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Response to a public consultation

Prescrire's contribution

to the public consultation on the EMA's

Reflection paper on the pharmaceutical development of medicines for use in the older population

Abstract

- **As part of a longstanding project on the development of medicines for older patients, the European Medicines Agency has released a reflection paper on this topic for public consultation.**
- ***Prescrire* would like to take this opportunity to present a list of possible ways of improving pharmacotherapy for older people, in particular with regard to: pharmaceutical research and development, information, packaging, usability, prescribing habits and treatment practices. These suggested improvements concern not only the EMA but also other European and national health authorities (the European Commission and Parliament, health ministries, drug regulatory agencies and organisations responsible for patient safety).**

Prescrire welcomes the EMA's initiative to start a debate on the development of medicines for the older population.

Pharmacotherapy and medication safety for older people clearly require more attention

The older population, i.e. persons aged 65 years and over, accounts for one-quarter of the French population and is the age group with the highest medicine use. In 2016, 19% of the French population were aged between 65 and 79 years, and 6% were aged 80 years or over. According to Eurostat projections, these figures are set to rise by 2070 to 26% and 13% respectively[i]. Alongside this demographic trend, it is essential to consider the specific characteristics of older patients: ageing of the body, comorbidity, polypharmacy, frailty, isolation, loss of autonomy, and dependence. Special attention must therefore be paid to the development, authorisation and use of medicines intended for older patients.

Older patients are at greatest risk of serious adverse effects. According to French epidemiological studies[ii], older patients are at particular risk of experiencing serious adverse effects from pharmacotherapy.

Insufficient consideration given to the effects of ageing. The main processes that determine the fate of drugs in the body are often affected by

ageing. Ageing is accompanied by gradual changes to various physiological, biological and physical functions[iii]. Functional and physiological changes affect drug pharmacodynamics and pharmacokinetics. Unfortunately, these aspects are not thoroughly studied in older adults.

Overconsumption and polypharmacy related to comorbidity: The increase in polypharmacy is due in part to the ageing of the population, since older people often have comorbidities and chronic diseases. In addition, a growing number of patients are prescribed preventive treatments. Due to the high number of medicines prescribed, extra attention must be paid to the increased risk of prescribing errors, the adverse effects of these drugs, possible drug interactions, and potential confusion between medicines with similar packaging.

Medicines that are unsuitable for older patients. An analysis of prescribing and drug administration practices in French nursing homes in 2016 showed that: 43% of residents were taking more than 8 drugs a day; 74% of the drugs were potentially inappropriate for older patients; and 8% of the prescriptions included at least one combination that carried a high risk of adverse effects[iv]. This study also found that medicines were sometimes incorrectly administered. Tablets were often inappropriately crushed, and capsules inappropriately opened for residents with swallowing difficulties, a psychological or behavioural disorder, or a feeding tube [v].

In summary, advanced age, polypharmacy, pharmaceutical forms unsuited to older people, packaging, lack of information and isolation are all factors that expose older patients to an increased risk of serious adverse effects[vi].

In the interests of older patients, their needs must be taken into account at every stage of drug regulation (R&D, authorisation, pharmacovigilance, postmarket monitoring)

Prescrire believes that the EMA should engage more effectively in the development of medicines suitable for use in the older population, first at the development stage, but also during authorisation procedures, to ensure in particular the usability and safety of their packaging, including the package leaflet and any devices provided. More should be done at the development stage to anticipate risks to patient safety once the medicine is authorised and in use. Medicines must remain protected and identifiable in all the healthcare settings in which they will be used. Tablets and capsules for widespread use must therefore be packaged in unit-dose blister packs. Failing this, given the variety of ways in which drugs are repackaged for autonomous older patients or to help the carers of non-autonomous older patients administer their medication, marketing authorisations must specify all the relevant the storage conditions and preparation instructions in the summary of product characteristics (SmPC) and the package leaflet. Finally, the EMA's role in postmarket monitoring must not be overlooked. This involves pharmacovigilance, but also a proactive approach to risk minimisation that

benefits older and younger patients alike, such as prohibiting bulk containers for medicines marketed to the general public, umbrella brands (due to the risk of confusion created by selling different drugs under the same brand name in look-alike packaging), and inaccurate dosing devices.

Here is a summary of *Prescrire*'s proposals on how the specific needs of the older population could be better taken into account.

Anticipate the needs of older patients from the start of drug development

- Enrol older patients into clinical trials, including those with comorbidities.
- Geriatric investigation plans are unnecessary provided older patients are identified in the drug development plan.
- Provide information on the drug's harm-benefit balance in different age groups in the EPAR, SmPC and the package leaflet, including for patients aged 65–74, 75–84 and >85 years. When the drug has not been tested in older patients, this must be stated in the EPAR and SmPC.
- Broaden usability studies by: including older patients in package leaflet readability testing and by extending the scope to test the legibility of the information displayed on the labelling; testing the usability of any dose preparation or administration devices, dropper bottles, etc.; and investigating solutions to protect children from accidental drug poisoning while allowing easy access for older patients (boxes with a safety catch, blister packs with a child-resistant film and a small tool in the box to help older people remove tablets, bottles of multidose liquid formulation with a child-proof cap and an accessory to attach to the cap to help older patients remove it).
- Take into account polypharmacy among older patients by conducting studies on its effects and risks and its influence on treatment adherence.

Take into account dose adjustment for older patients at every stage

It is essential to ensure the accuracy of doses administered to or taken by older patients. Unfortunately, this is not always possible. One problem is a lack of data on dosing and drug absorption, in particular when gastrointestinal access is compromised, for example by surgical modifications or gastroduodenal catheterisation; none of these situations is covered in marketing authorisations.
When the pharmaceutical form is unsuitable for administration to an older patient, healthcare professionals or caregivers have to modify the drug (e.g. by crushing tablets) but lack the information they need concerning possible physicochemical incompatibilities, the stability of the extemporaneous preparation and its compatibility with the materials from which any devices used are made, and find no advice in the SmPC or package leaflet.
And while the repackaging of medicines prior to administration to older patients is extremely common, marketing authorisations contain little or no data about their stability once removed from their original packaging. It seems to be assumed that drugs will be protected until the moment they are administered, as indeed they should be for safety reasons, yet this can only be enforced by regulation promoting unit-dose packaging as a basic requirement.

As a matter of priority, all the data needed in order to accurately adjust and adapt doses for older patients and to fulfil the related requirements outlined in Annex 1 of Directive 2001/83/EC must therefore be evaluated and made available to health professionals and patients.

Demand suitable dose strengths and draft guidelines on tablet subdivision. As older patients often have renal or hepatic impairment, drug regulatory agencies should check the compatibility of the range of strengths and the dosing proposed by the pharmaceutical company. For situations that require dose adjustment, low-dose small tablets (mini-tablets) are more accurate than breakable tablets and avoid the risks of manual error and confusion between forms that can be split into four parts (e.g. fluindione-Previscan°). The EMA urgently needs to draft guidelines to make tablet subdivision safer, both for the older population and other patients using drugs with a narrow therapeutic index. Marketing authorisations for divisible forms must include dose preparation tests involving target patient groups rather than simply relying on tests of weight uniformity after splitting.

Complex dosing regimens. For complex dosing regimens, such as dose titration or infrequent (e.g. weekly) dosing, blister wallets that keep the patient information with the dosage units are helpful in an ambulatory setting (e.g. aprepitant-Emend° or alendronic acid-Fosamax°), although they are not well suited to inpatient care.

Many improvements should be made to adapt packaging to the needs of older patients

A medicine's packaging makes an important contribution to its harm-benefit balance but is too often overlooked, thus exposing patients to preventable dangers. To ensure high-quality care, adapted to the needs of the older population, quality standards for packaging are required. National and/or European guidelines are necessary to complement the Directive 2001/83/EC so that no more marketing authorisations are granted for medicines whose packaging fails to provide the level of quality and safety to which patients are entitled.

All medicines agencies should analyse packaging. *Prescrire*'s analyses of the packaging of over 7000 medicines show that most expose patients to multiple dangers and are technically unsuited to many healthcare situations. Older patients are exposed to these dangers more than most.

Drug regulatory agencies and national pharmacovigilance organisations must: raise the bar for packaging quality and safety at least to the level of the recommendations issued by the Council of Europe in 2006; strengthen their teams' resources and expertise in packaging analysis; create task forces dedicated to assessing packaging-related risks and to developing new solutions to improve packaging safety and usability; and give priority to the protection of older patients' concerns. Marketing authorisation procedures

should include a medication error assessment report that would form the basis of a specific section in the EPAR.

Prohibit bulk packaging. Bulk packaging must be prohibited for all pharmaceutical forms (bulk bottles of oral solid formulations or oral liquid formulations, multidose injectable formulations, etc.) partly due to the risk of accidental ingestion and errors, but also because they can be difficult to use for older patients, especially those who are physically unable to remove the child-proof cap that is a necessary component of these forms of packaging.

Child-proof caps. Demanding the presence of a child-proof cap on all bulk bottles of tablets or oral liquid formulations, in order to protect children from the risk of drug poisoning is an absolute necessity but also requires finding technical solutions to help older patients open these closures, for example by investigating the inclusion of a tool in the box that can be attached to the closure to make it easier to remove.

Unit-dose packaging: best for clarity. Unit-dose packaging, where each dosage unit is packaged individually and fully labelled, is the best for clarity, provided there is sufficient area to print the labelling in a legible fashion. Sadly, although some medicines are available to hospitals in a unit-dose format, this is not the case for most medicines on the French market, and the standard of packaging for those available in primary care is generally very poor. The absence of unit-dose blister packs causes problems for drug dispensing processes in hospitals, nursing homes and in primary care, obliging often ill-equipped health professionals to remove medicines from their original packaging and repackage them in a pill organiser.

Unit-dose blister packs and childproof films. Demand that all tablets and capsules be packaged in blister strips, with full labelling of each blister, and that a childproof film be added for substances that are more dangerous than most drugs, including a tool in the box to help older patients puncture the film.

Blister pockets: cases of inadvertent ingestion. Although precut unit-dose blister packs are the gold standard for oral solid formulations, they are not without risk in geriatrics, where cases have been reported of older patients inadvertently ingesting the tablet while still inside the detached blister[vii]. This can cause other health problems, sometimes requiring surgery. Such accidents should be prevented through specific warnings aimed at healthcare professionals, relatives or other carers, specifying the action to be taken.

Oral liquid or orodispersible formulations for patients with swallowing difficulties. Oral liquid or orodispersible formulations are a better choice for patients who have difficulty swallowing. Multidose oral liquid formulations are convenient but the quality of such medicines is highly dependent on the quality of the dosing device. A recent study conducted by the French General Agency of Equipment and Health Products (AGEPS) broached the question of which pharmaceutical form is best suited to patients with swallowing disorders[viii]. The EMA urgently needs to answer this question and issue guidelines.

Unit-dose oral liquid or orodispersible formulations are better options. Unit-dose oral liquid formulations (solutions or suspensions in sachets) or orodispersible tablets are better options in terms of dosing accuracy and a reduced risk of dose preparation errors. Wherever possible, their development should be encouraged over that of multidose forms with a dosing device, making sure that the sachets are easy to open.

Minimise the risks of dosing devices. There are situations however in which multidose forms remain the best option, when the dose must be precisely adjusted (and this has been demonstrated in clinical trials) and when the number of dosage units required would be too high. In our view, the use of inappropriate dosing devices (a choice that often seems motivated by the desire to reduce manufacturing costs) could be prevented if the following few principles were applied:

- Recommend the systematic presence of a suitable dosing device, to prevent the use of household spoons to administer medicines;
- Avoid droppers: they are too inaccurate;
- Avoid measuring cups: they lead to dosing errors and are very imprecise;
- Take into account the risks of having to convert the number of milligrams prescribed into the number of millilitres to measure with a dosing device graduated in millilitres;
- Take into account the danger of dosing devices marked with 2 graduation scales, as they can confuse users;
- Omit any superfluous graduations, which can lead to overdosing or underdosing;
- Improve the legibility of graduations and other information;
- Prohibit multidose oral liquid formulations that are not supplied with a dosing device, and launch EU awareness campaigns for the general public about the dangers of measuring medicines with household spoons;
- Evaluate solutions to ensure that patients can identify the correct dosing device for their medicine (label the device, fit bottles with plastic holders into which users can insert the dosing device) and encourage pharmaceutical companies to develop more effective solutions;
- Encourage the European Pharmacopoeia, European medicines agencies and the US Food and Drug Administration to collaborate in evaluating the safety and usability of dosing devices, paying particular attention to the accuracy of oral delivery syringes;
- Demand that the harm-benefit balance of any new type of dosing device be evaluated and considered satisfactory before it can be introduced on the European market;
- Determine what the best dosing device would be (such as an oral delivery syringe graduated in milligrams or units), and the most suitable capacity and accuracy, then takes steps to ensure that it becomes the norm;
- Promote user testing of dosing devices by target patient groups (including older patients), checking that the instructions in the package leaflet are compatible with the dosing device, and use the results to assess their quality and safety.

Improving practices in relation to pharmacotherapy for older patients

Strengthen information about drug packaging. Health authorities should make more information publicly available to health professionals and patients: packaging items should be described and instructions for their use provided in the SmPC and package leaflet. In addition, the public should be informed: when changes to packaging items are liable to affect the way they are used by developing teaching and training programmes; when a packaging item has caused errors or the potential for error clearly exists (by publishing a detailed, publicly accessible analysis on the websites of the appropriate medicines agencies, linked to or included in European or national public assessment reports); and when a new marketing authorisation or major variation is granted (publishing mock-ups of all the packaging materials).

Make relevant information available immediately and permanently to patients and health professionals. Information that is crucial to correct medication use must in principle be printed in the package leaflet and on the packaging. Member States must ensure that patients have direct access to this information via the package leaflets present in the box. In addition, they must provide easy online access to up-to-date SmPCs and package leaflets published on a single website. Age-related impairments must be taken into account when evaluating the clarity and legibility of these documents for older patients. And health professionals must have appropriate tools to help and inform older patients who are unable to access these documents. The development of digital access to information, for example through QR codes printed on boxes and patient leaflets, should help patients access reliable, verified, non-promotional information, in accordance with conditions laid out in a guideline in order to ensure that it is complete and not usurped for the purposes of direct-to-consumer advertising. This technology should be used as an opportunity to help older patients consult the up-to-date information they need, to help health professionals communicate with these patients, and to provide health professionals with resources they can incorporate into their own initiatives to inform and educate their patients.

Unambiguous expression of strength and concentration in labelling. The European guideline EMA/707229/2009 on the expression of strength in the name of medicinal products should be modified to ensure that a medicine's strength and/or concentration is displayed more prominently in the labelling, and to do more to prevent medication errors.

Ensure that the INN is given due prominence in labelling. Demand that drug regulatory agencies, health technology assessment agencies and pharmaceutical companies prominently display the drug's international nonproprietary name (INN) and dose strength on labelling and package leaflets, to ensure that medicines are identified by their true name, the INN. The European Commission should also promote the teaching of INNs to healthcare professionals from undergraduate training onwards, and encourage patients to use them too.

Readability and comprehension testing. Conduct readability and comprehension tests on patients, including older patient, and even healthcare professionals, addressing all of the information that is written or depicted graphically on packaging (package leaflets, labelling, pictograms, dosing schedules, etc.). Prohibit the use of any graphical information on packaging that has not been evaluated or has been deemed unsatisfactory in tests. Given that eyesight tends to decline with age, particular attention must be paid to readability tests in this age group.

Investigate the use of colours within medicine ranges. Conduct a thorough debate in the European Union on the use of colours on packaging, particularly as a means to differentiate between various dose strengths from the same range, especially those intended for older patients.

Publish data on overdoses. Publish detailed data on overdoses and accidental poisoning with drugs or excipients in SmPCs and public assessment reports; make them freely accessible on the websites of European Union medicines agencies. Ensure that advocacy groups for patients and older people are duly informed of these problems and have access to these data.

Review produced collectively by the Prescrire Editorial Staff: no conflicts of interest

For more information

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EU Transparency Register: 982539711698-79

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