ELSEVIER

Drug repositioning and repurposing: terminology and definitions in literature

Joris Langedijk[1,2], Aukje K. Mantel-Teeuwisse[1], Diederick S. Slijkerman[2] and Marie-Hélène D.B. Schutjens[1,3]

[1] Department of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands
[2] Medicines Evaluation Board, Utrecht, The Netherlands
[3] Schutjens de Bruin, Tilburg, The Netherlands

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

Corresponding author: Mantel-Teeuwisse, A.K. (A.K.Mantel@uu.nl)

http://dx.doi.org/10.1016/j.drudis.2015.05.001

Please cite this article in press as: Langedijk, J. et al. Drug repositioning and repurposing: terminology and definitions in literature, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.05.001

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

Please cite this article in press as: Langedijk, J. et al. Drug repositioning and repurposing: terminology and definitions in literature, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.05.001