availability— sources, if possible manufacturers and trade names
7. Whether listing is requested as an individual medicine or as an example of a therapeutic group
8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)
9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)
10. Summary of comparative effectiveness in a variety of clinical settings:
    - Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)
    - Summary of available data (appraisal of quality, outcome measures, summary of results)
    - Summary of available estimates of comparative effectiveness
11. Summary of comparative evidence on safety:
    - Estimate of total patient exposure to date
    - Description of adverse effects/reactions
    - Identification of variation in safety due to health systems and patient factors
    - Summary of comparative safety against comparators
12. Summary of available data on comparative cost and cost effectiveness within the pharmacological class or therapeutic group:
    - Range of costs of the proposed medicine
    - Comparative cost effectiveness presented as range of cost per routine outcome (eg, cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality adjusted life year gained)
13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)
14. Availability of pharmacopoeial standards (*British Pharmacopoeia*, *International Pharmacopoeia*, *United States Pharmacopeia)*
15. Proposed (new/adapted) text for the WHO model formulary

Table 2 | Summary of problems with current WHO procedure for inclusion of new medicines in model list of essential medicines and possible solutions

Current problem	Possible solutions
Search strategy inconsistently reported, reasons for inclusion or exclusion of data not reported	A systematic search of the background evidence should be required and reported following the PRISMA or similar flowchart. The search strategy should be included in the application as an appendix
Target population, comparison groups, and outcomes of interest erratically reported	A PICO (population, intervention, comparisons, outcomes) format should be required. WHO could develop condition specific applications indicating the target population (new cases, non-responders, etc), the comparison groups (placebo, active comparators already included in the list, other active comparators), and the relevant outcomes (symptomatic, functional, short versus long term)
Quantitative summaries of overall treatment effect not systematically reported for each comparison and outcome	A tool such as GRADE should be required to report in a tabular format, for each outcome and comparison of interest, the number of studies and patients included, and the overall effect of the intervention
Quality of evidence erratically reported	A tool such as GRADE should be required to report, for each outcome and comparison of interest, the quality of the evidence base
Considerations not related to the evidence base inconsistently reported	WHO application form should include a box for considerations dealing with preferences, values, feasibility issues, and resource use
Conflicts of interest not clearly reported	WHO application form should include a box for reporting potential economic or intellectual competing interests
WHO expert committee narratively reports reasons for accepting or rejecting a medicine	WHO should develop a reporting template where judgments on the various aspects of the application are consistently and transparently reported

Improvement is needed

The WHO essential medicine list is in need of reform. Most applications that we reviewed were unsolicited, and it is not clear whether WHO has a long term strategic plan for the list or is just assessing all applications that are submitted. Currently, WHO does not report information on potential conflicts of interest of applicants. This is surprising given that such declarations are fairly standard in most areas of modern medical decision making, and WHO needs to be clear how conflicts of interest are dealt with in the decision making process and how the list is driven.

It seems inconsistent that WHO requires a structured, transparent approach for developing evidence based clinical guidelines but not for recommending essential medicines. Adoption of a standardised and methodologically sound procedure would reinforce and strengthen the validity of the list. Development of WHO clinical guidelines now follows the GRADE (Grading of Recommendations Assessment, Development and Evaluation) recommendations.[7] These help users to describe the evidence and rate its quality in an ordered and transparent way. GRADE should also always be used, where appropriate, for applications for inclusion in the essential medicines list, and the expert committee should not consider applications that do not adhere to such a standard of reporting. This would ensure that applicants search for the best evidence for a specific patient population, report its quality, and produce absolute and relative estimates of treatment effects for outcomes.

It is not clear whether WHO has a long term strategic plan for the list or is just assessing all applications that are submitted

But GRADE alone is not enough. WHO could be more proactive and specific about what it wants for patients, or from a specific drug. This may mean that in some cases it should raise the bar on the quality of evidence needed. For example, in psychotic disorders, whether the evidence on a new antipsychotic should be presented against placebo or active comparators, or only against the antipsychotics already included in the list is such a compelling issue that it is currently under debate at other international regulatory bodies, such as for example the European Medicines Agency.[8 9] WHO could also stipulate the outcomes it is most interested in so that applicants are obliged to search and analyse the literature accordingly.

GRADE does not cover all relevant information from a global health perspective.[10] WHO could improve reporting by developing application templates that indicate how preferences, values, feasibility issues, and other relevant considerations should be analysed and reported.

To achieve this improvement in applications, WHO should require a PICO (population, intervention, comparisons, outcomes) format. It could also develop condition specific applications indicating the target population, the required comparison groups (placebo, active comparators already included in the list, other active comparators), and the relevant outcomes (table 2).

Applicants should also be required to state what drugs on the list could be replaced by their proposed addition and justify the choice. This would highlight the comparative benefits and drawbacks of new and existing drugs.

It is not just the standard of applications that needs reform. The WHO expert committee should develop for the clarity of reporting their judgments and decisions (table 2). Currently, reasons for accepting or rejecting a medicine are narratively reported in WHO publications, but this text does not clarify the grounds on which decisions are made. A more structured template would represent a major step ahead in terms of consistency and transparency and help ensure the continued success of the essential medicines list.

Corrado Barbui associate professor of psychiatry

Marianna Purgato researcher, WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, Department of Public Health and Community Medicine, Section of Psychiatry, University of Verona, Policlinico GB Rossi, Piazzale Scuro 10, 37134 Verona, Italy

Correspondence to: C Barbui **corrado.barbui@univr.it**

Contributors and sources: CB and MP have long experience in issues related to the methodology of systematic reviews and evidence based guidelines. CB has studied and reported widely on issues related to the selection and inclusion of medicines in international formularies, and on global health issues related to the WHO. The idea for this article arose from discussions on applications submitted to WHO. CB and MP read WHO's documentation and extracted the data. CB conceived the paper and wrote the first draft. Both authors contributed to the writing, revised the text critically, and approved the final version. CB is guarantor.

Competing interests: CB is director of the WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation of the University of Verona and has acted on several occasions as consultant for the WHO department of mental health and substance use. He provides methodological support to the department in the development of evidence based recommendations using the GRADE approach.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Cite this as: *BMJ* 2014;349:g4798