feature

An analysis of FDA-approved drugs for neurological disorders

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Neuroscience remains a great challenge and opportunity in terms of new drug discovery and development. An assessment of FDA-approved new molecular entities (NMEs) reveals a low steady rate of new FDA approvals, which is interrupted by two bursts in activity, first in the 1950s and then in the 1990s. These trends are reflected in the approvals for NMEs targeting multiple indications in this field, including seizure, Parkinson's disease and neuromuscular disorders. The majority of drugs target ion channels or G-protein-coupled receptors (GPCRs) but the mechanistic basis for many NMEs remains unclear or controversial. These trends could suggest future opportunities for success in a crucial field with considerable unmet needs.

Analysis

Disorders of the nervous system encompass a broad array of maladies, ranging from restless leg syndrome to traumatic brain injury. Since the early days of the modern pharmaceutical industry, medicines for the treatment of neurological diseases have been a primary focus and the impact has been considerable. One of the earliest breakthrough medicines is also one of the most notorious. Methamphetamine has gained considerable notoriety in popular culture for its medical and (illegal) recreational use [1,2]. Methamphetamine was originally approved for use in the USA in 1943 for the treatment of narcolepsy and later became a popular supplement for its use as a utilitarian drug and as a weight-loss drug. However, widespread reports of its addictive properties caused the drug to be regulated as a schedule II drug following passage of the Controlled Substances Act of 1970 [3].

In total, 79 different new molecular entities (NMEs) have been approved with a primary indication within the spectrum of neurological disease. This figure excludes drugs for psychiatric indications and pain because these will be the focus of other articles in this series. When viewed over time, the accumulation of NMEs shows a relative low rate of approvals with three notable exceptions. First, a transient burst of approvals in the 1950s corresponded with improvements in the pharmaceutical industry's ability to design for certain types of cellular targets. Specifically, the data here suggest that increasing expertise in pharmacological targeting of G-protein-coupled receptors (GPCRs) and ion channels led to an array of new medicines for the treatment of epilepsy, Parkinson's disease and other neurological indications. These breakthroughs were largely achieved using phenotypic models of disease, which allow investigators to identify desired biological outcomes without necessarily having knowledge of the precise mechanistic basis [4–6] (Fig. 1).

A second burst of approvals occurred in the 1990s as a result of increased knowledge of the particular pathways and key molecules associated with brain function and neurological disorders. Such information facilitated the design of a new series of drugs, largely using targeted drug design. For example, increased understanding of the role of dopamine, epinephrine, gamma-aminobutyric acid (GABA) and their receptors increased the precision of targeting vital pathways.

In the years before and between these periods of punctuated approvals, the average rate of new approvals was remarkably consistent and in a range of about one new drug every two years. The analyses here demonstrate that this trend continues today when evaluating NMEs for neurological diseases with one notable exception. Whereas the rate for conventional neurological diseases remains at a range of 0.6 NMEs per year,

http://dx.doi.org/10.1016/j.drudis.2015.02.003

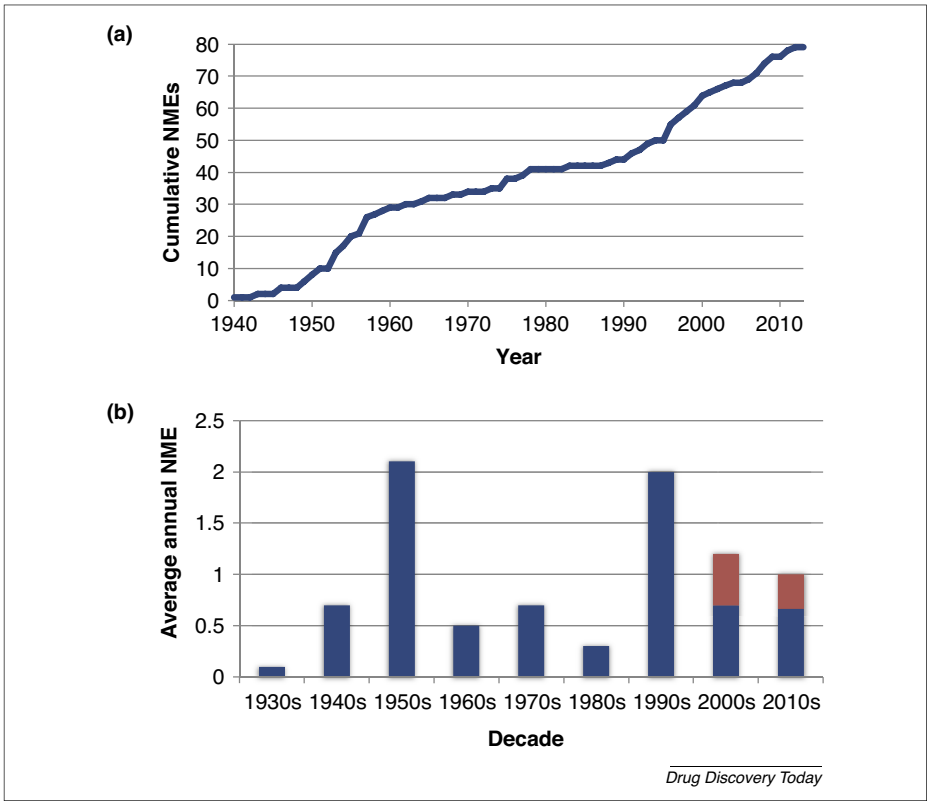

FIGURE 1

Accumulation of new molecular entities (NMEs) targeting neurological disorders. The cumulative number of NMEs approved for neurological disorders is shown on a **(a)** year-by-year basis or a **(b)** decade-by-decade basis. Note the increased rate of NME growth in the 1950s and 1990s. Blue bars indicate conventional approvals and red bars denote NMEs approved for an orphan indication.

there has been a recent increase in NMEs approved for orphan indications. Consequently, the average rate of neurological disease NMEs has almost doubled, relative to its baseline level, since the beginning of the new millennium.

To analyze such trends further, the specific indications for NMEs targeting neurological diseases were assessed (Fig. 2). Five groupings of indications capture 95% of all neurological NMEs. The largest grouping includes NMEs initially approved for seizure, mostly epilepsy, and encompasses 39% of all neurological disorder NMEs; this is followed by Parkinson's disease (23%), neuromuscular diseases (20%), Alzheimer's disease (7%) and narcolepsy (6%). When viewed over time, seizure medicines reflect not only the largest overall number of NMEs but also demonstrate the bursts of new approvals observed in the 1950s, the 1990s and more recently, with increased focus on orphan indications (e.g. Lennox–Gastaut syndrome) (Fig. 2).

In the course of evaluating NMEs for neurological disorders, other trends associated with the mechanistic basis of targeting were observed. Specifically, I sought to determine the mechanism of action for each NME based on contemporary knowledge. These findings revealed that most NMEs can be aggregated into two classes of targets. Specifically, GPCRs and ion channels each represent about one-third of all neurological disease NMEs. The remaining one-third of NMEs can be almost equally divided among esterases and other targets. It is important to note that this mechanistic information was based on present understanding although much of this current knowledge was not available at the time of the initial approval. Despite advances in this understanding (and, often, decades of research), the mechanistic action for 11% (one in nine) of NMEs remains unknown (Fig. 3).

The relatively large classification of unknown or unclear targeting information is rather unique to neurological disorders. This led to the further evaluations of the subset of one of nine NMEs with unknown or unclear mechanistic basis. When assessed over time, the number of NMEs with an unknown target or unclear mechanistic basis peaked in the 1950s, diminishing rapidly thereafter. Since the end of the 1970s, only one NME, felbamate, has a targeting mechanism that remains unclear. This particular seizure medication has been purported to promote some GABA receptors while blocking *N*-methyl-D-aspartate (NMDA) receptors, although challenges as to the validity of this mechanism have been raised [7–9].

The decrease in the frequency of new approvals in which the mechanistic basis is unclear or controversial is consistent with recent emphasis on target-based drug discovery. Also known as reverse pharmacology or rational drug design, this strategy emphasizes understanding of target function to assist the design of efficacious drugs while minimizing potential side effects [6,10,11]. Execution of this strategy generally involves selective targeting of the purified molecule (e.g. HTS or *in silico* structure-based design). The idea is that, by focusing on particular targets (or unique features or subdomains within these targets), one can maximize efficacious outcomes while minimizing the risks of off-target effects. This information is intended to 'de-risk' new drug development. Faced with pressure to minimize safety risks to the public, a prevailing perception is that regulatory agencies generally favor detailed mechanistic knowledge of efficacy and safety as a prerequisite for gaining FDA approval for experimental agents.

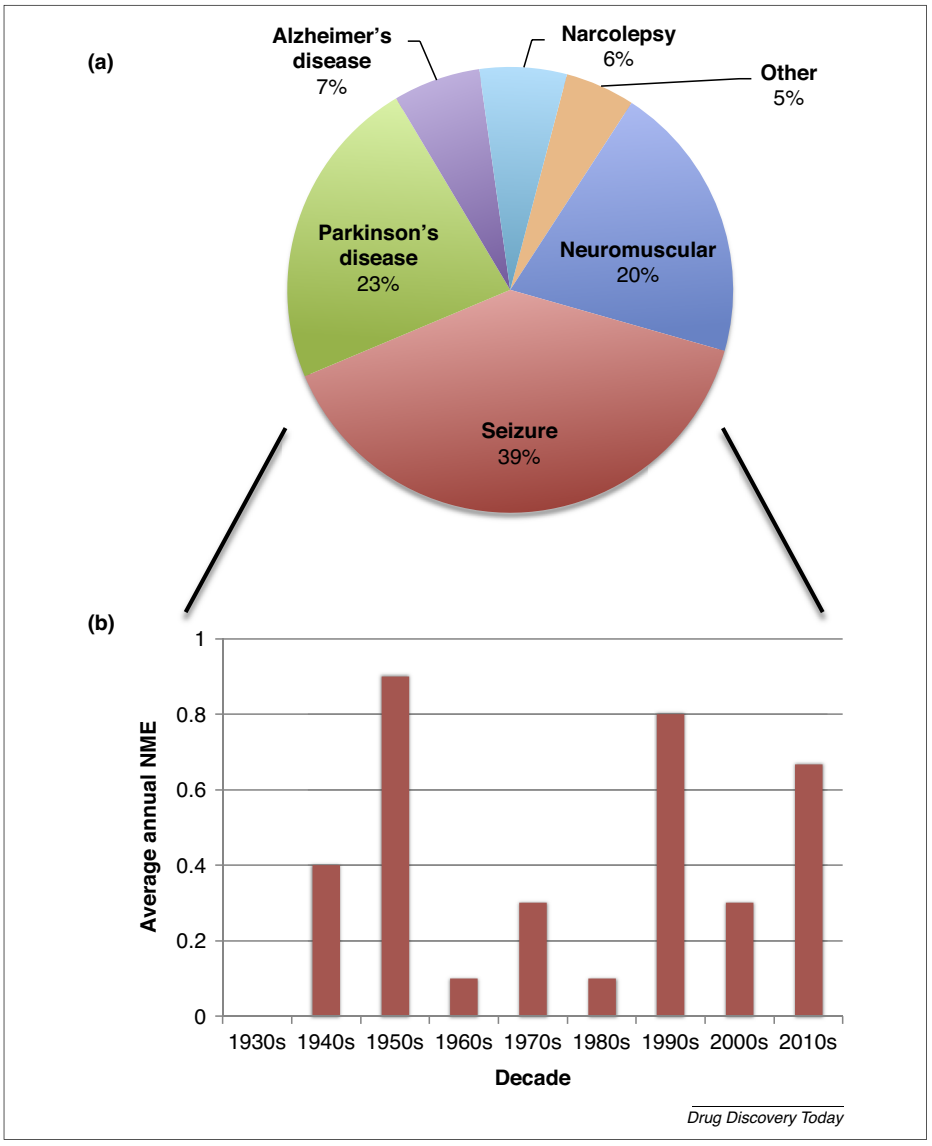

FIGURE 2

Indications targeted by new molecular entities (NMEs) for neurological disorders. **(a)** The relative frequency of major neurological indications is shown. **(b)** When viewed over time, the rate of new approvals for seizures reflects the overall rates of NME introduction, including the transient increases in the 1950s and 1990s.

Concluding remarks

Looking back on past approvals, it is not surprising that the mechanistic basis for many neurological disorder drugs is unknown. Early-stage discoveries were largely based on phenotypic assays (also known as classical or forward pharmacology) [4–6]. Many of these drugs were developed and approved years before the modern understanding of neural function. What does seem remarkable is that the mechanistic basis of efficacy remains unclear or controversial for a relatively large proportion of these drugs, even decades after their approval and widespread use.

Such findings might have important implications to assist modern drug discovery. Many drugs discovered using classical pharmacology have been efficacious and continue to be safe and effective today. Given a lapse of detailed knowledge of the mechanistic basis of efficacy (and safety), it is not clear whether such drugs would pass the scrutiny of the modern FDA approval process.

These findings raise questions as to whether it might be beneficial for modern research in neurological disorders (and other indications) to consider the benefits of returning to a classical pharmacology approach. The field of neurological disorders might be particularly suited to consider this idea in light of recent high-profile failures. Such concerns have led a number of high-profile biopharmaceutical companies to scale-back or withdraw from the field. In an impressive recent article, an assessment of biopharmaceutical research and development productivity revealed that uniquely the field of neuroscience is a negative predictor of success [12]. The negative relationship probably relates to a relative paucity of predictive models, particularly animal

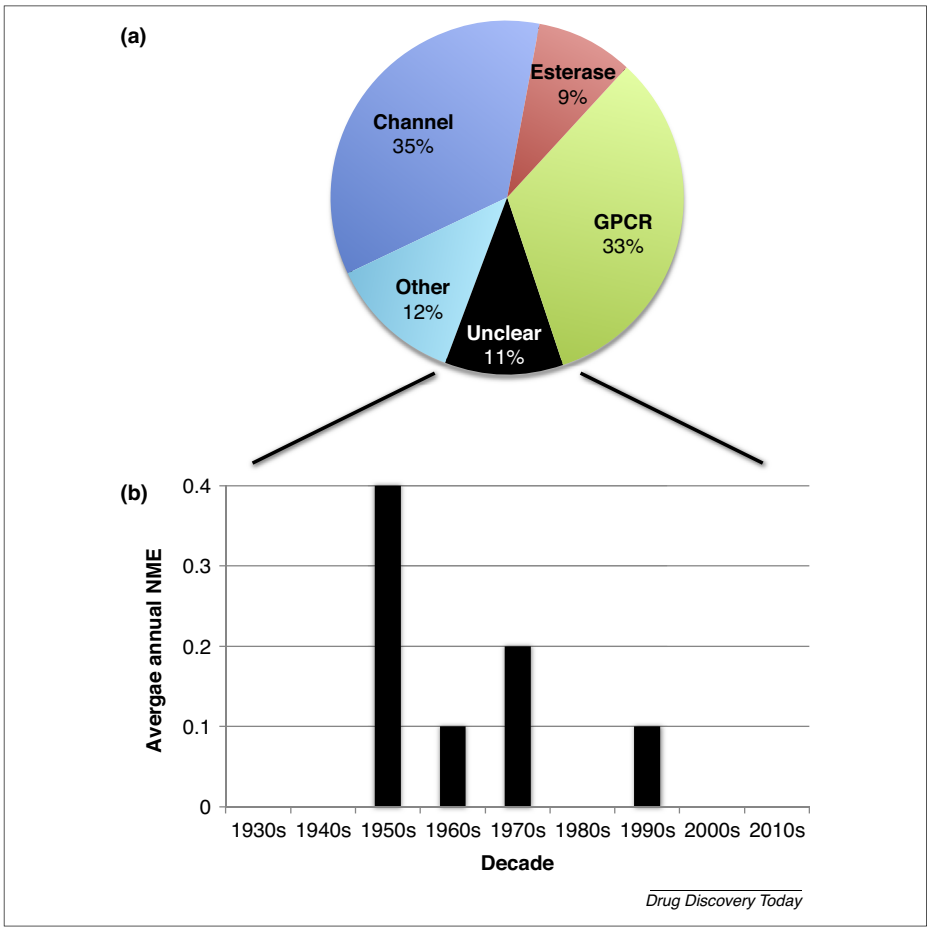

FIGURE 3

Mechanistic basis of new molecular entity (NME) activity. **(a)** The mechanism of action for NMEs is indicated. Note that this information is based on my contemporary knowledge (not necessarily understanding as of the time of approval). Despite increases in this understanding, 11% of NMEs for neurological disorders function in a manner that is unclear or controversial. When viewed over time, the number of NMEs with an unclear mechanistic basis has decreased, which largely reflects conventional *a priori* knowledge of the mechanism of action.

models. This presents a pressing challenge and opportunity for the academic community and funding agencies to develop innovative and applicable new models to fill this crucial need. In the meantime, another consideration is to re-evaluate older methods that led to a number of early successes in the field.

Acknowledgments

This work was conducted as part of a project at the Yale Center for Molecular Discovery (http://ycmd.yale.edu/) to develop a collection of all FDA-approved small molecules as a resource for screening to emphasize drug repurposing. Please contact the author if you or your organization would be interested in potential participation in this project.

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