

REVIEW ARTICLE

Me-too pharmaceutical products: History, definitions, examples, and relevance to drug shortages and essential medicines lists

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We define a *me-too drug* as a pharmacologically active compound that is structurally related to a first-in-class compound, regarded as belonging to the same therapeutic class as the original compound, and used for the same therapeutic purposes, but which may differ in some respects, such as specificity of pharmacological action, adverse reactions profile, or drug–drug interactions. We also offer definitions of related terms, including *follow-on drug* and *first-in-class*. The therapeutic advantages of me-too drugs may include improved target specificity, reduced risks of off-target adverse reactions and drug–drug interactions, increased chance of benefit in some patients, and improved drug delivery and pharmacokinetics. Me-too drugs can also demonstrate incremental innovation. Their availability may help in coping with drug shortages. However, they may occasionally cause unexpected adverse reactions that are not class effects. Tricyclic antidepressants, β -blockers, and statins illustrate the diversity of me-too drugs. Earlier compounds may be as effective as later ones, or more so. Tricyclic antidepressants have similar chemical structures, and compounds introduced after the first-in-class compound (imipramine) mostly offered little in the way of innovative features, but continue to be prescribed. In contrast, me-too β -blockers introduced after the first-in-class compound, pronethalol, have diverse structures and display several innovative features. Stereoisomers and biosimilars/bio-betters provide special examples of me-too drugs. Although many me-too drugs offer no significant advantages over their predecessors, over 60% of the drugs listed on the World Health Organization's essential list are me-toos. Different countries may choose different me-too drugs when constructing essential medicines lists, partly explaining transnational differences between them.

KEYWORDS

advertising, me-too drugs, pharmaceutical companies, pharmaceutical products

The authors contributed equally to the paper.

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1 | INTRODUCTION

Although the term *me-too drugs* was coined in the 1950s, there has been a dearth of articles about them, contrasting with first-in-class drugs. A PubMed search for the two terms (Figure 1) shows the difference. It is of course logical that more would want to describe first-in-class compounds than me-toos. Nevertheless, the me-toos greatly outnumber the medicines that are first in class, and the discrepancy in coverage seems disproportionate. With a few exceptions,^{1,2} published papers about me-too drugs either deal with specific compounds or are general commentaries, citing very little evidence. No satisfactory definitions have been published.

Here therefore we explore the term *me-too* as used to describe medicinal products and offer a definition and definitions of related terms.

We have given information on the earliest publications recorded in PubMed, although we are aware that in many cases the drugs had been described earlier, for example in patents and in texts on their medicinal chemistry. However, it is our intention to highlight the years in which the biomedical community would have first become aware of the existence of the drugs, rather than the history of their discovery. For that we recommend the thorough accounts by Sneider.^{3,4}

In each case we have also given the brand name of the medicinal product used in the first advertisements that appeared in the *British Medical Journal*,⁵ together with the name of the marketing company, which was not always the same as the company that developed the product.⁶

Finally, we describe the reasons for developing me-too drugs and the reasons for using them. We discuss specific examples and highlight the inclusion of me-too drugs in essential medicines lists.

2 | HISTORY

The first recorded use of the phrase *me too*, signifying sharing or agreement with a view, experience, or wish of another person, according to the *Oxford English Dictionary (OED)*, was in a letter by Lord Chesterfield in 1745: "I empower you to make what use you

please of my name as quitting with you; and I say as Will Seymour did, And me, too, sweet Jesus." It has since been widely used in this way, so commonly that no-one would dream of saying "I too" as a stand-alone phrase, even when the syntax demands it.

The noun, *a me-too*, denoting someone or something that imitates others, dates from the 1880s. But only much later did it start to be used attributively, describing medicines that are now known as *me-too drugs*. The *OED* lists the earliest instance ("me-too' products") as being from 1967, but we have found prior examples, the earliest from a 1956 symposium, in which Louis S. Goodman, co-editor of the famous therapeutics textbook colloquially known as *Goodman and Gilman*, referred to "the problem of the introduction of 'me too' drugs, that is, drugs without signal advantage of any sort".⁷ The inverted commas around *me too* suggest a newly or at least recently coined term.

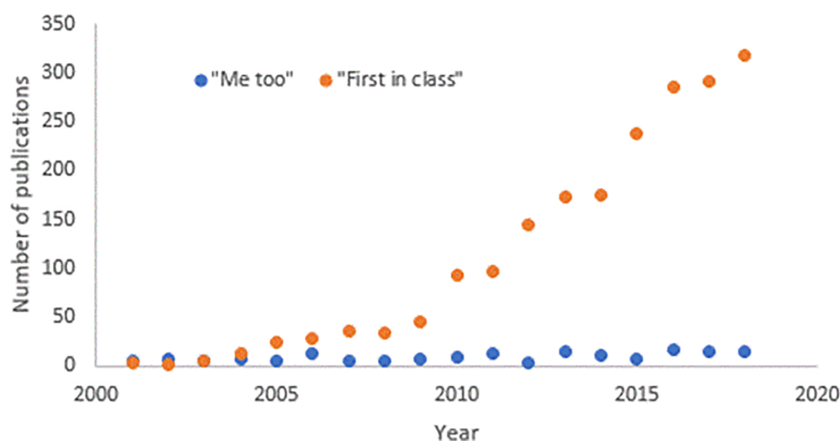
3 | DEFINITIONS

Several definitions of *me-too drugs* have previously been offered, none satisfactory. Goodman's dismissal of them as "drugs without signal advantage of any sort" was echoed in 1964 by Lasagna, who described them as being "hard to justify putting into man at all, let alone on the market".⁸ Similarly, in 1994 Desmond Laurence and John Carpenter defined *me-too drugs* as "Slang for a drug [sic] developed to allow a pharmaceutical company to gain a share of the existing market. Any gain to therapeutics is purely incidental."⁹ They added: "Where a company introduces a drug very similar to one of its own existing drugs, this has been called a *me-again* drug." However, we have not found the term *me-again drug* anywhere except in editions of Laurence's textbook *Clinical Pharmacology*.¹⁰

Here is a selection of other definitions of me-too drugs:

- "multiple drugs within the same therapeutic class"¹¹;
- "[drugs that are] chemically related to the prototype, or other chemical compounds which have an identical mechanism of action";

FIGURE 1 A PubMed search for "me too[tw]" in July 2019 gave 187 hits, the first from 1975, of which 37 had nothing to do with drugs or clinical pharmacology; the graph shows the annual numbers of the relevant hits in each year since 2001 ($n = 121$); the corresponding data for "first-in-class[tw]", which first appeared in 2001, are also shown ($n = 190$)



- “drugs which have more or less identical clinical outcomes to pre-existing drugs”¹²;
- “a drug with a similar chemical structure or the same mechanism of action as a drug that is already marketed”.¹³

In Table 1, we offer a more comprehensive definition, incorporating these ideas. To formulate this definition, we have also considered the definitions of related terms, starting with *therapeutic class* and proceeding to terms such as *first in class* and *first/second/etc. generation*.

Some have taken the related term *follow-on* to be synonymous with *me-too*. However, we distinguish these two terms on the basis of

structural similarities or differences, as our definition of *follow-on drug* shows (see Table 1).

4 | COMMERCIAL REASONS FOR DEVELOPING AND MARKETING ME-TOO DRUGS

Me-too drugs have been hugely successful. As the early cynical definitions show, they have often been regarded purely as a way of making money out of a large lucrative market without added therapeutic

TABLE 1 Proposed definitions of *me-too* drugs and related terms

Term	Definition	Examples
Therapeutic class	A group of compounds that are often, but not always, structurally related to each other, that are characterized by a common pharmacological mode of action, and that are primarily used for the same therapeutic indications	Similar structures: tricyclic antidepressants, selective serotonin reuptake inhibitors, benzodiazepines, angiotensin-converting enzyme inhibitors Varied structures: β -blockers, statins, antihistamines (H_1 receptor antagonists); histamine H_2 receptor antagonists
First-in-class drug	The first drug in a class of drugs to be given marketing authorization for one or more therapeutic indications; also called <i>breakthrough drug</i> or <i>originator drug</i>	(From the classes above) imipramine, zimeldine, chlordiazepoxide, captopril (but not the experimental precursor saralasin), pronethalol, simvastatin, piperoxan, cimetidine
Originator drug	A term that is synonymous with <i>first-in-class drug</i> , but typically used in reference to biologics for comparison with their biosimilars	Follitropin alfa, epoetin alfa, monoclonal antibodies
First/second generation etc.	Vague terms intended to distinguish groups of drugs that have similar properties from later drugs in the same class, but regarded as having properties that are thought important to distinguish	First-, second-, third-, fourth-generation antihistamines, cephalosporins, antipsychotics
Me-too drug	A pharmacologically active compound that is structurally related to a first-in-class compound, regarded as belonging to the same therapeutic class as the original compound, and used for the same therapeutic purposes, but which may differ in some respects, such as specificity of pharmacological action, adverse reactions profile, or drug-drug interactions	Amitriptyline, paroxetine, diazepam, enalapril, propranolol, atorvastatin, ranitidine Stereoisomers are special types of me-too drugs; for example, escitalopram, esketamine, and esomeprazole, which are the S-stereoisomers of the corresponding racemic mixtures (see text) Biosimilars of biologics can also be regarded as me-too drugs (see text)
Follow-on drug	A drug of a pharmacological class that is not structurally related to a first-in-class compound but is in other respects a me-too drug	Bisoprolol, loratadine
Spin-off drug	A compound with a similar structure to another compound, but a different pharmacological target	Some diuretics and some oral hypoglycaemic drugs derived from the first-in-class sulfonamide antibiotic sulfamidochrysoïdine (Prontosil); acecainide, a metabolite of procainamide
Me-too product	A medicinal product containing a me-too drug	
Follow-on product	A medicinal product containing a follow-on drug or a previously marketed drug in a different formulation	New (e.g. slow-release) formulations of existing drugs

advantage. However, there are other reasons, which impinge both positively and negatively on pharmaceutical companies and therapeutic practices.

An initial reason for a company to undertake research on a me-too drug after marketing a first-in-class compound is that it is researching a specific therapeutic area and screening structurally related groups of compounds. More than one candidate drug may look promising, and while one is selected for further development, another is chosen as a back-up in case the first fails, either at the pre-clinical stage or during clinical trials. The financial benefit to the company is obvious: staff are already trained in both preclinical and clinical development and the clinical trials structure is in place. By the time the first candidate drug has shown itself to be marketable the follow-on compound is so far on in development that it is worth finalizing and marketing. It may then demonstrate some therapeutic advantage.

Other justifiable aims include improved pharmacokinetics, such as once-a-day administration, or fewer drug–drug interactions. However, some advantages (or marginal disadvantages) only appear when development is so far along the road that marketing it is a rational financial decision. Occasionally, a pharmacokinetic difference occurs that might lead to adverse reactions; for example, in East Asian patients, exposure to rosuvastatin is about twice that experienced by other groups.¹⁴

A final point is that it is cheaper for a company to launch a me-too follow-up (me-again) drug than to launch the first in class. This may well release R&D money for undertaking more high-risk breakthrough products.

To understand the marketing of me-too drugs by other companies, we must first look at the discovery process, although we are not primarily concerned with that here. Research scientists from competing companies meet at the same scientific congresses and talk to the same academics. It is therefore rare for a company to have an approach to a therapeutic problem that is not being considered by competitors. Near parallel discovery and development of a new chemical entity is therefore common and, by the time patents have been obtained, serious money has been expended.

An advantage of having several related drugs on the market is that patients and doctors have the option of trying several compounds to obtain the compound with the fewest adverse effects and best therapeutic efficacy in individual cases, although we suspect that this does not often happen. Me-too drugs can be useful in cases of an adverse reaction to an excipient in another drug formulation. Furthermore, when a patient has, for instance, hepatic or renal insufficiency or is a poor metabolizer for a CYP enzymes, it may be helpful to have me-too drugs available that have different routes of elimination.

By contrast, a new me-too drug may introduce an adverse reaction that was not a feature of its predecessors, not being a class effect; practolol, mentioned below, is a good example of this.

Another advantage of me-too drugs is the availability of alternatives in case of drug shortages.

The entry of a second or even third compound in a therapeutic area tends not to reduce the market share, but to expand it; they may

be cost saving in the short term, but can increase costs in the longer term.^{15,16} Thus, as our studies on pharmaceutical advertising have made clear,^{5,6,17} companies spend substantial sums on advertising to emphasize marginal therapeutic differences between competing drugs, rather than attempting to compete on the basis of a lower price. A large advertising spend may erode the company's overall income, to the detriment of the R&D budget. Nevertheless, even a modest share of a large market (for example antidepressant drugs) can make the launch of a me-too drug worthwhile. This has led to cynicism about me-too drugs. These points are summarized in Table 2.

5 | EXAMPLES OF ME-TOO DRUGS

Early examples of me-too drugs include opiates, barbiturates, penicillins, and the phenothiazines (chlorpromazine, thioridazine, and trifluoperazine). Here we describe the properties and marketing of three classes of drugs that have given rise to many me-too and follow-on drugs: tricyclic antidepressants, β -blockers, and statins. Many consider the benzodiazepines to have been prototypical me-too drugs, 15 having been marketed in the UK between 1960 and 1982 (seven by Roche). However, we have not reviewed them, because the only important feature that differentiates them is their duration of action, making some more suitable as hypnotics rather than anxiolytics.

TABLE 2 Reasons for developing, marketing and using me-too and follow-on drugs

Reason	Examples
To gain a market share	Many examples (e.g. Tables 3–5)
To improve specificity at the target, thus reducing the risks of off-target adverse reactions and drug–drug interactions	Atypical antipsychotic drugs, which are more selective for dopamine D ₂ receptors than their typical predecessors
To reduce the risks of off-target adverse reactions and drug–drug interactions, without altering on-target specificity	Ranitidine vs cimetidine; statins and their different interactions with grapefruit juice
To increase the chance of benefit, perhaps in a subset of patients	Ampicillin (broader spectrum) vs benzylpenicillin
To develop drugs with similar structures but new targets (<i>spin-off</i> drugs)	See Table 1
To improve drug delivery and pharmacokinetics	Ampicillin (oral) vs benzylpenicillin (i.v.); amoxicillin vs ampicillin; congeners of insulin (e.g. insulin aspart)
To use as replacements when there are drug shortages	Not a primary reason for development, but sometimes useful (see text)
To offer cheaper alternatives	Many examples, but me-too drugs are not always cheaper and overall costs may rise (see text)
Incremental innovation	Beta-blockers (see text)

5.1 | Tricyclic antidepressants (Table 3)

The tricyclic antidepressants best illustrate the ability of medicinal chemists to modify a chemical structure with a known therapeutic effect to produce another active compound. Chemists at Geigy modified the 3-ring structure of chlorpromazine, which was originally developed as an antihistamine, by changing the middle ring from a 6-membered to a 7-membered heterocycle, thereby producing imipramine. Following reports of the antipsychotic action of chlorpromazine, imipramine was examined in various psychiatric conditions and found to be antidepressant, not antipsychotic.

Imipramine was first advertised in the *British Medical Journal* in 1959, and its therapeutic usefulness encouraged further modifications to the tricyclic structure, resulting in a flood of me-too compounds (Table 3), all closely structurally related. Clinical differences in these drugs were modest; some claimed either greater or lesser sedation or less atropine-like action as selling points, but none claimed greater efficacy. For example, a 1968 advert for iprindole asserted that it was “no more effective BUT...”. And a 1971 advert for clomipramine (Anafranil) implicitly acknowledged that it was joining a crowded market. What is interesting about clomipramine is that it is a relatively selective serotonin uptake inhibitor,¹⁸ anticipating the emergence onto the market of the structurally different selective serotonin reuptake inhibitors (zimeldine and fluoxetine) by about 10 years. Most of the tricyclics are also antihistamines, and doxepin in particular has been used to treat chronic itch. Their innovative features, such as they are, are not striking; nevertheless, they continue to be prescribed (Table 3).

5.2 | Beta-blockers (Table 4)

In contrast to the tricyclics, the β -blockers were discovered as a result of logical pharmacological research. James Black at ICI Pharmaceuticals recognized that the heart could be protected by blocking the actions of adrenaline and noradrenaline and developed the first-in-class β -blocker pronethalol. The advert included the terms *receptor* and *antagonist*, perhaps the first time such terms had been used in advertising. Pronethalol was soon withdrawn because of toxicity in preclinical studies, but ICI followed it with the much more potent drug propranolol and a few years later with practolol, which was structurally related. Practolol was cardioselective, acting only on β -1 adrenoceptors, but it was also later withdrawn because of serious adverse reactions, while several other nonselective β -antagonists, of widely varying structures (i.e. me-too and follow-on drugs), became available from other companies. The problem with practolol was not a class effect, and other cardioselective drugs later became available, including metoprolol and acebutolol. Atenolol was the first to be advertised as requiring only once-daily dosing. Others followed in emulating this dosing schedule.

Although all β -blockers are antagonists at β -adrenoceptors,¹⁹ some are more cardioselective than others; furthermore, they have other widely different pharmacological properties, such as membrane-stabilizing activity and calcium channel-blocking actions, promoting vasodilatation (Table 4). The differences between successive compounds can be described as incremental innovation,²⁰ which has also been promoted as a good reason for developing new anticancer drugs, each of which may confer only a little additional benefit, but which

TABLE 3 First-in-class and me-too tricyclic antidepressants and their innovative features

Tricyclic antidepressant	Year of earliest publication ^a	Marketing company ^b , brand name	Innovative feature(s)	Current prescriptions ^c
Imipramine	1958	Geigy, Tofranil	Novel pharmacological target (first in class)	152 487
Amitriptyline	1960	Merck Sharp & Dohme, Tryptizol	None	13 898 163
Desipramine [metabolite of imipramine]	1961	Geigy, Pertofran	Less anticholinergic	Not listed
Nortriptyline [metabolite of amitriptyline]	1962	Dista, Allegron	Fewer drug–drug interactions	644 348
Trimipramine	1963	May & Baker, Surmontil	None [weak reuptake inhibitor]	30 559
Dosulepin (dothiepin)	1963	Crookes, Prothiaden	None	582 596
Protriptyline	1964	Merck Sharp & Dohme, Concordin	Not sedative	0
Iprindole	1965	Wyeth, Prondol	None	Not listed
Doxepin	1965	Pfizer, Sinequan	None	24 237
Dibenzepin	1965	Wander, Noveril	None	Not listed
Clomipramine	1968	Geigy, Anafranil	Selective serotonin uptake inhibitor	230 066
Lofepramine	1975	E Merck, Gamanil	None	173 154

^aFrom PubMed and see the text.

^bWhich may be different from the originator company.

^cNumber of generic items prescribed by general practitioners in NHS England from December 2018 to November 2019 (source openprescribing.net).

TABLE 4 First-in-class and me-too β -blockers and their innovative features

Beta-blocker	Year of earliest publication ^a	Marketing company ^b , brand name	Innovative feature(s)	Current prescriptions ^c
Nethalide Pronethalol ^d	1962, 1963	ICI, Alderlin	Novel pharmacological target (first in class)	Not listed
Propranolol	1964	ICI, Inderal	First therapeutically useful β -blocker	5 627 688
Sotalol	1967	Duncan Flockhart, Beta-Cardon	[Beta-blocker and] class III antiarrhythmic drug; hydrophilic	474 393
Practolol^e	1969	ICI, Eraldin	Beta ₁ selective	Not listed
Oxprenolol	1970	Ciba, Trasicor	Partial agonist	50
Acebutolol	1972	May & Baker, Sectral	Hydrophilic, partial agonist	Not listed
Atenolol	1972	Stuart, Tenormin	Hydrophilic [and β_1 selective]	6 555 115
Metoprolol	1974	Geigy, Lopresor	Short-acting [and β_1 selective]	406 185
Labetalol	1975	Allen & Hanbury, Trandate	Alpha-blocker [and β -blocker]	96 385
Nadolol	1975	E R Squibb, Corgard	Very long acting [and hydrophilic]	12 864
Celiprolol	1978	Rhône-Poulenc Rorer, Celectol	Vasodilatory	32 834
Esmolol	1982	Baxter, Brevibloc	Very short-acting	Not listed
Bisoprolol	1984	Merck, Cardicor	Highly β_1 selective [and vasodilatory]	24 710 964

^aFrom PubMed and see the text.

^bWhich may be different from the originator company.

^cNumber of generic items prescribed by GPs in NHS England from December 2018 to November 2019 (source openprescribing.net).

^dOriginally called nethalide; renamed pronethalol in 1963.

^eFailed owing to adverse reactions.

cumulatively add up to significant advances.²¹ In contrast to the tricyclics and benzodiazepines, the β -blockers demonstrate many useful innovative features. They are still widely prescribed (Table 4).

5.3 | Statins (Table 5)

The first HMG CoA reductase inhibitor, mevastatin (compactin), was discovered in 1976 when it was isolated from cultures of the fungus *Penicillium citrinum*. This was followed by the discovery of lovastatin in *Aspergillus terreus*, and the synthesis of other statins (Table 5). The

statins all have similar effects in inhibiting HMG Co-A reductase, the main differences between them being the nature of the enzymes by which they are metabolized, giving different potential drug–drug interactions. Cerivastatin was particularly involved in such interactions and was consequently withdrawn from the market.

5.4 | Stereoisomers

If a carbon atom has four different substituents it is called asymmetric, and the conformation of the four atoms or molecules around it can

TABLE 5 First-in-class and me-too statins and their routes of metabolism

Statin	Year of earliest publication ^a	Marketing company ^b , brand name	CYP metabolism	Current prescriptions ^c
Lovastatin^d	1976	Merck, Sharp & Dohme, Mevacor	3A and 2C8	Not listed
Simvastatin	1986	Merck, Sharp & Dohme, Zocor	3A4	21 978 774
Pravastatin	1986	Sankyo Pharm Inc., Pravachol	–	2 524 216
Atorvastatin	1990	Pfizer, Lipitor	3A4	45 284 640
Fluvastatin	1990	Novartis, Lescol	Mostly 2C9 (also 3A4 and 2C8)	110 761
Cerivastatin^e	1996	Baycol, Baycor	2C8 and 3A4	0
Pitavastatin	1997	Kowa Pharmaceuticals, Livalo	2C9	Not listed
Rosuvastatin	2001	AstraZeneca, Crestor	2C9	0

^aFrom PubMed and see the text.

^bWhich may be different from the originator company.

^cNumber of generic items prescribed by GPs in NHS England from December 2018 to November 2019 (source openprescribing.net).

^dAn earlier statin, **mevastatin** (compactin), was never marketed; lovastatin was also called monacolin K and mevinolin.

^eFailed owing to adverse reactions.

vary. Other atoms (such as phosphorus) can also be asymmetric. This asymmetry leads to forms with different optical activities, rotating polarized light to the left or right. By convention, a substance that rotates polarized light to the right is called dextrorotatory (*d*) and a substance that rotates polarized light to the left is called laevorotatory (*l*). If the actual spatial arrangement of the molecules is known, the right- and left-handedness of the configuration about an asymmetric atom is designated by *R* and *S* or *D* and *L*. Stereoisomers of this kind are of two types, enantiomers and diastereomers (or *epimers*). In enantiomers, asymmetry occurs at all the centres of potential asymmetry (chiral centres); enantiomers have similar physicochemical properties to each other. In diastereomers, asymmetry occurs at only one chiral centre, even though the molecule may have more than one; in such cases the isomers are not mirror images of each other. Diastereomers (e.g. quinine and quinidine) do not usually share similar physicochemical properties.

About 40% per cent of the drugs used in routine clinical practice are chiral, and about 90% of these are marketed in the racemic form (as an equal mixture of the two stereoisomers). Examples of drugs that are marketed as single stereoisomers include naproxen, levodopa (*L*-dopa), levothyroxine (*L*-thyroxine), and dextrose (*D*-glucose). Often there are important pharmacological differences between stereoisomers, as the following examples show:

- *S*-warfarin is about five times more potent than *R*-warfarin; the two isomers are metabolized differently and are subject to different drug interactions;
- *L*-sotalol is a β -adrenoceptor antagonist while *D*-sotalol is a Class III antiarrhythmic drug;
- *R*-thalidomide is a hypnotic, while *S*-thalidomide is immunomodulatory and teratogenic.

Although it is theoretically desirable to take advantage of these differences by using individual isomers, it is generally too difficult to prepare them in practice, and in any case administration of a single isomer often results in back-conversion to the racemic form *in vivo*. In a few cases drug companies have extended the patent lives of some of their drugs by marketing the isomers as individual formulations; examples include escitalopram and esomeprazole. These formulations generally have few or no advantages over the corresponding racemic mixtures, as shown in systematic reviews of comparative studies^{22,23} and they can be regarded as me-too drugs.

5.5 | Biosimilars

Biosimilars are defined as biologics that are similar to other biologics already authorized for use.²⁴ They are versions of first-in-class (originator) molecules, with the same amino acid sequences, but produced from different clones and manufacturing processes. When a biosimilar protein is synthesized, the primary amino-acid sequence is likely to be preserved, but there can be differences in glycosylation, deamination, or oxidation, and in the 3-dimensional structure, which can affect the

interaction of the protein with other molecules. Thus, biosimilars accord with our proposed definition of me-too drugs. They should not be regarded as generic equivalents of the corresponding originator biologics, because they may differ more from the originator molecules than generic versions of nonbiologics. One cannot be sure that two biosimilars will have similar benefits and harms.

However, there are principles to ensure that biosimilars are similar enough.²⁵ For example, US and European regulators demand that biosimilars should be “highly similar to the reference medicinal product in physicochemical and biological terms.”²⁶ This includes, for example, pharmacokinetic and pharmacodynamic similarity and being used in the same doses as the originator product. Furthermore, “any observed differences have to be duly justified with regard to their potential impact on safety and efficacy.” The principles are included in guidance from the US Food and Drug Administration,²⁷ and the UK’s National Institute for Health and Care Excellence has provisions for recommending the use of biosimilars when appropriate.²⁸

Allied to biosimilars are *biobetters*, biologics that have been engineered with the intention of producing improved properties.²⁹ They can also be regarded as me-too drugs. For example, erythropoietin is a naturally occurring hormone. Recombinant human erythropoietin, used in the treatment of anaemia, is called epoetin. As different biosimilars of epoetin emerged, they were given Greek suffixes, epoetin alfa, beta, omega, zeta. One biosimilar was sufficiently distinct from the others to be given a separate name, darbepoetin; it could be regarded as a biobetter, since it has a longer duration of action. Since then other biobetters have emerged, such as methoxy PEG-epoetin β .³⁰

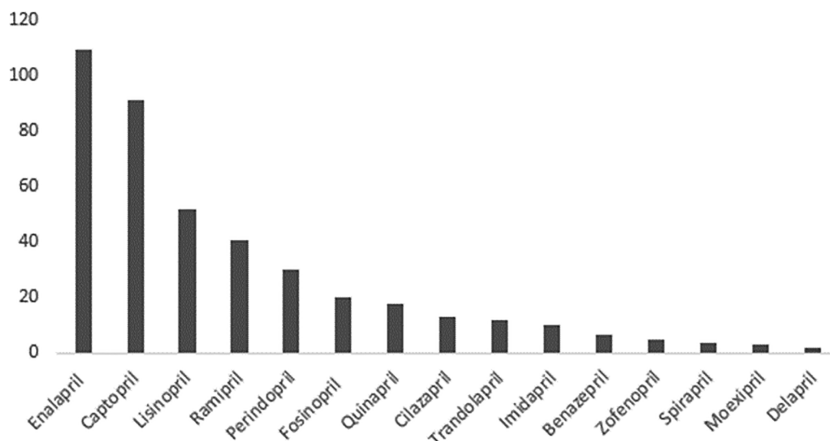
6 | DRUG SHORTAGES

In recent years drug shortages have become more common and problematic. There are many causes³¹ and few reliable solutions. However, the availability of me-too drugs provides one way of coping, by substituting one medicine with another in the same class.³² Nevertheless, care must be taken when doing so. Although the mechanism of action of the substitute may be the same, it may have different pharmacodynamic properties (e.g. partial agonism and a different dose-response curve) and different pharmacokinetic properties (with, for example, the potential for drug-drug interactions), resulting in a different dosage regimen, with which the prescriber may not be familiar. Adverse reactions can occur and have indeed been reported in such cases.³³ Substitution of biologics with biosimilars is also possible.²⁴

7 | ESSENTIAL MEDICINES LISTS

The World Health Organization (WHO) published its first model list of essential medicines in 1977. Since then different countries have devised their own lists for local use. More than 5 billion people live in countries that use essential medicines lists, intended to meet their priority healthcare needs. The WHO’s list includes over 370 medicines,

FIGURE 2 The numbers of national essential medicines lists in 137 countries that include one or more of 15 different angiotensin-converting enzyme inhibitors, ranging from enalapril (108 lists) down to delapril (two lists)



of which about 60% are me-too drugs. Other lists contain between 44 and 983 medicines (median = 310; interquartile range = 269–422). There are major differences between essential medicines lists from country to country, and the differences are not explicable on the basis of characteristics such as region, population size, life expectancy, infant mortality, gross domestic product, and health care expenditure.³⁴

Take the angiotensin-converting enzyme (ACE) inhibitors as an example. Captopril was the first in class and enalapril the first me-too drug, with the major advantage of once daily therapy. Since then many me-too drugs have emerged, none with any important advantages. The WHO list contains one ACE inhibitor only, enalapril. However, a total of 15 different ACE inhibitors are included in the lists of 137 countries. Most of the lists include enalapril (108 countries in all), but 91 include captopril either as well or instead, 52 lisinopril, 41 perindopril, and so on (Figure 2). About 80% include up to four different drugs and the rest include five or more. One country's list contains 12 ACE inhibitors in all.

This analysis suggests that the availability of a range of similar me-too drugs may in part explain the differences between the lists in different countries, although in some cases the dominant presence of particular pharmaceutical companies may also be a factor. There are no major innovative features that distinguish most ACE inhibitors from each other, and it would be sufficient to include one only in each list. Enalapril would normally be the choice, but countries may have good reasons for choosing another instead. If there are negligible differences between drugs in a class, a list of recommended drugs could simply name the class, from which countries could choose the single drug that they prefer.

8 | CONCLUSIONS

Most me-too and follow-on products are marketed in order to gain a fraction of a lucrative market, as illustrated by the examples shown here. However, they have advantages apart from financial gain, and disadvantages as well. The therapeutic advantages include

improved target specificity, reduced risks of off-target adverse reactions and drug–drug interactions, increased chance of benefit in some patients, and improved drug delivery and pharmacokinetics. However, they may cause unexpected adverse reactions that are not class effects.

Some me-too drugs feature major innovations, such as β -blockers and penicillins. This is partly reflected in current prescribing figures (Tables 3–5), which suggest that newness does not by itself guarantee that a me-too product will be prescribed more often than its predecessors, or even be more efficacious. Any specific advantage for a drug may not be apparent for some time after it reaches the market. An extreme example of this is given by the results of a recent network meta-analysis of the effects of amitriptyline, the second tricyclic to have entered the market (Table 3), which was found to be the most effective drug for severe depression, even when measured against more recent nontricyclic compounds.³⁵ However, me-too drugs that appear to have no advantages over their predecessors also continue to be prescribed.

Me-too drugs may be useful when equivalent drugs can replace each other in the event of shortages.

The presence of more than one me-too drug in national lists of essential medicines could be rationalized.

8.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

COMPETING INTERESTS

There are no competing interests to declare.

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