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Drug repositioning and repurposing: terminology and definitions in literature

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Drug repositioning and similar terms have been a trending topic in literature and represent novel drug development strategies. We analysed in a quantitative and qualitative manner how these terms were used and defined in the literature. In total, 217 articles referred to 'drug repositioning', 'drug repurposing', 'drug reprofiling', 'drug redirecting' and/or 'drug rediscovery'. Only 67 included a definition ranging from brief and general to extensive and specific. No common definition was identified. Nevertheless, four common features were found: concept, action, use and product. The different wording used for these features often leads to essential differences in meaning between definitions. In case a clear definition is needed, for example from a legal or regulatory perspective, the features can provide further guidance.

Introduction

In 2004, Ashburn and Thor wrote their landmark article 'Drug repositioning: identifying and developing new uses for existing drugs', in which they outlined the opportunities for drug repositioning [1]. They stated that: 'the process of finding new uses outside the scope of the original medical indication for existing drugs is also known as redirecting, repurposing, repositioning and reprofiling'. Drug repositioning is believed to offer great benefits over *de novo* drug discovery, the traditional way of drug discovery by searching for a new active substance. Ashburn and Thor explained that the development risks would be reduced, because drug repositioning candidates could be developed quicker owing to the use of existing knowledge about the drug [1]. Since the well-known article by Ashburn and Thor, other authors have written about drug repositioning and similar terms [2]. Although Ashburn and Thor defined drug repositioning and suggested that the different terms they mentioned are interchangeable, the different scopes for which these terms are sometimes used by others suggest that they can have different meanings. For instance, Oprea and Mestres [3] related 'drug repurposing' to innovation with already approved drugs, whereas Allarakhia [4] included 'potential drug candidates' as starting material for drug repositioning. Moreover, the definitions used are often vague and unclear and seem to contain different elements.

Terminology matters because it prevents misinterpretation and confusion. Weise *et al.* addressed the proper use of the term 'biosimilar', because they were concerned about the implications of misinterpretation and inconsistent use of this term, which could cause negative perception and impaired acceptance of biosimilars among prescribers and patients [5]. Neubert *et al.* searched for common definitions of 'off-label' and 'unlicensed use of medicines' for children [6], because a shared definition among European Union (EU) member states was missing, which made comparison of use of medicinal products in children problematic.

Several governments worldwide are investing in drug repositioning and related activities. For example the National Centre for Advancing Translational Sciences (NCATS) in the USA has launched the Discovering New Therapeutic Uses for Existing

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Molecules Programme. The aim of the programme is 'to improve the complex and time-consuming process of developing new treatments and cures for disease by finding new uses for agents that already have cleared several key steps along the development path' [7]. In the UK, researchers can apply for funding for repurposing clinical studies under the Developmental Pathway Funding Scheme of the Medical Research Council (MRC) [8]. The Netherlands Organisation for Health Research and Development (ZonMw) funded a project about 'stimulation of drug rediscovery' which relates to drug repositioning [9]. However, these governmental organisations use a different definition than Ashburn and Thor.

In the future, drug-repositioning-related activities could be further stimulated to increase the number of new therapeutic uses that actually reach clinical practice. In the past, regulatory schemes have been established to provide incentives for specific drug development such as for orphan medicinal products and paediatric medicinal products. In the USA and the EU the number of orphan drugs increased substantially as a result of incentives such as specific market exclusivity and fee reductions [10,11]. Similarly, the development of paediatric medicinal products increased in the USA and the EU after the introduction of specific market exclusivity with regard to paediatric indications [12–14]. Under those regulations the definitions that establish what orphan medicinal products and paediatric medicinal products are determine the applicability of the regulation to a specific product and subsequently whether it benefits from the incentives and has to comply with additional requirements.

Currently, there is no overview of the different terms used for the concept of drug repositioning and of definitions for those terms. In anticipation of the introduction of future incentives to enhance the concept of drug repositioning, we analysed the use of the term drug repositioning and similar terms in academic literature. Our aim was to analyse in a quantitative and qualitative manner how drug repositioning and similar terms were used and defined in academic literature, including an assessment of the nature and frequency of used definitions and differences and commonalities in their features.

Approach

We searched PubMed for all articles published until August 2013 using the keywords 'drug' AND ('repositioning' or 'repurposing' or 'redirecting' or 'reprofiling' or 'rediscovery') in the title or abstract. The search was limited to English language and journal articles, thereby excluding books, letters and assay guides.

Articles addressing the repositioning of drugs were selected regardless of the nature of the article (e.g. original research or commentary). However, articles in which the repositioning did not relate to drugs were excluded from the analysis, for example an article about the physical repositioning of implants. For articles with an abstract in PubMed the selection was based on the title and abstract. If no full-text copy was available in any library in The Netherlands, the authors were sent a request for a copy of that article. For articles without an abstract in PubMed a digital copy was extracted from the Utrecht University library to determine its relevance for further analysis. If no digital copy was available the article was excluded.

Articles were first scored for the use of the following terms: 'drug repositioning', 'drug repurposing', 'drug reprofiling', 'drug redirecting' or 'drug rediscovery'. Combinations such as 'drug repositioning or repurposing' were scored twice as 'drug repositioning' and 'drug repurposing'. In addition, other terms that were obviously related to drug repositioning but were not included in the PubMed search, were also noted.

Subsequently, the articles were searched for definitions of any of the abovementioned terms. If an article used several definitions for the same term (e.g. in the abstract and in the main text), the most detailed definition was selected for analysis. Any phrase that included an explanation of the meaning of drug repositioning, for example 'Drug repositioning, or drug repurposing, is…' [15] or 'A more efficient strategy for drug development is to…, so-called drug 'repurposing' or 'repositioning' [16], was considered as a definition. The definitions were analysed for features: particular commonalities or differences between definitions. Definitions that contained multiple references to the same feature were scored multiple times.

The articles were analysed in a quantitative manner for the use of the terms: 'drug repositioning', 'drug repurposing', 'drug reprofiling', 'drug redirecting' or 'drug rediscovery', as well as for definitions of those terms. The number of articles was assessed by year. The features were analysed in a qualitative manner by categorising the wording used for each feature. A chi-square test was performed to compare frequency of specific wording used in the definitions for drug repositioning and drug repurposing.

Main findings

In total, 511 articles were found based on the predefined search in PubMed. One or more of the terms drug repositioning, drug repurposing, drug reprofiling, drug redirecting or drug rediscovery were used in 217 of those articles (Fig. 1). Before 2004 no articles about drug repositioning were found and the number of articles started to increase after 2010 in particular (Fig. 2). The majority of the articles were published in 2012 and 2013, the year 2013 only included articles published until August 2013. Drug repositioning and drug repurposing were most often used in the selected articles. Of the 217 articles, 138 (64%) referred to drug repositioning and 126 (58%) to drug repurposing. Only five (2%) articles referred to drug reprofiling, five (2%) to drug rediscovery and three (1%) to drug redirecting. In total, 52 articles (24%) used drug repositioning and drug repurposing interchangeably.

A total of 67 (31%) of the 217 articles contained a definition for the used terminology (see Supplementary Material online for a full reference list). Ten examples of definitions as used in these articles are listed in Table 1. These definitions represent the range of definitions from nonspecific to specific as observed in those 67 articles. For instance Cheng *et al.* referred just to 'new usages' [17] whereas Sistigu *et al.* specifically stated: 'novel indication underscoring a new mode of action that predicts innovative therapeutic options' [18].

In the definitions four features were identified based on the categorisation of wording used in the retrieved definitions: concept, action, use and product (Table 2). Concept relates to whether drug repositioning is a concept of drug development. It was included in 31 (46%) of the 67 definitions and was referred to as a strategy ($n = 10$), a process (six articles), an approach ($n = 5$) and other concept-related wordings ($n = 10$). The other three

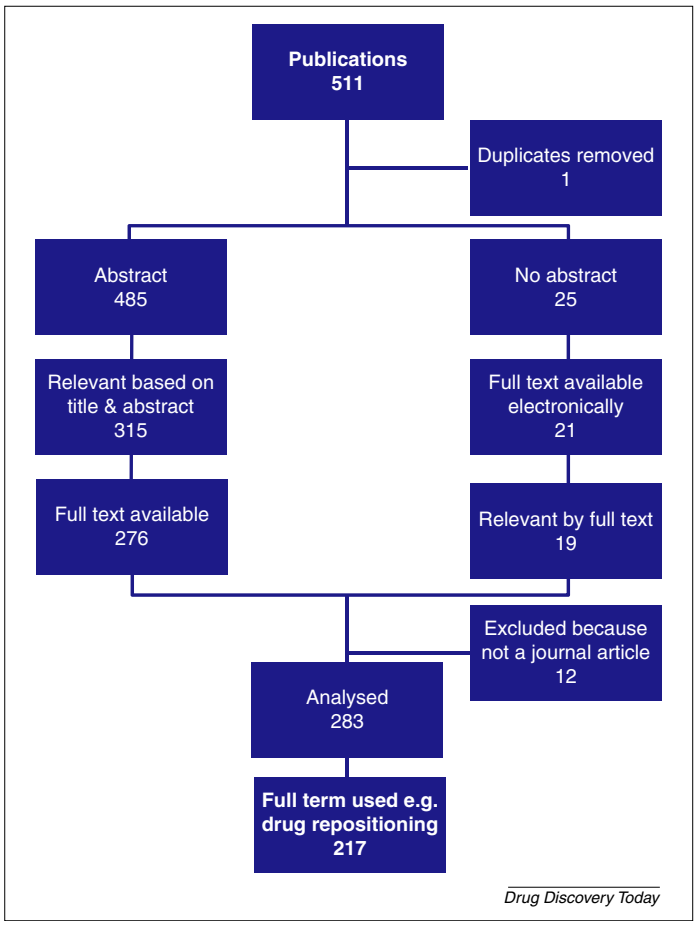

FIGURE 1

Overview of the results of the PubMed search and the articles eligible for analysis.

features were included in all definitions. Action relates to the main aim of drug repositioning. The action was referred to as: to identify ($n = 31$), to apply ($n = 15$), to develop ($n = 6$) and other action-related wordings ($n = 4$). The feature product describes which type of product is involved in the action. It was referred to by a wide variety of terms including: drugs ($n = 4$), existing drugs ($n = 33$), approved drugs ($n = 14$), old drugs ($n = 8$), existing compounds ($n = 7$), abandoned drugs ($n = 6$), biologicals ($n = 2$) and other ($n = 7$). Use relates to what would be the new use, such as a medical application or therapeutic indication. It was referred to as use, usages, application, indication, disease, among others. Within this element three main categories were identified: definitions that refer to terms as use ($n = 31$), indication ($n = 28$) and other use-related wordings ($n = 14$). In all instances it was referred to as being new, novel, alternative, secondary, outside the scope of the original or similar terms indicating that for the purpose of drug repositioning the medicine was or will be used outside the original indication. As can be observed in Table 2, there was a great variety of wording used for the common features for each of the studied terms, often leading to essential differences in meaning between definitions used per term. Between drug repositioning and drug repurposing no disproportionality was observed in the use of specific wording for the common features mentioned in Table 2.

In addition to the five terms searched for in PubMed, six other terms were identified that were used as synonyms of drug repositioning namely: 'drug re-tasking' [19,20], 'indication switching' [21], 'indication switch' [22], 'therapeutic switching' [19,23], 'indication expansion' [20], 'candidate or compound repurposing' [24]. The terms 'in silico drug repositioning' [15,25,26], 'on-target repositioning' and 'off-target repositioning' [27] were used as a further specification of drug repositioning. In silico drug repositioning refers to drug repositioning by computational screening. On-target repositioning applies a drug's known pharmacological mechanisms to different therapeutic indications and off-target repositioning attempts to elucidate still unclear pharmacological mechanisms for known molecules [27]. 'Drug rescue' was another term sporadically used in the context of drug repositioning, but seemed to have a different scope by specifically focusing on products that failed in the development for their primary intended purpose [28,29].

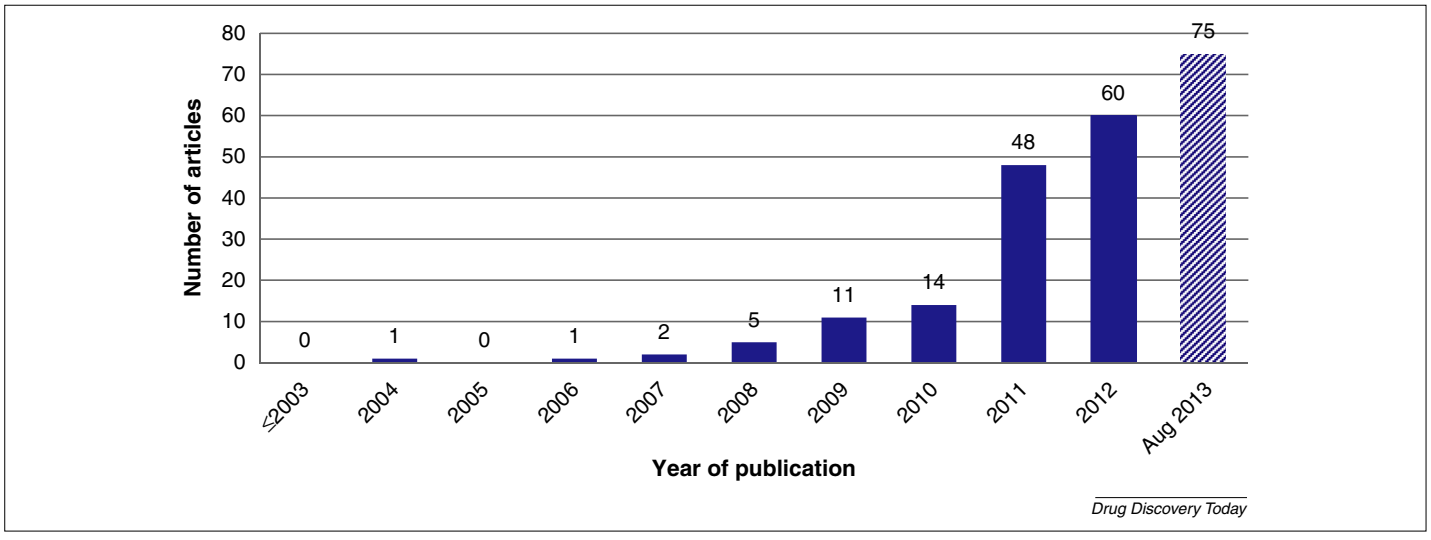

FIGURE 2

The number of articles using the terms drug repositioning, drug repurposing, drug redirecting, drug reprofiling or drug rediscovery per year.

TABLE 1

Examples of definitions of drug repositioning and drug repurposing used in the articles analysed

Definition[a]	Refs
Drug repositioning is giving new usages for old drugs	[17]
Drug repositioning is a concept to reuse existing drugs for new targets	[39]
Drug repositioning and drug repurposing are finding a new use for an existing drug	[40]
Drug repositioning and drug repurposing refer to the use of an old drug for a new indication	[41]
Drug repositioning, drug repurposing, drug redirecting and drug reprofiling are the process of finding new uses outside the scope of the original medical indication for existing drugs	[1]
Drug repositioning and drug repurposing are taking an approved drug that has already been optimised for safety and efficacy in a particular indication and obtaining regulatory approval for novel therapeutic applications	[3]
Drug repositioning refers to the utilization of a known compound in a novel indication underscoring a new mode of action that predicts innovative therapeutic options	[18]
Drug repositioning is a strategy for pharmaceutical R&D in which an established active pharmaceutical ingredient is applied in a new way – for example, for a new indication – and often combined with an alternative method of presentation, such as a novel delivery route	[23]
Drug repositioning and drug repurposing are a strategy to find new uses for previously approved drugs and 'parked' or 'off the shelf' molecules that reached the clinic without any safety concerns but did not show sufficient efficacy against their intended primary disease target	[42]
Drug repositioning involves: finding new indications for existing drugs or potential drug candidates, including those in clinical development where mechanism-of-action is relevant to multiple diseases; drugs that have failed to demonstrate efficacy for a particular indication during Phase II or III trials but have no major safety concerns; drugs that have been discontinued for commercial reasons; marketed drugs for which patents are close to expiry; and drug candidates from academic institutions and public sector laboratories not yet fully pursued	[4]

[a] The definitions were extracted from the context of the articles and sentences were rephrased if necessary for grammatical reasons.

Discussion

This study showed that in literature a variety of terms and definitions were used for drug repositioning with drug repurposing as the most common and interchangeable alternative. The definitions identified in this study range from brief and general to extensive and specific. Although no notable differences were identified in the variety of definitions among the five terms mentioned, four features were identified in the definitions: concept, action, use, and product. All definitions contained the latter three features and about half of the definitions contained the feature of concept. However, authors used different wording per feature, often leading to essential differences between definitions, as outlined below.

Use

The identified definitions referred to new uses, usages, clinical use, therapeutics applications, indications, therapeutic indications, therapies and more. Despite the variety of terms, in essence all authors meant the treatment of a disease. The development of a drug for the treatment of new diseases might involve new patient populations, dosage forms or routes of administration. However, wording like a new 'application' does not necessarily mean the treatment of a new disease. It can also relate to the development of a drug for new patient populations, new dosage forms, routes of administration or line of treatment. For example, fentanyl was approved in the 1980s as solution for infusion and nowadays is authorised as nasal spray, transdermal patch, buccal tablet and lozenge for oromucosal use. Those new dosage forms and routes of administration would fall within the scope of drug repositioning as well, which is not necessarily the intention of a person who used 'new application' in a definition of drug repositioning. Less ambiguous wording could better indicate the intended scope of drug-repositioning-related activities.

Furthermore, it should be considered what 'new' means. Most definitions refer to new as new, novel, secondary, alternative or outside the scope of the original medical indication. This raises questions regarding from which perspective the use should be new. For instance, would a use be new if previously mentioned in literature but not used in clinical practice? Or is a use considered new as long as it is not included in a marketing authorisation? From this point of view, off-label use, ranging from experimental, for example pregabalin for treatment-resistant insomnia [30], to common practice, for example nifedipine as a tocolytic, could be a source for drug repositioning because it still might be considered as new.

Product

Authors used a wide variety of terms to indicate the product. Some referred to the product as a 'drug' leaving it open as to whether they meant an active pharmaceutical ingredient or medicinal product complete with a dosage form and ready to be used. Furthermore, in the identified definitions the product often related to stages of the drug life-cycle such as 'drug candidates', 'abandoned drugs', 'approved drugs' and 'old drugs'. However, from the definitions itself it is unclear what is meant by drug candidates, old drugs and abandoned drugs. Drug candidate could indicate that the active pharmaceutical ingredient is still under development for its first intended medical use, when it is discovered to be effective for the treatment of another condition, for example sildenafil for erectile dysfunction and duloxetine for stress urinary incontinence [1,17]. Old drugs could imply that the medicinal products are already on the market and intellectual property protection on the active pharmaceutical ingredient might have expired. An illustration is ibuprofen (Pedea®) which was authorised in Europe in 2004 for the treatment of patent ductus arteriosus, a heart problem

TABLE 2

Number of articles referring to a specific category for each term

	Drug repositioning	Drug repurposing	Drug redirecting	Drug reprofiling	Drug rediscovery	Total[b]
Total[a]	53	37	2	6	2	67
Use						
Use(s), usages, clinical use, application(s), therapeutic applications, therapeutic uses, modality of use	23	16		1	1	31
Indications, medical indications, therapeutic indications, disease indications, therapies	21	15	1	4		28
Other[c]	12	7	1	1	1	14
Product						
Existing drug(s)/medication(s), known drugs, existing pharmacotherapies	24	19	2	6	3	33
Existing approved drug, (FDA-)approved drugs/medicines, drug approved to treat one condition, previously registered drugs, approved pharmaceutical compounds, marketed drug	10	8			1	14
Old drug(s), established drugs, well-known drugs	8	3				8
Existing compounds, established drug compounds, established active pharmaceutical ingredient, known compound, existing pharmacopeia including failed candidate compounds	5	3			1	7
Abandoned drugs/pharmacotherapies, drug candidate, developmental drugs, developmental drug that failed for primary intended purpose	3	4			1	6
Drug(s); not otherwise specified	4	1				4
Biological(s); not otherwise specified	1	1		2	1	2
Other[d]	6	6		1	1	7
Action						
Identification/identified/identifying/to identify, discovery/discovers, finding/to find, to seek, screening, to suggest	31	24	1	4	2	39
Applying/to apply/application, using/used/the use/to reuse, the utilization, making alternative uses	15	6			1	18
Developing/development, giving	6	4	1	3	1	7
Other[e]	4	5				6
Concept						
Strategy	8	7				10
Process	6	4	1	3	1	6
Approach	4	3				5
Other[f]	8	8	1	2	1	10

Definitions that referred to multiple terms were scored for each term. Moreover, definitions that included multiple wordings to a feature were scored accordingly. For example, a definition that referred to 'drugs' and 'biological' was scored twice.

[a] Number of definitions for this term.

[b] Total number of definitions for the five terms and the wording used in the definition per feature.

[c] For example effect(s), novel indication underscoring a new mode of action that predicts innovative therapeutic options and previously unrecognized, therapeutic activities.

[d] For example drugs that have failed to demonstrate efficacy for a particular indication during Phase II or III trials but have no major safety concerns; drugs that have been discontinued for commercial reasons; and marketed drugs for which patents are close to expiry and drug candidates from academic institutions and public sector laboratories not yet fully pursued.

[e] For example to obtain regulatory approval for novel therapeutic applications, to promote and to speed up the drug discovery process by identifying.

[f] For example action, concept and alternative to *de novo* drug development.

in new borns. Abandoned drugs are drugs that failed for their primary intended purpose.

The wording used to describe the product affects the scope of drug repositioning. For instance, definitions that refer to 'new uses for old drugs' exclude new uses for drug candidates, abandoned drugs and recently approved drugs. Furthermore, references to terms such as 'existing drugs' are unclear as well, because they could include drug candidates and/or approved drugs.

The use of the more specific term drug rescue can be considered to indicate the development of new uses for failed or abandoned drugs [28,29]. Interestingly, 'withdrawn' medicinal products were not mentioned as candidates for drug repositioning, despite the fact that thalidomide is one of the most cited and famous examples of drug repositioning [1,31,32].

Action

The main purpose of drug repositioning results from the wording used to describe the action feature. The action could be: (i) identification of new applications (i.e. screening of active pharmaceutical ingredients to discover or to suggest new uses); (ii) using drugs for new applications (i.e. off-label use in the treatment of actual patient); or (iii) the development of new applications (i.e. development towards a marketing authorisation).

Implications of the findings

Drug repositioning constitutes an emerging and dynamic field of drug development, which includes different and related activities, as is also implied by the wide variety of wording used for the identified common features. The increase in drug-repositioning-related

activities, as indicated by the considerable increase in number of publications on this topic, shows that the observed inconsistent use of terminology and ambiguous definitions might not be problematic from a practical point of view but could merely reflect the different origins and approaches taken by those involved in this dynamic and emerging field. However, currently, drug repositioning might not yet reach its full potential in terms of authorised new treatment options for patients. Many potential new uses are suggested in the literature, which have not yet found their way to clinical practice for example through the inclusion in a marketing authorisation [21,33–35]. As aforementioned, in the past, specific regulatory schemes have been established in similar situations where full benefits lagged behind the potential, such as for orphan medicinal products and paediatric medicinal products. To enhance drug repositioning further, similar incentives might be needed to stimulate this emerging field. From such a perspective a clear definition of drug repositioning and similar terms would be needed, because there would be consequences in terms of benefits and requirements attached to complying with the definition. Legal or regulatory reforms could also take into account how differences in regulatory frameworks (e.g. between the USA and the EU) affect drug development by the concept of drug repositioning, which could be examined in future studies.

The present analysis identified four common features in the definitions currently used in academic literature that could be helpful in constructing definitions in future legal and regulatory reforms to stimulate drug repositioning. In addition, based on our findings, academia, regulators and industry could become aware of the diversity in the current use of terminology and the potential ambiguousness of definitions. In this respect we encourage them to use the term they choose consistently in their own writings and to define it thoroughly by making well-considered choices on the intended scope of the chosen term. The scheme in Fig. 3 displays the choices to consider.

Moreover, it might be useful to allocate different terms to different activities when defining terms for the concept of drug repositioning in future legal or regulatory reforms. This might require the use of terms not included in our analysis to clarify the distinction between activities. In this respect it should be noted that we studied terminology as used in academic literature. Outside academic literature terminology and definitions can be used that have not been reflected in academic literature, although a quick scan did not reveal a consistent use of well-defined terminology in other sources [36–38].

A limitation of this study is that not all articles were full-text available ($n = 43$). This includes 39 of the 315 articles that were considered relevant based on title or abstract and four of the 25 articles that had no abstract in PubMed. This limitation does not affect the meaning of our results, because the articles and definitions included in the study would outnumber the articles and definitions not included. Moreover, we performed an extensive PubMed search with few exclusion criteria. Besides, we checked Embase with the same search strategy, which resulted in a similar list of articles. Therefore it was decided not to include other databases in this study. However, during the study other terms were identified that were obviously related to the terms that were

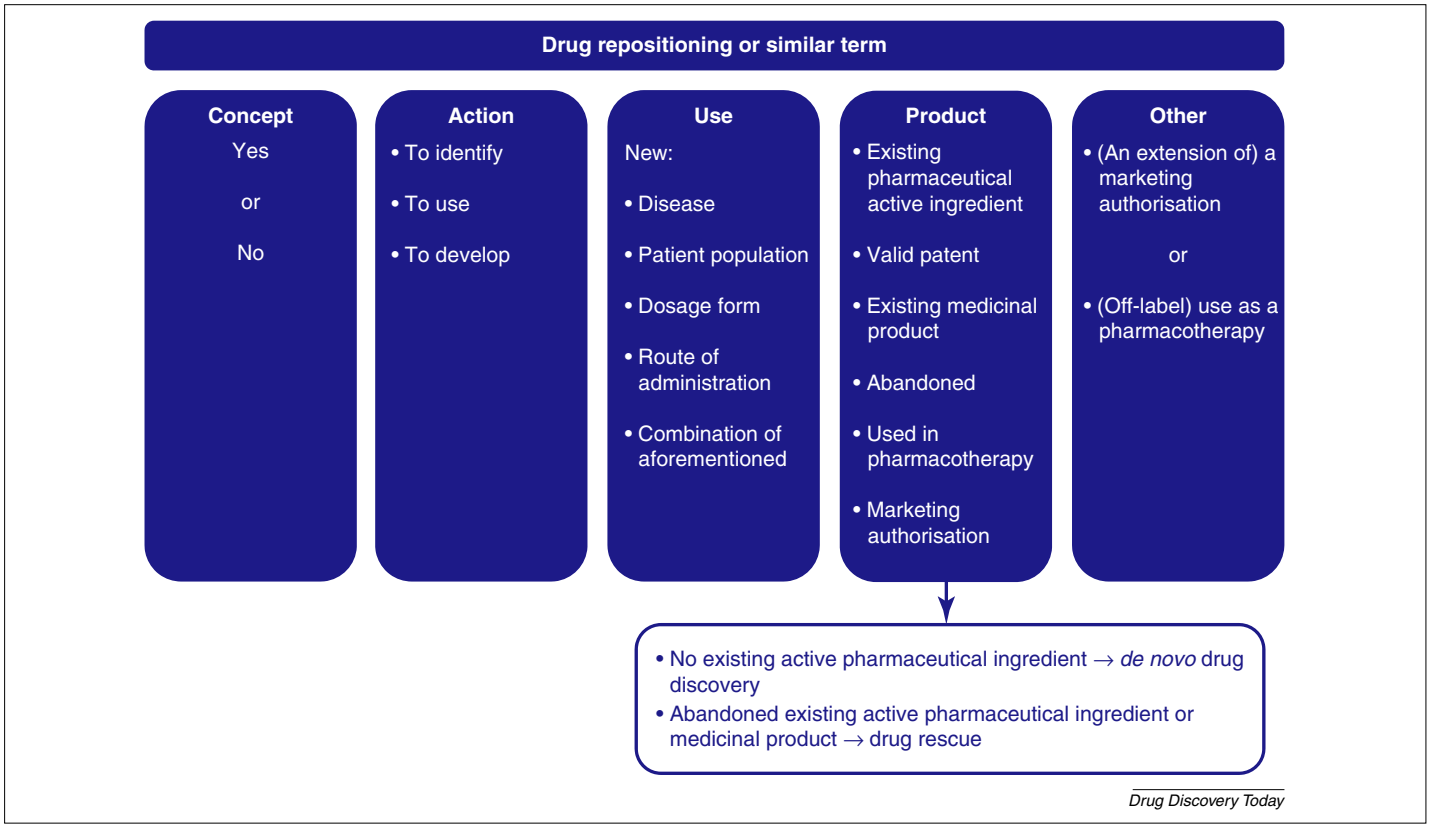

FIGURE 3

Choices regarding what to include and exclude in a definition of drug repositioning or a similar term.

used for the search. The PubMed search was not extended to those terms. Finally, although this study includes only articles up to August 2013, we have continuously monitored subsequently published literature regarding drug repositioning. We have not noticed any development that would change our conclusions. Therefore we have no reason to assume that the inclusion of more-recent articles would yield different findings with regard to the consistent use of terminology and definitions.

Concluding remarks

The term drug repositioning is frequently used in the literature and has several synonyms such as drug repurposing, which have been used interchangeably. No common definition of drug repositioning or indeed for other similar terms has been found in the literature. Moreover, the definitions differed significantly in their wording used for the features, often leading to essential differences in their meaning. In the future, incentives might be established to stimulate drug repositioning and related activities that – from a legal or regulatory perspective – require clear terminology and a consistent definition. The four identified common features could provide further guidance in this respect.

Conflicts of interest

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position the Medicines Evaluation Board (MEB). The authors declare no potential conflicts of interest with respect that are directly relevant to the content of this article. A.M.T. has received unrestricted research funding from The Netherlands Organisation for Health Research and Development (ZonMw), the private–public funded Top Institute Pharma (http://www.tipharma.com/, includes co-funding from universities, government and industry), EU 7th Framework Program (FP7), the Dutch Medicines Evaluation Board and the Dutch Ministry of Health.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drudis.2015.05.001.

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