



Drug Repurposing for Rare Diseases: A Role for Academia

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Background: The European Commission highlights in its Pharmaceutical Strategy the role of academic researchers in drug repurposing, especially in the development of orphan medicinal products (OMPs). This study summarizes the contribution of academia over the last 5 years to registered repurposed OMPs and describes barriers to success, based upon three real world cases.

Methods: OMPs granted marketing authorization between January 2016 and December 2020 were reviewed for repurposing and whether the idea originated from academia or industry. Three cases of drug repurposing were selected from different therapeutic areas and stages of development to identify obstacles to success.

Results: Thirteen of the 68 OMPs were the result of drug repurposing. In three OMPs, there were two developments such as both a new indication and a modified application. In total, twelve developments originated from academia and four from industry. The three cases showed as barriers to success: lack of outlook for sufficient return of investments (abatacept), lack of regulatory alignment and timing of interaction between healthcare professionals and regulators (etidronate), failure to register an old drug for a fair price, resulting in commercialization as a high priced orphan drug (mexiletine).

Conclusion: While the majority of repurposed OMPs originates in academia, a gap exists between healthcare professionals, regulators and industry. Future strategies should aim to overcome these hurdles leading to more patient benefit through sustainable access of repurposed drugs. Potential solutions include improved regulatory and reimbursement knowledge by academia and the right for regulators to integrate new effectiveness data into product labels.

Keywords: drug repurposing, mexiletine, etidronate, abatacept, orphan drugs, off-label, reimbursement, rare diseases

INTRODUCTION

Drug repurposing, or drug repositioning, is the application of an already known active substance in a new way—such as a new indication or alternative method of presentation (Langedijk et al., 2015). The major advantage of drug repurposing is the availability of clinical and regulatory knowledge on the active substance's safety profile, pharmacokinetics, dose, quality and production process, hence typically lowering overall risk and development costs (Sardana et al., 2011; Pushpakom et al., 2018).

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Drug repurposing has especially been coined as a possible relevant strategy for development of medicines for rare diseases (Caban et al., 2017; Davies et al., 2017; Tambuyzer et al., 2020; Kort & Jovinge., 2021). A recent analysis showed that almost half of the drug repurposing collaborations in the Excelra database were targeted at rare diseases (Polamreddy and Gattu, 2019). However, drug repurposing often does not lead to formal regulatory approval due to a variety of legal, regulatory and market constraints, among others. First, since newly discovered treatment targets are frequently reported in literature, it may be difficult or impossible to obtain intellectual property protection. In addition, the strength of second-use patents to protect against competitors is often weak (Pushpakom et al., 2018; Verbaanderd et al., 2020). Second, additional costly clinical development investments may be needed to prove efficacy for the new indication, as well as possible additional requirements with respect to dosing and safety (Kort & Jovinge., 2021; Verbaanderd et al., 2021). These additional costs may limit the prospects for sufficient profitability, especially when low-priced generic versions of the originator are already used off-label (Breckenridge & Jacob., 2018; Verbaanderd et al., 2020). Off-label use may by itself be problematic: if the level of evidence for the new application is low, access, pharmacovigilance and reimbursement may be variable.

In November 2020, the European Commission highlighted in its Pharmaceutical Strategy for Europe the role of academic researchers and not-for-profit stakeholders to promote and develop repurposing of off-patent medicines for new therapeutic uses (European Commission, 2020). Industry engagement as part of public-private partnerships in this process is emphasized to close the loop to formal authorisation, as industry has valuable experience and knowledge about regulatory processes. However, academia may face several obstacles to successfully operate in this field: for example a lack of infrastructure, resources and expertise in regulatory affairs and academic incentives for fast publications, hampering the protection of intellectual property (Verbaanderd et al., 2020).

Because drug repurposing has the potential to deliver treatments to patients with rare diseases with an unmet medical need, it is important that such discoveries also become available and accessible for patients. In this exploratory study, we therefore addressed the following research questions: 1) What is the contribution of academia over the last 5 years regarding authorised drug repurposing for rare diseases? 2) What are the hurdles that hinder drug repurposing for rare diseases started by academia? We answer these questions by looking at the origin of drug repurposing of authorised orphan medicinal products (OMPs) and by describing three real world ongoing cases of drug repurposing by academia for rare diseases in different stages of development.

Methods

To determine the contribution of academia to drug repurposing for rare diseases, we selected all OMPs with a valid marketing authorization granted by the European Commission between January 2016 and December 2020 (68 OMPs). Data extraction was performed on December 16th, 2020 from the EMA website (EMA, 2020).

A drug was defined as “repurposed” when the active substance was either used in clinical practice for another indication, or for the same indication, but with a modified application (e.g., other formulation/mode of administration). The original indication or application should have been in place for at least 10 years before the marketing authorization of the OMP to exclude new active substances. For each OMP, PubMed was searched to retrieve published evidence of prior clinical use and analyzed whether the active substance was registered for the original indication 1) and/or for another indication 2) (“Indication”). If 1) was the case, we investigated whether there was a modified application (“Modified”). The results were grouped by anatomical therapeutic chemical classification system (ATC) code, that classifies active ingredients based on anatomic, therapeutic and pharmacologic properties (WHO Collaborating Centre for Drug Statistics Methodology, 2021).

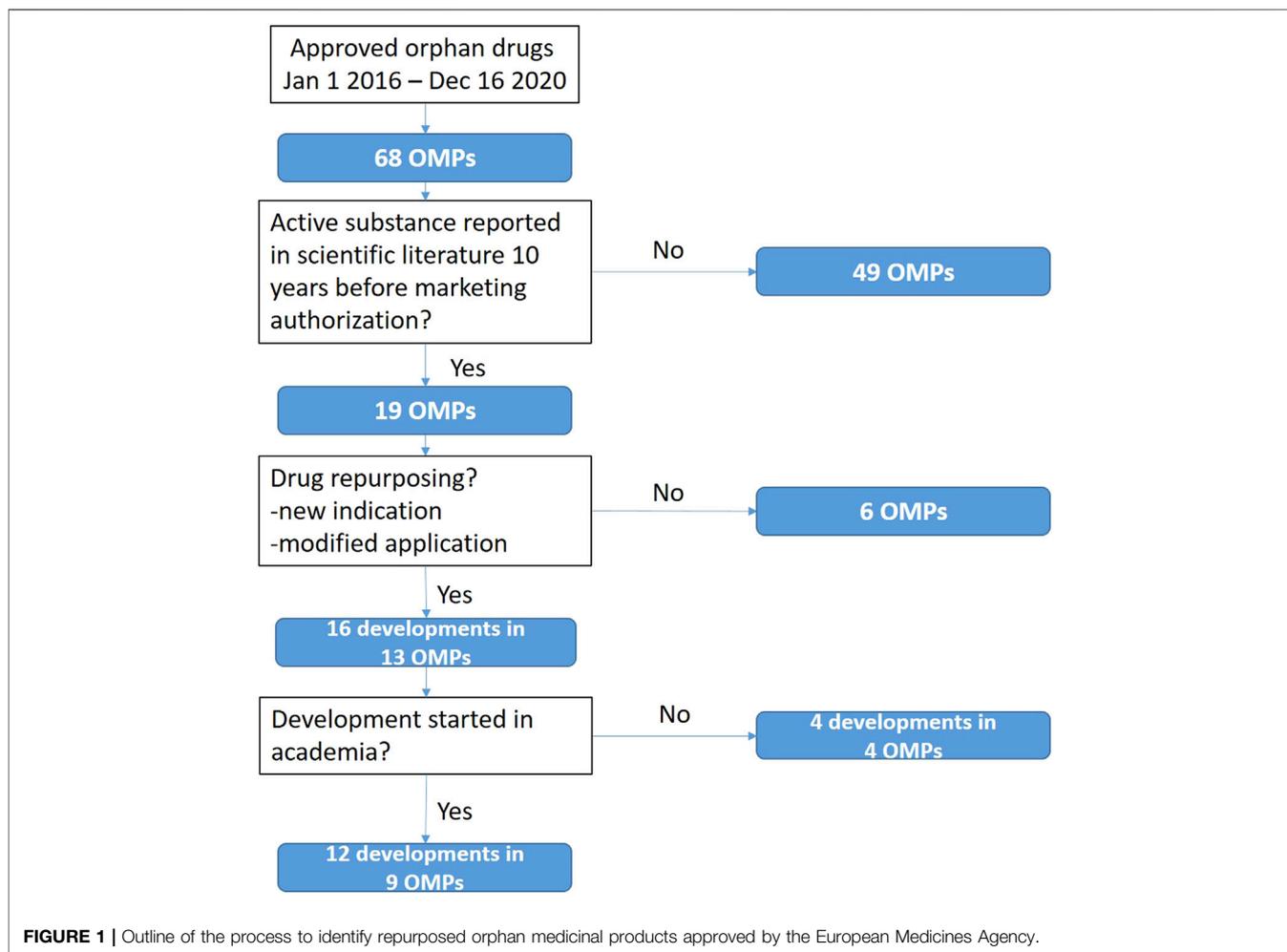
Whether the drug repurposing originated from academia or industry was determined upon the first description of the development (Indication or Modified application) in scientific publications (PubMed) or clinicaltrials.gov. Affiliations, sponsors, acknowledgements and conflict of interest (CoI) statement were reviewed. If there was at least one commercial entity involved in one of those domains, the development was labelled as initiated by industry. If there were only academic entities involved or when the full text described the emergence of the idea in academia, the development was labelled as initiated by academia.

To identify and elaborate on hurdles for drug repurposing for rare diseases whose development starts in academia, we purposively selected three cases to show the diversity and variation of issues that hinder drug repurposing for rare diseases from academia. All cases take place in the Netherlands and came to our attention through national media or through activities for the academic platform “Medicine for Society” (www.medicijnvoordemaatschappij.nl) (Volkskrant, 2018; Volkskrant, 2019). One author (SvdB) held unstructured interviews with the involved researchers from academic medical centers, who are all physicians treating patients with the rare disease. Afterwards, the interviewees verified the findings and gave consent for publication. As the study does not fall under the definition used for medical scientific research, it has therefore not been assessed by the medical ethics committee. The three selected real life cases represent different therapeutic areas and stage of development: a case in the area of immunology, in early developmental stage with only a few published case reports, a case in the area of metabolism where clinical trials have been performed and a case in the area of neurology where an old drug was registered as an OMP.

RESULTS

Contribution of Academia to Drug Repurposing for Rare Diseases

Thirteen of 68 OMPs licensed in Europe during a 5-year period (2016–2020) were repurposed drugs (Figure 1). Three OMPs have been repurposed twice (e.g., both indication and



formulation), leading to 16 developments. Twelve developments (75%) in nine OMPs started in academia and four developments (25%) in four OMPs started in industry. Ten of the 12 (83%) academia-originating developments were for a new therapeutic indication, while 75% (3/4) developments started in industry were a modified application. **Table 1** presents an overview of all repurposed orphan drugs and the nature of the developments.

Most developments in repurposed OMPs are in ATC class L (5, Antineoplastic and immunomodulating agents), followed by ATC class A (3, Alimentary tract and metabolism), S (3, Sensory organs) and J (2, Anti-infectives for systemic use). Other ATC classes appear once. The majority (75%) of the innovations started in industry were in ATC class L.

Hurdles for Drug Repurposing for Rare Diseases: Three Cases

Abatacept for Cytotoxic T-Lymphocyte Antigen 4 Haploinsufficiency: Too Rare for Investment in Trials

Abatacept is a product marketed as Orencia® and available as a subcutaneous injection. It was registered in Europe in 2007 to

treat rheumatoid arthritis and a number of other forms of arthritis. Abatacept is an analogue of cytotoxic T-lymphocyte antigen 4 (CTLA-4) that acts as a barrier to T-cell activation and is an important immune modulator. Since a number of years, abatacept is also used off-label to treat patients with the very rare disease CTLA-4 haploinsufficiency (prevalence <1 in 1,000,000), which causes severe immune dysregulation (Kuehn et al., 2014; Lapides & McDonald, 2020). Thus far, case reports of patients treated with abatacept reported a prompt response that resolved the inflammatory condition and substantial clinical improvements (Shields et al., 2016; Lee et al., 2016; Van Leeuwen et al., 2018; Lanz et al., 2021).

The new indication for abatacept as treatment of CTLA-4 haploinsufficiency was discovered in academia and was not included in the license by the original marketing authorization holder. The patent on the formulation of abatacept, disputed but not revoked (Holman, 2019), will expire in 2027 (US8476239B2). In the absence of involvement of the marketing authorization holder in a pivotal clinical trial meeting regulatory standards, it is very unlikely that registration for this rare indication will still occur during the patented period. And after patent expiration, the

TABLE 1 | Repurposed orphan medicinal products approved between January 1st, 2016 and December 16th, 2020. Col: conflict of interest.

Active substance	Therapeutic indication (current therapeutic indication in case of only a “Modified” innovation, otherwise previous therapeutic indication)	Innovation	Trade name	Pharmaceutical form	Start of drug repurposing	ATC Class current indication	References	Remarks
Amikacin sulfate	Infections with Gram-negative and Gram-positive organisms	Indication: Non-tuberculous mycobacterial lung infections Modified: Liposomal	Arikayce liposomal	Nebuliser dispersion	Indication: Academia Modified: Industry	J—Antiinfectives for systemic use	Forslöw et al. (2003) Weers et al. (2009)	No Col, acknowledgement suggests no industry funding
Budesonide	Asthma, allergic rhinitis, nasal polyps	Indication: Eosinophilic esophagitis	Jorveza	Orodispersible tablet	Academia	A—Alimentary tract and metabolism	Aceves et al. (2007)	No acknowledgement, Col describes industry funding
Cannabidiol	Lennox Gastaut syndrome, Dravet syndrome, seizures associated with tuberous sclerosis complex	Indication: Registered for subset of known indications	Epidyolex	Oral solution	Academia	N—Nervous system	Izquierdo et al. (1973)	No Col, acknowledgement suggests no industry funding
Chenodeoxycholic acid	Gallstones	Indication: Cerebrotendinous xanthomatosis	Chenodeoxycholic acid Leadiant	Hard capsule	Academia	A—Alimentary tract and metabolism	Salen et al. (1974)	No Col, acknowledgement suggests no industry funding
Chlormethine	Mycosis fungoides-type cutaneous T-cell lymphoma	Modified: Gel	Ledaga	Gel	Industry	L—Antineoplastic and immunomodulating agents	Lessin et al. (2013)	
Ciclosporin	Prevention of graft rejection following solid organ transplantation	Indication: Severe vernal keratoconjunctivitis	Verkazia	Eye drops	Academia	S—Sensory organs	BenEzra et al. (1986)	No full text, no Col, no acknowledgement
Daunorubicin hydrochloride, cytarabine	Newly diagnosed, therapy-related acute myeloid leukemia or acute myeloid leukemia with myelodysplasia-related changes	Modified: Combination therapy	Vyxeos liposomal	Powder for concentrate for solution for infusion	Modified: Academia	L—Antineoplastic and immunomodulating agents	Crowther et al. (1970) Tardi et al. (2009)	No Col, acknowledgement mentions industry but introduction describes the choice of compounds from academia
Glibenclamide	Diabetes mellitus type 2	Modified: Combination as liposomal Indication: Neonatal diabetes mellitus	Amglidia	Oral suspension	Modified: Industry Academia	A—Alimentary tract and metabolism	Sagen et al. (2004); Zung et al. (2004)	Both: no Col, acknowledgement describes government funding
Irinotecan hydrochloride trihydrate	Colorectal cancer, small cell lung cancer	Indication: Metastatic adenocarcinoma of the pancreas	Onivyde pegylated liposomal	Concentrate for dispersion for infusion	Academia	L—Antineoplastic and immunomodulating agents	Sakata et al. (1994); Wagener et al. (1995)	Sakata: no full text, no Col, no acknowledgement. Wagener: No Col, no acknowledgement
Mercaptamine hydrochloride	Cystinosis	Indication: Corneal cystine crystal deposits Modified: viscous formulation	Cystadrops	Eye drops solution	Indication: Academia Modified: Academia	S—Sensory organs	Dufier et al. (1987) Bozdag et al. (2008)	No full text, no Col, no acknowledgement No Col, acknowledgement suggests no industry funding
Mexiletine hydrochloride	Ventricular arrhythmias	Indication: Non-dystrophic myotonic disorders	Namuscla	Hard capsule	Academia	C—Cardiovascular system	Pouget & Serratrice, (1983)	No full text, no Col, no acknowledgement
Treosulfan	Ovarian cancer	Indication: Conditioning treatment prior to allogeneic haematopoietic stem cell transplantation	Treondi	Powder for solution for infusion	Industry	L—Antineoplastic and immunomodulating agents	Schmidt-Hieber, (2007)	
Treprostinil sodium	Pulmonary arterial hypertension	Indication: WHO functional class III or IV and chronic thromboembolic pulmonary hypertension	Trepulmix	Solution for infusion	Academia	B- Blood and blood forming organs	Skoro-Sajer et al. (2007)	No acknowledgement, Col describes government funding

availability of a cheaper biosimilar would probably hinder a higher price, needed to recoup investments in clinical trials and registration procedures.

Reimbursement of off-label abatacept use will then only be possible on a case-by-case basis, subject to agreements with either the hospital or the individual health insurance company. This situation hampers access to patients, while there is consensus amongst doctors to use abatacept off-label and the rationale for its use based upon its pathophysiological mechanisms is clear. The costs of chronic abatacept treatment differ between patients depending on dosing, but are expected to be above €4,000 per month based on 125 mg every 2 weeks (Zorginstituut Nederland, 2021a). An alternative for national or official reimbursement is acceptance of the treatment by insurance companies as standard of care, after scrutinizing the evidence of effectiveness and safety. In the case of abatacept for CTLA-4 deficiency it may be almost impossible to collect sufficient evidence as there are only few case studies published yet and a small single-center clinical trial (funded by the National Institute of Allergy and Infectious Diseases) is not expected to finish until 2026 (Shields et al., 2016; Lee et al., 2016; Van Leeuwen et al., 2018; NCT03733067). Also, obtaining reimbursement in this case is challenging, time-consuming and procedures differ from country to country. For example in Australia, reimbursement of treatment with abatacept is not available even when genetic sequencing indicates suitability for abatacept treatment (Siggs et al., 2019). An analysis in Germany showed a success rate of 75% of acceptance for reimbursement requests for off-label dermatological indications (Seidenschner et al., 2017). In Belgium, there is no option to get official reimbursement for off-label use, but occasionally costs are covered by the company or solidarity funds (Dooms et al., 2016).

Etidronate for Pseudoxanthoma Elasticum: No Longer Commercially Available

Etidronate is a bisphosphonate and was originally developed to prevent and treat osteoporosis. The product has been replaced by alternative bisphosphonates with a better benefit-risk profile over time (Wiesner et al., 2021). This led to the discontinuation of marketing of virtually all etidronate products in Europe (Ministerie van Volksgezondheid, Welzijn en Sport, 2018). However, drug repurposing experiments in an academic hospital had pointed towards etidronate as the bisphosphonate with the highest potential to delay ectopic mineralization given its predominant inhibition of calcium precipitation and hydroxyapatite binding instead of inhibiting osteoclasts like newer bisphosphonates do (Kranenburg et al., 2018; Bartstra et al., 2020). This investigator-initiated single-center, randomized, placebo-controlled trial with 74 patients held in 2015–2016 showed promising effects of etidronate in patients with pseudoxanthoma elasticum (PXE) (Kranenburg et al., 2018; Bartstra et al., 2020). Hence, the compound could be effective for the treatment of PXE, a rare autosomal recessive disorder (prevalence 1–9 in 100,000) (Orphanet, 2021) that leads to ectopic calcification of elastic tissues, including the arteries, skin and Bruch's membrane (BM) in the retina. (Bartstra et al., 2020; Risseeuw et al., 2020).

The availability of etidronate has been driven essentially by the dynamics of the osteoporosis market: when better or safer alternatives entered the market, they replaced etidronate. The lack of commercially available etidronate hampered both clinical development and clinical use for the new rare indication by academics. The earlier trial was not designed for regulatory purposes and regulators may need different or additional data for the next steps to commercialization. For example, regulators may prefer other endpoints than clinical researchers or require extensive or long-term safety data. The clinician from the academic hospital who performed the trial was driven by scientific curiosity and the need to treat patients. A lack of understanding of regulatory requirements by clinicians and appropriate timing of interaction with regulators or guidance delayed the commercialization of this academic invention.

Mexiletine for Non-dystrophic Myotonia: Failure to Register an Old Drug for a Fair Price

Mexiletine is a class 1b anti-arrhythmic drug and has been on the European market since the 1970s. (Postema et al., 2020). Newer anti-arrhythmic drugs have largely replaced mexiletine, but a small group of patients have no alternative. Over time, mexiletine products have been taken off the European market and since 2004 patient access is maintained by import mainly from Japan, Canada and the United States and local pharmacy preparations (compounding). Next to its use for cardiological indications, mexiletine has been used off-label since the 1980s worldwide for the treatment of non-dystrophic myotonias (NDMs) (Pouget & Serratrice, 1983; Trip et al., 2006). NDMs are rare muscle hyperexcitability disorders and characterized by delayed muscle relaxation after voluntary contraction. This leads to symptoms of pain, fatigue, muscle stiffness and weakness (Stunnenberg et al., 2020). In December 2018, mexiletine received a European marketing authorization as a repurposed OMP for the treatment of NDM. Because it is registered as an OMP, a market exclusivity of at least 10 years apply creating a *de facto* monopoly. The price of the newly registered mexiletine, in the same dosage and method of administration (capsule for oral use), has been criticized heavily and rejected by some payers (Postema et al., 2020; Zorginstituut Nederland, 2021b; National Institute for Care and Health Excellence, 2021).

The orphan drug license of mexiletine for NDM is largely based on academic clinical studies and could be seen as a successful repurposing trajectory because it resulted in an officially registered OMP. However, the unexpected price increase has had an opposite effect, hampering access for both indications instead of stimulating rare disease treatment accessibility.

DISCUSSION

The data indicate that in recent years about one out of five OMPs has been repurposed. This is similar to findings by Davies et al. (2017). Langedijk et al. (2016) found, not specific for OMPs, that 13% of all approved drugs by EMA in 2014 and 2015 were repurposed. We established that developments that start in

TABLE 2 | Identified hurdles in the three cases of drug repurposing for rare diseases. CTLA-4 HIS: cytotoxic T-lymphocyte antigen four haploinsufficiency. PXE: pseudoxanthoma elasticum. NDM: Non-dystrophic myotonia.

	Hurdles	Abatacept CTLA-4 HIS	Etidronate PXE	Mexiletine NDM
Healthcare professionals involved in drug repurposing	1. Lack of knowledge of and alignment with the regulatory and reimbursement frameworks	Obtaining reimbursement is challenging and time-consuming	No incentive for clinicians to engage in regulatory activities	—
Private sector	2. Off-label use is not a major concern if sufficiently supported by scientific evidence. This slows down evidence development	Consensus amongst doctors based upon pathophysiological mechanisms	Unavailability hampers clinical use and scientific development	Has been used off-label since the 1980s
	3. Private actors do not invest because of uncertain regulatory and reimbursement outcomes	Viable business case not likely due to patent expiration	—	—
Payers	4. Failure to register an old drug for a fair price, resulting in commercialization as a high priced orphan drug	—	—	Price increase as a result of monopoly position
	5. Hesitant to pay for off-label use, when scientific evidence is limited	Reimbursement only on case-by-case basis	—	—
Regulators	6. Regulatory frameworks not fully adapted for repurposing, both in terms of processes and data/evidence requirements	Case studies not eligible for regulatory purposes	Investigator-initiated trial not eligible for regulatory purposes	—
	7. Regulators are not used to other types of applicants than industry, e.g. academics, doctors, public-private partnerships	—	No appropriate guidance or timing of interaction	—

academia encompass mainly the advancement of existing drugs for new indications in a diverse set of therapeutic areas. In contrast, the developments that started in industry mostly focus on modified applications and the field of oncology. This stresses the potential of academia driven drug repurposing to benefit a broader range of patients.

However, the three cases illustrate that academia faces a diversity of hurdles in different stages of drug development. We summarized the issues by key actor involved as outlined in **Table 2**. The main hurdles from the side of healthcare professionals involved in drug repurposing were that they have little knowledge about regulatory and reimbursement processes and instead are focused on scientific progress and patient care. In the case of etidronate for pseudoxanthoma elasticum for example, clinicians seem to focus mainly on providing the scientific evidence in drug repurposing and due to lack of knowledge about the regulatory framework as well as restricted time in academia, ideas for drug repurposing might fail unnecessarily or are prematurely halted (Verbaanderd et al., 2020; Starokozhko et al., 2021). In addition, when a drug is available for patients and reimbursed without registration, e.g., as off-label use, they may not be motivated and incentivized to assist in steps towards commercialization. This is supported by the findings of Dooms et al. (2016). Another scenario is that they fail to create access to patients, since they are not aware that regulatory authorities and payers keep other – often higher – standards for either registration or reimbursement. Similar issues were identified for abatacept for CTLA-4 haploinsufficiency. This case, however, in addition highlights, the perceived lack of perspective of sufficient return of investments. The very small and uncertain market in combination with a product already being available for another indication may de-incentivize commercial development and reimbursement. A similar situation may have existed for mexiletine. This drug was ultimately marketed as a repurposed orphan drug for an extremely high price. No private party or academic initiative had led to a timely intervention, to secure access to patients through a formal

authorization procedure. Also in this case, without the incentive of market exclusivity, investors are probably reluctant to go through the burden of compiling a dossier. However, monopolization of the market to re-introduce old drugs—as also was the case for CDCA (Sheldon, 2018)—should not be encouraged (Postema et al., 2020). In fact, the orphan drug regulation has never been set up to stimulate this kind of developments, which may even have the opposite effect: drugs become inaccessible due to the extreme price (Technopolis Group & Ecorys, 2020). This, and also the length of market exclusivity has received attention in the evaluation of the orphan drug legislation which is currently taking place (European Commission, 2021). The outcomes of the evaluation could impact drug repurposing for rare diseases as specific incentives, such as the market exclusivity, may change.

Limitations

The cases illustrate some hurdles but we certainly did not provide a structured review of all potential barriers to development of repurposed orphan drugs.

The 5-year period 2016–2020 that we investigated is the most recent period but not necessarily a good reflection of the dynamics in the OMP market. The regulation on OMPs in the European Union went into force in 2000 and until 2017, 142 OMPs were authorized (Technopolis Group & Ecorys, 2020). More than half of these OMPs were authorized between 2012 and 2017. Also, the therapeutic areas of authorized OMPs shifted over time (Technopolis Group & Ecorys, 2020). Altogether, the nature of OMPs, and also the amount of drug repurposing, may have differed in more distant time periods. Although we have shown that indeed drug repurposing by academia plays an important role for OMPs, it would also be interesting to study their contribution to development of non-orphan as a comparison.

In addition, industry may have been involved in more drug repurposing activities than we were able to trace due to publication bias or the availability of only brief abstracts. Also,

for older publications the CoI statements were sometimes not included in an article where collaborations with industry may have otherwise been mentioned. Lastly, although we show that drug repurposing for rare diseases mostly starts in academia, it is unclear how the contribution of academia relates to the contribution of industry in registering an OMP. It would be interesting to investigate what activities still had to be done from the moment that industry got involved. This may help to smoothen the collaboration between academia and industry.

Recommendations and Outlook to the Future

An integrated solution for the described hurdles may require both changes in the interaction between key actors and changes in legislation. Suggestions for change have been made by Austin et al. (2021) including, amongst others, improved education, financial and regulatory incentives that create viable business cases, and reimbursement strategies for off-label use. We propose the following recommendations for changes in legislation that build on these suggestions:

First, when reality shows that some repurposed drugs are not being registered and widespread off-label use is the result, supported by scientific evidence, other options to reach long-term availability and appropriate use driven by academia could be explored (“label change last” (Austin et al., 2021)). For example, this could entail close monitoring and structured assessment of off-label use by regulators and reimbursement authorities, and providing regulators with the right to change a label or add an indication to a label as proposed by Gyawali et al. (2021). Second, society should be willing to support rare disease drug repurposing by facilitating reimbursement at a fair price. When payers pressure for the lowest possible prices for generic drugs, sustainable commercial drug repurposing is not feasible. For example, a solution could be that governments compensate companies that repurpose drugs based on costs (Van den Berg et al., 2021), or that repurposed drugs are exempted from external reference pricing policies.

Next to changes in legislation, we propose two recommendations for improved interaction between key actors:

First, healthcare professionals involved in drug repurposing should become better educated in the regulatory field and understand the advantages of a marketing authorization over off-label use. Increasing knowledge in academia about the regulatory system, perhaps centralized on a national level as well as international efforts such as the STARS initiative can increase alignment (Starokozhko et al., 2021). Second, healthcare professionals involved in drug repurposing together with private and regulatory actors will have to learn and understand each

other’s drive and language. Early dialogue between healthcare professionals involved in drug repurposing, industry, payers and regulators, will help to create a common ground and clear route to long-term availability and appropriate use of a drug. Also, involvement of academia may lead to public-private partnerships in which societal values are captured, limiting the possibilities for exploitation of monopolies.

CONCLUSION

This study shows that drug repurposing for rare diseases mainly starts in academia, but there are many hurdles for these repurposed drugs to successfully reach patients. The results of our study may be used to operationalize the role of academic researchers and not-for-profit stakeholders in drug repurposing as highlighted by the European Commission (European Commission, 2020). We proposed changes in legislation or reimbursement schemes to ensure sustainable commercial drug repurposing. Yet, also the needs and skills of healthcare professionals involved in drug repurposing, industry and regulators need to become better aligned to stimulate successful marketing and reimbursement of repurposed drugs for patients with a rare disease.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Concept and design: SvdB, HL, CH Acquisition of data: SvdB Analysis and interpretation of data: SvdB, SdV, HL, CH Drafting of the manuscript: SvdB, SdV, CH Critical revision of the paper for important intellectual content: SvdB, SdV, HL, CH Supervision: SdV, HL, CH.

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Conflict of Interest: SvdB, SdV and CH are members of the platform Medicine for Society, an academic initiative that aims to support sustainable access to medicines for rare diseases (including mexiletine).

The reviewer HS declared a shared affiliation, with no collaboration, with one of the authors HGML, to the handling editor at the time of the review

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