CHAPTER 23

The Future of Drug Repositioning: Old Drugs, New Opportunities

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1. INTRODUCTION

Drug repositioning is a promising field in drug discovery that identifies new therapeutic opportunities for existing drugs. In order to circumvent some of the most expensive drug discovery processes, companies pursue this strategy to increase their productivity (new drugs to market) by reducing the discovery and development timeline. This decreases the overall cost of bringing the drug to market because the safety and pharmacokinetic profiles of the repositioned candidates are already established.

The term ''drug repositioning'' has been used interchangeably with ''drug repurposing'' or ''drug reprofiling.'' All these expressions are relatively synonymous for describing the process that seeks to discover new applications for an existing drug that were not previously referenced and not currently prescribed or investigated (Table 1). For consistency, this review will refer to all research that explores the multiple therapeutic applications of drugs as drug repositioning.

Several comprehensive reviews on the strategy and advantages of drug repositioning have been published [1–3,12–14]. This review will summarize novel methods being used to accelerate the discovery of old drugs that could potentially treat new indications, either *via* the established mechanism of action or by identification of new ones. Representative case studies of these approaches to therapeutics discovery will also be highlighted. Researchers have previously identified repositioned drugs by serendipity [1], novel insights, or target searching. The innovative strategies directed toward drug repositioning discussed in this review are phenotypic, high throughput, and *in silico* screening of commercial, public, and pharmaceutical compound libraries, the prospective mining of drug/activity databases, the exchange of compound information in collaborative networks, and data collection from the internet and social networks (Figure 2).

2. PERSPECTIVES OF DRUG REPOSITIONING

During the past two decades, the drug repositioning mindset has led to the discovery of several important and profitable drugs. Such an approach often allows pharmaceutical companies to extend a drug's patent life and to reduce the cost of drug development.

2.1. Previous case studies

Sildenafil (**1**; Figure 1), also known as Viagra®, is one of the most notable drugs that has been repositioned. It is a phosphodiesterase (PDE) type 5 inhibitor that was originally developed to treat angina, but it was

Table 1 Descriptions of various terms for drug repositioning

Term	Description
Drug repositioning	Finding new uses outside the scope of the original medical indication for existing drugs [1] or developing new indications for existing drugs or biologics [2]
Drug repurposing	Identifying, developing, and commercializing new uses for existing or abandoned drugs [3]
Drug reprofiling	Reducing the risks and costs associated with drug development with the advantage that the drug has already undergone preclinical and clinical testing [4]
Drug rediscovery	Investigating new uses for currently prescribed drugs [5]
Drug redirecting	Described as drug repositioning [1]
Drug reformulating	Finding ways to modify a formulation to allow a drug to enter a new market [6]
Therapeutic switching	Opening up new possibilities for old medicines that were not appreciated at the time of original discovery and can be made therapeutically different through new formulations [7]
Indication switching	Exploiting established drugs that have already been approved for treatment [8]
Indications discovery	Identifying new indications for clinical candidates that have been discontinued for their primary indications for reasons other than safety [9]; or research units that aim to find new uses for compounds that had failed in clinical trials or still in development [10,11]

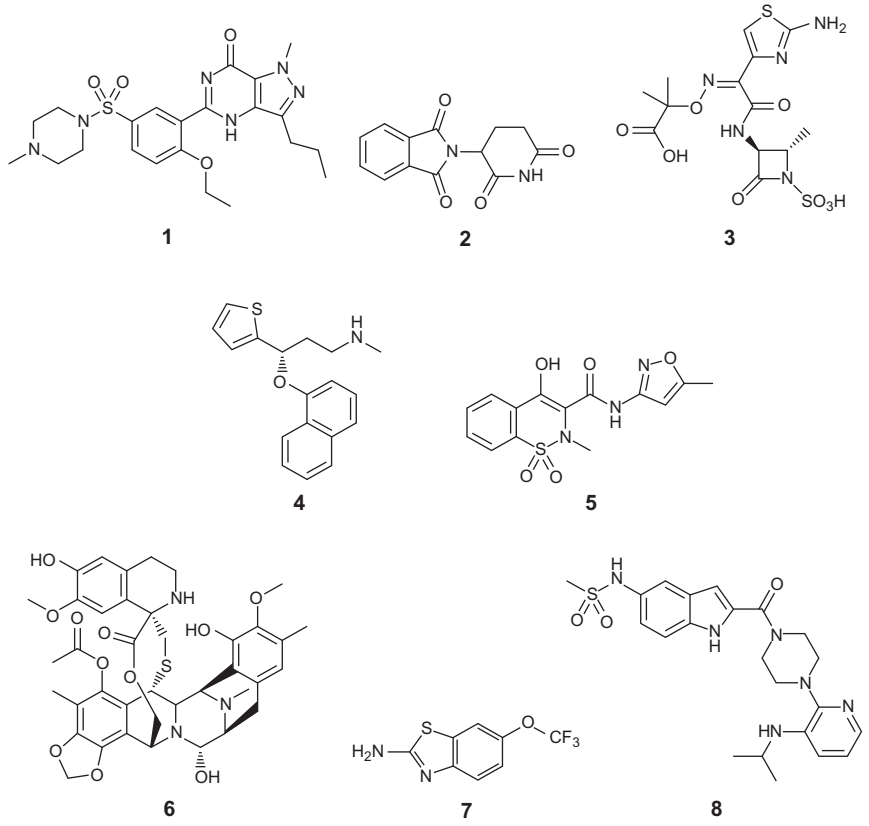

Figure 1 Repositioned drugs of relevance to this review.

repositioned during clinical testing to treat male erectile dysfunction in order to fully take advantage of its therapeutically relevant side effect profile [15]. As a result of this serendipitous repositioning, sildenafil citrate has grossed over $15 billion in revenue since its release in 1998 [16].

Another notable example is thalidomide (**2**), a sedative that received much notoriety in the early 1960s due to its severe teratogenic effects [17]. Despite its infamy, thalidomide was repositioned to treat erythema nodosum leprosum and was approved for the treatment of this form of leprosy by the Food and Drug Administration (FDA) in 1998 (Thalomid®) with the caveat of its teratogenic effects [18]. Moreover, thalidomide was repositioned again to treat multiple myeloma and FDA approved in 2006 in combination with dexamethasone for newly diagnosed multiple myeloma patients [19].

2.2. Recent case studies

Some recent examples of drug repositioning include aztreonam (**3**) and duloxetine (**4**). Aztreonam is a monobactam antibiotic that was approved in 1986 for the treatment of Gram-negative bacterial infections *via* intravenous or intramuscular injection (Azactam®) [20]. This drug was marketed to treat bacterial infections and is safe for patients with penicillin allergies [21]. Previously, aztreonam was only approved for intravenous or intramuscular injection but not for inhalation because the solution for aztreonam contains an arginine buffer. Arginine is a substrate for nitric oxide production in many organs, and the generation of nitric oxide can lead to tissue injury [22]. Previous inhalation studies in patients with cystic fibrosis demonstrated that long-term use of inhaled arginine was associated with airway inflammation and deterioration of symptoms [23]. Aztreonam was later repositioned as Cayston® for inhalation by reformulating the solution to contain lysine rather than arginine [24]. In February 2010, the FDA approved aztreonam for inhalation *via* an ultrasonic nebulizer for the treatment of pulmonary *Pseudomonas aeruginosa* infections in cystic fibrosis patients [25].

Duloxetine is a serotonin and norepinephrine reuptake inhibitor which is marketed for major depressive disorder (Cymbalta®) in the United States and for stress urinary incontinence (Yentreve®) in Europe [1]. Trial studies revealed that duloxetine reduced painful physical symptoms in depressed patients [26], which led to its FDA approval for the management of diabetic peripheral neuropathic pain (DPNP) in 2004 [27] and fibromyalgia in 2008 [28]. Due to its effectiveness at relieving pain in DPNP and fibromyalgia patients, its effect on chronic lower back pain (CLBP) was evaluated in patients with CLBP. Double-blind studies on the analgesic effects of duloxetine showed significant improvement in patients with CLBP with a maintained analgesic effect for over 40 weeks [29,30]. In November 2010, the FDA approved the use of duloxetine to treat chronic musculoskeletal pain, including discomfort from osteoarthritis and CLBP [31]. Duloxetine has earned over $9 billion in revenue since its release in 2004 for all of its indications [32].

3. NEW STRATEGIES TOWARD DRUG REPOSITIONING

This section reviews the novel approaches toward drug repositioning being developed in both academic institutions and the pharmaceutical industry (Figure 2). These strategies utilize advances in modern technology to explore possible indications for drugs that have entered clinical trials or are clinically approved. The methods described herein could discover drugs that could be directly repositioned, find lead compounds

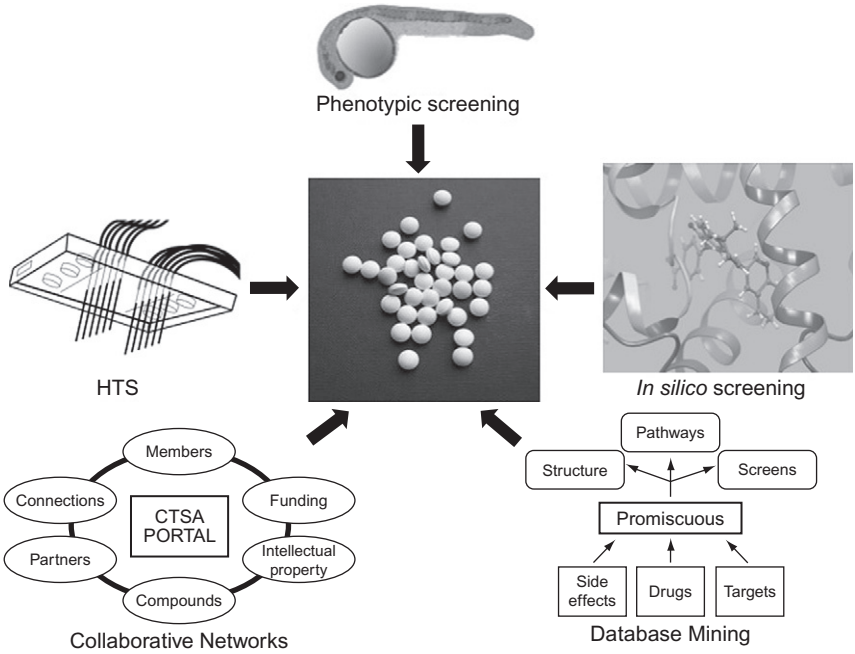

Figure 2 New strategies for drug repositioning.

that could suggest the screening of other drugs in their class, or identify drugs that would require minor structural changes for optimization against their new target. It should be made clear that the strategy of drug repositioning, while holding out the promises of being less costly and taking less time than other methods of drug discovery and development, is never a trivial exercise and may eventually prove to be as costly and time consuming as other drug development strategies. Moreover, repositioning approaches that yield only nonoptimal starting compounds will most likely offer only slight advantages over more standard routes to new drugs.

3.1. Phenotypic screening

The use of zebrafish (*Danio rerio*) as an animal model for developmental research allows quick and economical testing of the efficacy and safety of hundreds of compounds, often in parallel [33]. Zebrafish are small freshwater tropical vertebrates whose embryos develop *ex utero* within 2–3 days [34] and are ideal organisms for high-throughput phenotyping because their embryos are optically transparent. This allows for visual detection of functional and morphological changes without

sacrificing the organism. Moreover, females are able to produce up to 300 eggs at a time, and these embryos are less than a millimeter in diameter. Due to their small size and large quantities, numerous embryos can be screened simultaneously [33]. A drug repositioning screen using larval zebrafish allows for rapid *in vivo* screening and is a cost-effective way of determining potential candidates for further development. Recent improvements in automated high-throughput chemical assays involving zebrafish have increased productivity and aided the data assessment of these high content screens [34].

3.2. HTS methods

The high-throughout screening of libraries of known drugs has become a popular method of discovering compounds for repositioning. Advances in technology have engendered innovations in automation, imaging software, and liquid-handling robots to support high-throughput screening (HTS). These advances allow researchers to test a multitude of compounds against targets of interest or in various assays. Additionally, new software has been developed to interpret, calculate, or generate data from these screens [14,35,36]. Flow cytometry is a sensitive and quantitative platform for the measurement of particle fluorescence [37] and has been employed in the drug repositioning efforts toward HIV combination therapy [38]. Microfluidic chip technology allows the miniaturization, integration, automation, and parallelization of chemical or biochemical assays on a silicon or glass chip [39,40]. This lab-on-a-chip technology is cost-effective, and the chips offer increased sensitivity and high throughput by implementing parallel sample processing and miniaturization of integrated on-chip components [41].

3.3. *In silico* screening

A prospective approach for drug repositioning using molecular modeling, cheminformatics and virtual screening (VS) can be effective and efficient because of its inherently low cost and rapid testing of multiple hypotheses. VS can be broadly grouped into two categories: ligand-based VS (based on the similarity of ligands) and structure- or target-based VS (based on the predicted interactions of ligands with enzymes or receptors). This latter category is generally considered to include computational docking of agents into experimentally determined target structures, or into computationally predicted structures. A recent review categorized the types of protein families pursued by VS approaches and compared of the successes of ligand- versus target-based VS [42]. While there is more literature precedence for structure-based VS efforts versus those that are ligand-based, the latter can generate more potent hits,

particularly when both two- and three-dimensional approaches are implemented. Thus, developments in algorithms for VS-based drug discovery can support new target repositioning programs. Though VS of targets against *in silico* libraries of approved drugs has been successful for initiating drug repositioning campaigns [43], VS of much larger, target-agnostic compound libraries is far more common. Nonetheless, *in silico* screens of large libraries that contain approved agents can also ultimately identify established drugs.

3.4. Database mining

The field of systems biology offers unprecedented opportunities to mine data bases for drug repositioning [44]. Systems biology examines the relationships between biological targets and pathways to formulate models as frameworks to integrate and interpret multiple data sources for drug discovery and development [45]. The goal of this approach is to understand the physiology of the disease from the perspective of the whole organism through the use of computational and informatics tools, rather than only focusing on one or two biological targets [44].

For example, PROMISCUOUS is a publicly available, network-focused program that combines three different types of data: drugs, proteins, and side effects [46]. This resource provides data on protein–protein and protein–drug [47] interactions along with side effects [48] and structural information and enables the investigation of off-target effects that may be useful in drug repositioning. The network consists of 25,000 drugs, 12,000 proteins, 104,000 associated protein–protein interactions, and 21,500 drug–protein relationships acquired from public databases [46]. With PROMISCUOUS, researchers can identify potential candidates for drug repositioning by examining the side effect data and the different interactions available from the databases.

3.5. Collaborative networks

An important new direction in compound repositioning is the development of collaborative networks that bridge the gap between pharmaceutical companies, biotechnology firms, and academic institutions. One new effort in this area is the Clinical and Translational Science Award (CTSA) Pharmaceutical Assets Portal [49,50]. This collaborative network is constructed on the foundation of the CTSA consortium which is currently comprised of 55 research institutions and was launched in 2006 by the NIH [51]. The primary goal of the consortium is to speed the translation of medical research into treatment and strategies for patients. The Portal is headquartered at the University of California-Davis' Clinical and Translational Science Center and was established in 2008 to collect

discontinued, late-stage compounds of pharmaceutical companies and allow academic and nonprofit researchers to investigate the repositioning of these compounds to treat disease [52]. The Portal is sponsored jointly by Pfizer and the National Center for Research Resources (NCRR). It contains many of the core functions that would be necessary to make the Portal successful: Foci-of-Expertise, Partnership for Cures (a nonprofit organization that funds ''Rediscovery Research'' project), University-Industry Demonstration Project, and the Center for World Health and Medicine (CWHM) [53]. The Portal plans to house, maintain, and distribute a repository of discontinued compounds (compounds that are no longer preclinical or clinical candidates). In early 2011, the Portal issued a request to the pharmaceutical industry to establish a consortium with the goal of collecting discontinued compounds for this central repository. In an example of how such a Portal might work, Pfizer signed a collaborative agreement with Washington University in St. Louis, MO in 2010, allowing researchers access to information about discontinued compounds from the Pfizer collection [11]. Another collaborative network is sponsored by Collaborative Drug Discovery (CDD) [54]. CDD aggregates and hosts public access data relevant to drug discovery that is deposited with them by leading research groups worldwide. These data could open the door to the discovery of new uses for old drugs, primarily in the area of neglected diseases.

4. CASE STUDIES OF DRUG REPOSITIONING STRATEGIES

The following case studies provide glimpses into current efforts toward drug repositioning employing the aforementioned strategies. Further research and development efforts could bring these already approved drugs or lead compounds to the public for use in new indications.

4.1. Phenotypic screening

Phenotypic screening with zebrafish larvae offers the advantage of allowing the drug response in whole organism to be monitored with the added advantage that zebrafish have been shown to have a high degree of conservation of drug responses with humans [55]. This approach was utilized to identify potential candidates to treat multiple sclerosis (MS) [56]. The aim was to identify a potential candidate for therapeutic remyelination enhancement *via* a phenotypic screen with zebrafish [4]. For this study, a library of 1170 compounds that contained marketed drugs and known bioactive substances was screened. Dorsally migrated $olig2^+$ cells in the zebrafish were monitored in a three-screen cascade: the first screen blindly counted the number of migrated $olig2^+$ cells in response to

compound exposure; the second screen identified oligodendrocyte differentiation and myelination by active compounds from the first screen and compounds of interest from the literature; then, selected compounds were subject to a series of tertiary screens [4]. The researchers were able to identify several compounds from the first two screens that were known to have effects on oligodendrocytes or myelination, which validates their screening approach. The study also uncovered potential remyelination-promoting compounds, including the cyclooxygenase (COX-2) inhibitor isoxicam, **5**, that were not previously tested for this indication [57].

4.2. HTS methods

The National Institutes of Health's Chemical Genomics Center (NCGC) has created a collection of approved and investigational drugs for HTS purposes. This allows researchers to screen these drugs against new targets in an effort to reposition them for other indications, such as rare and neglected diseases [58]. With its quantitative HTS approach, the NCGC has screened their collection against more than 200 cell-based models of disease and characterized the pharmacology of each compound. The NCGC Pharmaceutical Collection (NPC) is publicly accessible *via* PubChem and serves as a resource for validating new models of disease and understanding the molecular basis of disease pathology and intervention [59]. In addition to repositioning the drugs, the NCGC will also screen the collection in their Tox21 system, which is a high-speed robotic screening system that evaluates potential compound toxicities [60]. Other public and private collections of clinically approved drugs are also available for HTS [11,14,35,61].

A quantitative HTS format was utilized to assess approximately 2800 clinically approved drugs from the NPC at 15 different concentrations in search of small-molecule inhibitors of NF-κB signaling [62]. Regulation of the NF-κB pathway is implicated in a myriad of important physiological processes, while dysregulation of this transcription factor is associated with autoimmune diseases and cancer [63]. A NF-κB mediated β-lactamase reporter gene assay was used to determine inhibition of the NF-κB signaling pathway, which is activated by tumor necrosis factor alpha (TNFα), interleukin-1, and bacterial lipopolysaccharides [64]. By adding TNFα as a positive control, researchers were able to perform fluorescence resonance energy transfer (FRET) analysis to determine β-lactamase expression. From the initial screen of 2816 NPC compounds, 55 compounds exhibited activity, and 19 compounds were further analyzed for their mechanism of inhibition, effect on apoptosis, and cytotoxicity [62]. Overall, many agents were identified that were previously approved for other clinical uses, including several anticancer drugs not previously known to inhibit the NF-κB pathway. The most potent compound for

NF-κB pathway inhibition was found to be ectinascidin 743 (**6**), which is approved for the treatment of ovarian cancer [65].

4.3. *In silico* screening

The simultaneous inhibition of pteridine reductase (PTR1) and dihydrofolate reductase (DHFR) in *Leishmania major* represents an innovative approach to the development of new antiparasitic drugs [66]. In a search for non-folate inhibitors of *L. major* PTR1, an initial virtual screen of ~350,000 compounds from the Available Chemicals Directory (ACD) database was performed against the published three-dimensional crystal structure of LmjPTR1 [67]. A comprehensive summary of the *in silico* screen is outlined in Figure 3 [68]. Filtering of the 21,394 docked structures was performed on the basis of the quality of the docked molecules' interactions with the LmDHFR binding site, followed by visual assessment of the specific ligand–protein interactions. This second assessment identified unique interactions between ligands and LmDHFR that were not present in the human DHFR (hDHFR). From this, a set of 53 molecules was selected for screening and compound **9** was found to be the most potent inhibitor of LmjPTR1.

From aminothiadiazole **9**, design of analogs was performed by iterative analysis of active compounds docked into the drug binding site, with cross-docking against hDHFR to eliminate those likely to bind to the human enzyme. Taken together, these docking experiments led to the extension of the thiadiazole ring of **9** into an adjacent lipophilic pocket, providing benzothiazole **10**, which displayed a threefold improvement in potency and retained selectivity over hDHFR. Further explorations of the core provided **7** (riluzole) [69], an established CNS agent that is currently utilized for amyotrophic lateral sclerosis. Importantly, though the authors

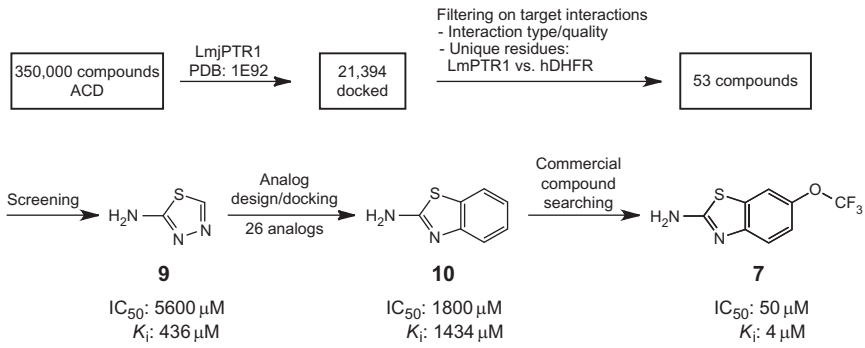

Figure 3 *In silico* identification of anti-leishmanial agents.

initially intended to identify novel LmDHFR inhibitors from a commercial compound set, they identified an established drug that has potential as an anti-leishmanial therapy. This result suggests this type of *in silico* screening approach could be more directly applied to drug repositioning by selection of agents from libraries of approved drugs (rather than from large, random libraries).

5. FUTURE DIRECTIONS OF DRUG REPOSITIONING

5.1. Predicting new targets for known drugs

In this age of target-based drug discovery, the notion of unselective drugs is commonly considered to be undesirable, as off-target effects can be a source of toxicity or drug side effects. However, ''selectivity'' is often an illusion; while it is conceivable to screen compounds for cross-reactivity against all *known* off-targets, there are always emerging targets and pathways that could not possibly be considered during a drug discovery program. Indeed, for a number of drugs, polypharmacology is desirable for the intended effects, as the inhibition of parallel or redundant pathways may be required [70]. In addition, it would be attractive to utilize cross-reactivity between targets to generate new therapeutic approaches.

A method for identifying likely molecular targets for drugs based on ligand similarity properties has been described [71]. This approach could detect new targets for established drugs that may be pursued for drug repositioning and could help reveal the source of adverse side effects. This was achieved by comparing drugs and investigational agents to a database of established ligand/target combinations. While it is tempting to focus on target sequence/structure similarity, this study showed that *ligand similarity* is in many cases better able to provide compelling predictions. Using a similarity ensemble approach [72], the authors were able to make a prospective prediction of pharmacology based only on ligand similarities, and to suggest new pharmacology of known agents. In a striking example, the HIV protease inhibitor delavirdine (**8**) was predicted and confirmed to bind to the histamine H_4 receptor (which does not bear structural similarity to HIV protease) with a K_i of 5.3 μM. While the potency difference between target and off-target is high in this case, the K_i against H_4 is within the steady-state plasma concentrations for the drug (15 μM), and thus the H_4 activity can help explain the known side-effect profile of the drug. While this is a demonstration of the impact that this cheminformatic approach can have on predicting toxicology and side-effect profiles, these methods can also provide a new approach towards drug repositioning by providing initial starting points for assessment of known agents against targets of putative importance to disease.

5.2. Pharmacovigilance 2.0

The future of drug repositioning may be driven by proactive analysis collections of side-effect data with new methods of data mining and new sources of side-effect information. The tracking of side effects, or adverse drug reactions (ADR), is commonly referred to as pharmacovigilance [73]. Pharmacovigilance has been accepted as the so-called clinical Phase IV, or postmarketing surveillance, of compound development and is undertaken to detect rare or long-term adverse events that were not detectable in Phase I–III trials. The potential of enhanced pharmacovigilance in drug repurposing has recently been highlighted by ''type 2'' pharmacovigilance [74] or pharmacovigilance 2.0 (PV2.0), which will use data from the internet and exploit the distributed knowledge or interests of large groups to the collection and analysis of potentially useful drug side effects (Figure 4).

Pharmacovigilance typically involves the passive monitoring of ADR by telephone systems like RADAR [75] (Research on Adverse Drug events And Reports) at Northwestern's Feinberg School of Medicine or the FDA's MedWatch [76]. While retrospective data mining of electronic health records (EHR) and other databases has been a staple of pharmacovigilance for some time [77,78], barriers to this process have recently been lowered by the use of ASTER, a spontaneous triggered electronic reporting system that collects data from physicians as they enter it into the EHR [79]. Rather than using electronic records, surveying physicians, or mining governmental databases, PV2.0 strategies will feature the active

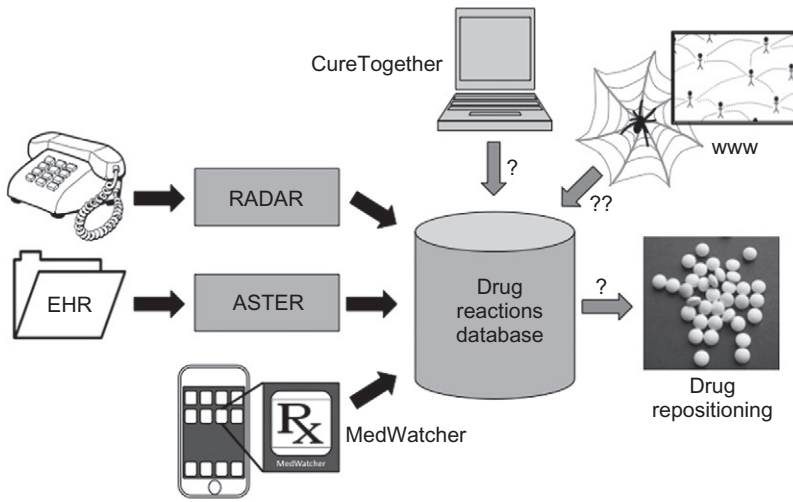

Figure 4 Potential sources of drug side effect data in pharmacovigilance and PV2.0.

mining of the web and social networking information to collect DRs that could potentially be used to reposition known drugs. Pharmacovigilance has already entered the internet age in both passive and active forms. In the passive mode, data on drug side effects are collected using data mining of information gathered from web search virtual robots. For example, passive data mining has been used to obtain patient comments on the effects and side effects of antidepressants [80]. The active mode involves the collection of data through smart phone applications, like MedWatcher (a program that allows the reporting and distribution of adverse events) [81], or affinity communities on the web, like CureTogether (a sharing website for patients to offer views on their medications) [82]. A mix of passive and active data gathering has already been employed to track patient views on the deployment of the H1N1 vaccine in Canada [83].

In work that is suggestive of how PV2.0 could be deployed to a broader audience, drug anticounterfeiting efforts linked by cell phone applications have been developed [84]. This process features scratch-off numeric codes on the pharmaceutical product that the purchaser sends as a text message to the analytics company to determine the product's authenticity. During this cell phone transaction, the analytics company can also survey the individual. It is reasonable to assume that similar feedback systems could be used to extract beneficial DRs from consumers that could be used in repositioning efforts. With the technology of text analytics and smart phone applications becoming more readily available, data mining of web sites and active engagement of social media networks could soon be more widely applied to the repositioning of drugs.

6. CONCLUSION

With economic and financial demands on the pharmaceutical industry to produce more drugs for its pipeline, methods that accelerate drug repositioning efforts are becoming increasingly important. This review presented a wide variety of innovative approaches currently being used to jumpstart repositioning efforts. These strategies include phenotypic, high throughput, and *in silico* screening, database mining, and the formation of collaborative networks. Case studies for the different screening strategies were provided to add insight into the use of modern technology in the field and approaches that go beyond the scope of the current drug repositioning efforts were addressed. The field of drug repositioning appears to be moving toward a broad, consortium approach. This trend is exemplified by groups like the CTSA Pharmaceutical Assets Portal and the development of more collaborative academic–industrial partnerships. In addition, there is the potential for drug repositioning to capitalize on the

popularity of social media with the emergence of strategies like PV2.0. Presumably, consumers could eventually be directly involved in the discovery of new therapeutic uses for existing drugs.

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