Chapter

Drug Repurposing in Neurological Diseases: Opportunities and Challenges

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Abstract

Drug repurposing or repositioning refers to "studying of clinically approved drugs in one disease to see if they have therapeutic value and do not trigger side effects in other diseases." Nowadays, it is a vital drug discovery approach to explore new therapeutic benefits of existing drugs or drug candidates in various human diseases including neurological disorders. This approach overcomes the shortage faced during traditional drug development in grounds of financial support and timeline. It is especially hopeful in some refractory diseases including neurological diseases. The feature that structure complexity of the nervous system and influence of blood–brain barrier permeability often becomes more difficult to develop new drugs in neuropathological conditions than diseases in other organs; therefore, drug repurposing is particularly of utmost importance. In this chapter, we discuss the role of drug repurposing in neurological diseases and make a summarization of repurposing candidates currently in clinical trials for neurological diseases and potential mechanisms as well as preliminary results. Subsequently we also outline drug repurposing approaches and limitations and challenges in the future investigations.

Keywords: drug repurposing, brain injury, neurological diseases, therapeutics

1. Introduction

Neurological disorders are devastating diseases which usually occur in the brain, spinal cord, cranial nerves, peripheral nerves, and so on. It has reported that there are more than 600 kinds of neuropathological conditions including epilepsy, brain tumor, Parkinson's disease, Alzheimer's disease, and stroke. Nowadays, it is estimated that more than 1 billion people suffer from neurological disorders, seriously affecting people's life quality [1]. These kinds of diseases are especially prevalent in developing countries at any stage of age [2, 3]. There are several factors contributing to etiology of neurological disorders such as aggravating tendency of aging population, irregular diet, and insufficient exercise [4].

Drug therapy is an important way for curing neurological diseases in the clinic. Nevertheless, serious neurological disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) are usually incurable in late stages of diseases with current therapeutic intervention [5, 6]. In the meantime, drug treatment often becomes less effective and causes serious side effects due to individual differences. Taking

epilepsy as example, nearly 30% of epileptic patients are unable to obtain seizure control following treatment with marketed drugs [7, 8]. In addition, they have no significant effect on the improvement of cognitive dysfunction in patients with severe epilepsy [9]. Thus, it is essential for investigation of more effective and/or less toxic CNS targeted drugs.

Drug repurposing, also known as drug reprofiling or drug repositioning, includes the development of new uses and dosage forms for existing drugs or drug candidates. It is regarded as an economic and practical strategy [10]. Drug repurposing avoids the defects of new drug development. Compared to the drug repurposing, development of new drugs consumes much more time and huge investments. It is roughly reported that the cost from basic research for a new drug to clinical trials is 2.6 billion US dollars [11] and it often takes an average of 13–15 years [12]. Although more and more drug candidates are developed, many cases have failed in recent years [13]. Most of new drugs are withdrawn from the market due to unsatisfactory efficacy or intolerable side effects [14, 15]. Therefore, reusing existing drugs, namely, drug repurposing, has attracted great attention, as this approach has the capacity of saving cost and expediting drug development process.

The purpose of this chapter is to discuss the role of drug repurposing in human diseases especially neurological diseases and summarize repurposing candidates currently in clinical trials for neurological diseases and potential mechanisms as well as preliminary results. Subsequently we also list drug repurposing approaches and limitations and challenges in the future investigations.

2. Repurposed drugs in neurological diseases

Prior to development of repurposed drugs for neurological diseases therapeutics, it is emphasized how the drug reposition process is carried out. Generally, there are three stages in drug repurposing. First, diverse approaches including serendipitous clinical observation, cellular drug activity assays, in silico drug screens, and data mining of clinical drug interaction are employed to obtain drug candidates [16]. The detailed illustrations in grounds of methodologies are summarized as mentioned above [17]. Second, preclinical investigations including in vivo rodent models and in vitro cell lines for these drugs are conducted in neurological diseases [18]. Finally, large-scale and multicenter clinical trials are implemented for evaluating efficacy and safety of repurposed drugs [19]. Up to date, there are plenty of drugs which are repurposed in neurological diseases through the above approaches. Then, in the following section, we also cite several repurposed drugs to elaborate how they function in neurological diseases. **Table 1** summarizes various repurposed drugs in the treatment of neurological disorders.

2.1 Verapamil

Verapamil, a classical calcium channel blocker, is mainly used in the treatment of hypertension, angina pectoris, arrhythmia, and other diseases, especially for paroxysmal supraventricular tachycardia [20]. It has been found that administration of verapamil greatly improves seizure control in drug-resistant epileptic patients via inhibiting P-glycoprotein (Pgp). Pgp is responsible for the transport of antiepileptic drug (AED) into the blood vessels through the blood–brain barrier (BBB). And there is evidence supporting that overexpression of Pgp in the brain represents a major mechanism underlying drug resistance in epileptic patients [21]. Verapamil is found to suppress Pgp expression and subsequently facilitates the entry of this

Name of drug	Original indication	Novel indication	Target	Summarization of evidence
Verapamil	Hypertension Angina pectoris Arrhythmia	Intractable epilepsy Subarachnoid hemorrhage Stroke Resistant depression	P-glycoprotein	I. Improving life quality in drug-resistant epileptic patients II. Preventing behavior phenotype in a mouse model of focal ischemia III. Showing no adverse effect in patients with stroke
Bumetanide	Liver disease Heart failure Stubborn edema Acute and chronic renal failure	Epilepsy Autism	NKCC1 protein	I. Improving anticonvulsant effect of phenobarbital in hypoxic rats II. Decreasing neuronal discharge in vitro and in vivo
Minocycline	Antibacterial	Epilepsy Spinal cord injury Brain inflammation Neurodegenerative diseases	Activated microglia IL-6, TNF-α TrkB/BDNF PPAR-γ/NF-κB LKB1/AMPK	I. Reducing seizure duration in rats II. Inhibiting inflammatory cytokines and cell death in kainic acid-induced epilepsy models
Fenfluramine	Simple obesity Diabetes Hypertension	Epilepsy Parkinson's disease	5-HT receptors	I. Alleviating epilepsy in patients with Dravet syndrome II. Anticonvulsant effects on photosensitive or induced convulsions
Propranolol	Hypertension Supraventricular tachycardia Prolonged Q-T interval Thyrotoxicosis	Migraine Traumatic brain injury Parkinson's disease	IL-6 β-adrenergic	I. Alleviating headache in patients with angina pectoris II. Reducing mortality within 24 h of admission in patients with TBI III. Preventing neuronal necrosis in a pig model of TBI
Sunitinib	Gastrointestinal stromal tumor Non-small-cell lung cancer Renal cell carcinoma	Glioma Pheochromocytoma Alzheimer's disease'	Acetylcholinesterase CGNs, SH-SY5Y	I. Penetrating the blood–brain barrier in clinical studies II. Alleviating glioma progression and glioma-induced neurodegeneration in vivo III. Preventing neuronal death induced by neurotoxins in vivo

Name of drug	Original indication	Novel indication	Target	Summarization of evidence
Angiotensin receptor blockers	Essential hypertension Renal disease Diabetes	Alzheimer's disease Episodic migraine	AT1 receptor Angiotensin II	I. Reducing Aβ accumulation and aggregation in vivo II. Alleviating AD in epidemiological studies and RCTs
Amantadine	Antiviral	Parkinson's disease Chronic traumatic brain injury	N-methyl-D-aspartate (NMDA) Anticholinergic	I. Improving motor symptoms in a female PD patient II. Activating the dopamine system in several preclinical data demonstrate

Table 1.
List of repurposed drugs in neurological disease.

drug into epileptogenic zones. As a marketed drug, verapamil treatment in patients with intractable epilepsy can doubtfully alleviate brain injury caused by repetitive seizures [22]. Actually, in clinical trials, verapamil has previously shown to exhibit great efficacy in intractable depression or mania via inhibiting the function of Pgp [23, 24]. Moreover, it is documented that verapamil has been approved to treat cerebral vasospasm secondary to subarachnoid hemorrhage due to its vasodilatory effects [25]. Intra-arterial (IA) treatment with verapamil, which was physiologically feasible, safe, and neuroprotective as a therapeutic adjunct in stroke, significantly reduces infarct volume and improved functional outcome [26], although there are still some mysteries about the mechanism.

2.2 Bumetanide

As a potent diuretic agent, bumetanide, which is mainly employed to cure liver disease, heart failure, and various kinds of stubborn edema in clinic [27], is a specific inhibitor of Na^+-K^+-$2Cl^-$ cotransporter isoform 1 (NKCC1) [28]. Mechanically, NKCC1 significantly modulates the content of intracellular Cl^-. Upregulation of NKCC1 leads to elevation of intracellular concentration of Cl^-, which is associated with pathogenesis of neurological diseases. It has been unequivocally proven that many of the available drugs have anti-seizure potential via activating GABAA-mediated hyperpolarization due to accumulation of neuronal Cl^- [29]. Indeed, current investigations have confirmed that bumetanide exerts antiepileptic effect via switching the GABA-mediated inhibitory postsynaptic potential in neurons from depolarization to hyperpolarization, resulting in decreased neuronal discharge [30, 31]. In addition, previous work reinforces that bumetanide can enhance the anticonvulsant effect of phenobarbital in hypoxic rats [32]. It suggests that the combination of phenobarbital and bumetanide may provide a promising therapeutic strategy for ceasing seizures in neonatal epilepsy and may increase the neuroprotective effect of hypothermia on asphyxiated newborns [33]. Persuasively, a current clinically pilot study further demonstrated that bumetanide, as a specific NKCC1 antagonist, considerably reduced seizure frequency in adult patients with temporal lobe epilepsy [34]. Additionally, as a consequence of a randomized controlled trial, bumetanide may also be effective for treatment of autism [35]. It should be considered that there are two obstacles for bumetanide treatment in neurological disorders [31, 36]. It has been shown that the highly potent diuretic effect of bumetanide can lead to hypokalemic alkalosis and the poor penetration into brain exists. This indicates that reuse of bumetanide in neurological diseases brings about opportunities and challenges in the future.

2.3 Minocycline

Minocycline is the second generation of semisynthetic broad-spectrum antibacterial tetracycline analogues. It has immunomodulatory, anti-inflammatory, and anti-apoptosis effects. Minocycline has neuroprotective effects in rodent models of ischemia, spinal cord injury, and infection [37]. It can efficiently penetrate the BBB and has a good effect on activated microglia, which indicates a possible role in the treatment of epilepsy. Minocycline may have synergistic effects with other compounds in manipulating epilepsy. Minocycline has been found to remarkably obviate epileptic conditions and reduce seizure-induced brain impairment at early stage [38]. In addition, minocycline also inhibits pro-inflammatory cytokines through caspase-dependent and caspase-independent pathways, thus inhibiting cell death in kainic acid-induced status epilepticus [39]. An obvious improvement of seizure phenotype is also observed in a rat model of amygdala kindling [40]. Additionally,

increasing studies have reported the neuroprotective effects of minocycline in neurologic diseases, such as ischemic stroke, multiple sclerosis (MS), and traumatic brain injury (TBI) [41–43]. In in vivo animal model, minocycline promotes M2 microglia polarization via activation of tyrosine kinase receptor B (TrkB)/brain-derived neurotrophic factors (BDNF) pathway and facilitates neurogenesis after intracerebral hemorrhage (ICH) [44]. In the process of acute cerebral infarct, minocycline also effectively inhibits oxidative stress via elevating the activity of superoxide dismutase (SOD) and activating the liver kinase B1 (LKB1)/adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) signaling pathway [45]. However, repurposing of minocycline in treating neurological diseases requires to be re-evaluated as there is a clinical study showing serious neurodegeneration TBI [46].

2.4 Fenfluramine

Fenfluramine, which has been successfully applied in obesity, diabetes, and hypertension [47], is a potent 5-hydroxytryptamine (5-HT) releaser activating multiple 5-HT receptor subtypes. Of note, elevation of extracellular 5-HT levels inhibits focal and generalized seizures, while depletion of 5-HT lowers the threshold of epileptic seizures [48]. Therefore, 5-HT agonist fenfluramine is assessed for treatment of epilepsy. In a small-scale retrospective study, it has reported that adjuvant treatment with fenfluramine has evidently obtained seizure control in patients with Dravet syndrome. As the side effects is not serious, it does not lead to the termination of treatment [49]. This drug may have anticonvulsant effects on other severe epilepsy syndromes, especially those characterized by photosensitive or induced convulsions [50, 51]. Encouragingly, a recent investigation has unveiled that fenfluramine significantly reduces convulsive seizure frequency compared with placebo and exhibits good tolerance [52]. It indicates that fenfluramine could be functioned as a potent novel therapeutic regime for patients with Dravet syndrome. It is noteworthy that fenfluramine also alleviates L-DOPA-induced dyskinesia via stimulation of 5-HT1A receptor in PD [53].

2.5 Propranolol

Propranolol as a β-adrenoceptor antagonist (b-blocker) has been commonly used in hypertension, supraventricular tachycardia, prolonged Q-T interval, and thyrotoxicosis in clinic [54]. Since 1996, in patients who were being treated for angina pectoris, Rabkin et al. has disclosed the therapeutic effect of propranolol on migraine headache [55]. Meanwhile, further clinical studies have noted that administration of propranolol within 24 h of admission after TBI triggers lower mortality [56]. The evidence also arises from a recent study that propranolol blocks the upregulation of IL-6 and prevents neuronal cell necrosis in CA1 and CA3 hippocampus in a pig model of TBI [57]. Given that propranolol has neuroprotective potential in neuropathological conditions, it is likely to serve as a neuroprotective drug in epilepsy. Additionally, both clinical and experimental studies have demonstrated the potential of propranolol to resist dyskinesia in PD, as modulation of β-adrenergic receptors (βAR), which is abundantly, expressed in striatum, is involved L-DOPA-induced dyskinesia (LID) [58, 59].

2.6 Sunitinib

Sunitinib, which is an oral, small molecule receptor tyrosine kinase inhibitor approved by the US Food and Drug Administration, has been currently implemented in the treatment of various cancers such as gastrointestinal stromal tumor

(GIST), non-small-cell lung cancer, and renal cell carcinoma [60]. Clinical evidence has revealed that oral administration of sunitinib penetrates the BBB and subsequently facilitates the entry into central nervous system [61]. Furthermore, on the basis of its potent antiangiogenic and antitumoral characteristics, it has discovered that sunitinib can alleviate glioma-induced neurodegeneration and glioma progression in vivo models [60]. Meanwhile, sunitinib has been found to exert therapeutic effects on learning and memory deficits in a mouse model of AD through inhibition of acetylcholinesterase (AChE) [62]. Additionally, sunitinib has also demonstrated to prevent neuronal death induced by neurotoxins via inhibiting NO overproduction in cerebellar granule neurons (CGNs) and SH-SY5Y cells following exposure with low potassium or 1-methyl-4-phenylpyridinium ion (MPP^+)-induced neuronal apoptosis [63]. It indicates that sunitinib may improve brain dysfunction via inhibition of oxidative stress.

2.7 Angiotensin receptor blockers

In in vitro studies, angiotensin receptor blockers (ARBs) are generally known to treat essential hypertension by influencing the level of angiotensin II (Ang II) via two distinct pathways, namely, through interrupting the AT_1 receptor and augmentation of Ang II processing which plays a critical role in cognition regulation [64]. For example, valsartan, which has previously been found to penetrate BBB and elicit antihypertensive responses in the brain, has been demonstrated to reduce Aβ accumulation and aggregation in vivo and in vitro [65]. Actually, similar situation exists in losartan and telmisartan, which are also classical ARBs [66, 67]. Overall, it indicates ARBs are potential candidates for treating AD. Significantly, several clinically epidemiological studies and RCTs certify the efficacy of ARBs in AD. A large-scale retrospective cohort study has revealed an obvious reduction of dementia in patients treated with ARBs compared with other cardiovascular agents [68]. Likewise, the further UK-based study also reports a similar trend, with a 50% reduction in AD after ARBs treatment [69]. In brief, ARBs, the conventional cardiovascular medicine, have been confirmed to exert a vital effect in AD, and it is further deserved to identify the most suitable dosage in clinic.

2.8 Amantadine

Amantadine is a classic antiviral compound which has been found to moderately ameliorate impaired motor behavior in Parkinson's disease [70]. Intriguingly, in 1969, it was coincident that Schwab et al. found an improvement of motor symptoms in a female PD patient, who took 200 mg amantadine daily for antiviral prophylaxis [71]. Subsequently, three potential mechanisms have been proposed to explain the efficacy of amantadine in PD. Several preclinical data demonstrate an activation of the dopamine system's both presynaptic and postsynaptic actions [72], and amantadine also inhibits the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors [72, 73]. The mild anticholinergic effect is also involved [74]. Surprisingly, PD is well known to be frequently associated with depression, and antagonism of NMDA receptors is also a promising target for new antidepressants, although there is no definite evidence to certify its efficacy in depressive disorder.

3. Approaches to drug repurposing

There are three important stages in the field of drug repurposing: generation of candidate compounds, preclinical investigation, and clinical trial. Determination

of appropriate drugs for potential indications is crucial for production of candidate compounds. At present, two approaches are widely used for drug repurposing including experimental screening approaches and molecular docking by computer. In the following items, we make a detailed description of these two methods in drug repurposing process.

3.1 Experimental approaches

Experimental screening approaches are usually regarded as the first stage in the process of drug discovery and drug repurposing. Proteomic techniques such as affinity chromatography and mass spectrometry have been widely employed to identify drug candidates [75]. Nowadays, drug target analysis and drug repurposing are inseparable. Drug repurposing is distinct from drug discovery in terms of alteration of drug target. Cellular thermo stability assay technique can predict the affinity of drug ligands by mapping the contact patterns of intracellular targets [76]. The molecular on and off targets have been disclosed for many clinically approved drugs via this method. Especially in the field of kinases, new targets of well-known drugs are obtained through affinity matrices [77, 78]. For example, imatinib, a tyrosine kinase inhibitor, has been successfully reused in the treatment of gastrointestinal stromal tumors [79].

In addition, chemical compounds with disease-related effects can be defined in the model through phenotype screening [80]. Phenotype screening has always been more successful than target screening in the facet of drug development [81, 82]. In the case of drug repurposing, if the compounds selected through phenotypical assays are approved clinical drugs or ongoing clinical trials, they are probable to reuse. Several drugs approved for tobacco dependence have been evaluated, and it has been found that topiramate changes nicotine- or ethanol-induced behavior in zebrafish models [83]. However, there are some challenges that the efficacy of drug candidates in in vitro experiments require to be validated in human diseases [84].

3.2 Computational approaches

Molecular docking by a computer is also an important method for evaluating drug target binding kinetics and drug residence times of existing drugs or drug candidates [85]. Large amounts of computational drug repositioning methods choose transcriptomic data to identify potential new indications for drugs. Furthermore, these methods have applied techniques such as comparison of gene expression profiles between a disease model and drug-treated condition [86], network integration [87], prediction of drug-protein interactions [88], and utilization of genotype–phenotype associations. Recently, a proteotranscriptomic-based computational drug repositioning method named Drug Repositioning Perturbation Score/Class (DRPS/C) for Alzheimer's disease occurs on the basis of inverse associations between disease-induced or drug-induced gene and protein perturbation patterns [89]. Briefly, these approaches can be applicable to discovery of drug targets or biomarkers.

It should be considered that for many neurological disorders, drugs require good penetration into BBB. Then, the therapeutic approaches of targeting brain have been classified as invasive and noninvasive categories [90, 91]. The invasive approaches contain the temporary increase of BBB permeability, and noninvasive approaches involve modification of drug molecule via physiological, chemical, or colloidal carrier system approach. Meanwhile, these methods are also related

to computational approaches. Influx clearance into the brain (K_{in}), which is the unidirectional influx constant from the blood to brain, can be used to calculate the transport of drugs in the brain. Similar computational approaches conclude the permeability surface area (PS), brain/plasma ratio (K_p), brain uptake index (BUI), and apparent permeability (P_{app}) [92–95]. Consequently, drug repurposing in neurological diseases covers various manners to participate in integrating the role of transporters and pathophysiological complexity of BBB to establish a suitable model for high-throughput screening.

4. Concluding remarks and perspectives

Drug repurposing is a vital strategy for developing new therapeutic values of existing drugs or drug candidates due to its ability to save time and reduce cost [96]. This type of innovative concept will undoubtedly expedite the drug development process. Meanwhile, some limitations need to be considered during drug repurposing process in neurological diseases. Owing to complex molecular and cellular signaling mechanisms in neuropathological states, drug repurposing may be difficult. Additionally, drugs not only respond to a single target but also affect multiple targets [97], causing a variety of adverse reactions. A comprehensive assessment of the advantages and disadvantages of these side effects can help us understand drug repositioning from a more all-round perspective [98, 99].

In order to overcome limitations faced during drug repurposing, we make proposals in the following descriptions. Firstly, it is foremost to establish a comprehensive data analysis platform to maximize data sharing. Information science services and artificial intelligence can help unlock and reanalyze the large amount of data accumulated by approved drugs or drug candidates to clinical trials. These data may be stored in a diversified way. Storage locations, formats, and types may vary, including different storage locations, formats, and types. The data obtained from clinical trials and biological databases are too large and complex that the traditional data processing methods cannot deal with it, which leads to the bottleneck in the research process [99]. Big data can significantly improve our understanding of the disease and make more accurate disease-related strategies. However, there is a big gap between generating biomedical data and data analysis [99, 100]. To ensure the efficiency of research, it takes time, energy, and expertise to find technical solutions to integrate them. Secondly, it is encouraged to provide more financial support for clinical trials of drug repurposing, including technical support. The preclinical research of drug repurposing requires financial support to obtain the data in clinical trials. In this case, drugs that can be developed to treat rare diseases are more likely to apply in clinical neurological diseases therapeutics [101]. Finally, in order to facilitate drug repurposing process, we advocate it is indispensable to solve patent restrictions and take reasonable supervision. All applications of drug repurposing should be accompanied by a risk management plan. Drug's safety can be supported by clinical trial data or post marketing data.

In conclusion, drug repurposing is a novel approach for expediting drug development process in neurological diseases. Repurposed drugs may provide an efficient avenue for improving a plethora of pathological conditions including neurological disorders. In the future, it is essential to exploit molecular mechanisms during drug repurposing processes due to the possibility that targets of repurposed drugs in neurological diseases are distinct from original targets in treating other diseases, in order to make these drugs more effective and safe.

Acknowledgements

The authors apologize to all the investigators whose work cannot be cited in this paper due to space constraint. This work was partly supported by the National Natural Science Foundation of China (No. 81974502 and 81671293).

Conflict of interest

There is no potential conflict of interest.

Abbreviations

CNS	central nervous system
AD	Alzheimer's disease
PD	Parkinson's disease
AED	antiepileptic drug
BBB	blood–brain barrier
Pgp	P-glycoprotein
NKCC1	Na^+-K^+-2Cl-cotransporter isoform 1
GABAA	gamma-aminobutyric acid
MS	multiple sclerosis
TBI	traumatic brain injury
TrkB	tyrosine kinase receptor B
BDNF	brain-derived neurotrophic factors
ICH	intracerebral hemorrhage
SOD	superoxide dismutase
LKB1	liver kinase B1
AMPK	adenosine 5′-monophosphate (AMP)-activated protein kinase
5-HT	5-hydroxytryptamine
LID	L-DOPA-induced dyskinesia
βAR	β-adrenergic receptors
AChE	acetylcholinesterase
CGNs	cerebellar granule neurons
ARBs	angiotensin receptor blockers
Ang II	angiotensin II
NMDA	N-methyl-D-aspartate

DOI: http://dx.doi.org/10.5772/intechopen.93093

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