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Challenges in the clinical development of new antiepileptic drugs

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A B S T R A C T

Despite the current availability in the market of over two dozen antiepileptic drugs (AEDs), about one third of people with epilepsy fail to achieve complete freedom from seizures with existing medications. Moreover, currently available AEDs have significant limitations in terms of safety, tolerability and propensity to cause or be a target for clinically important adverse drug interactions. A review of the evidence shows that there are many misperceptions about the viability of investing into new therapies for epilepsy. In fact, there are clear incentives to develop newer and more efficacious medications. Developing truly innovative drugs requires a shift in the paradigms for drug discovery, which is already taking place by building on greatly expanded knowledge about the mechanisms involved in epileptogenesis, seizure generation, seizure spread and development of co-morbidities. AED development can also benefit by a review of the methodology currently applied in clinical AED development, in order to address a number of ethical and scientific concerns. As discussed in this article, many processes of clinical drug development, from proof-of-concept-studies to ambitious programs aimed at demonstrating antiepileptogenesis and disease-modification, can be facilitated by a greater integration of preclinical and clinical science, and by application of knowledge acquired during decades of controlled epilepsy trials.

1. Introduction

When the first wave of so-called new generation AEDs started to become available in the early 90s, there were widespread expectations that the new agents would prove effective in achieving complete freedom from seizures in a sizeable proportion of patients refractory to older drugs. Unfortunately, to a large extent those expectations have not been fulfilled [1]. The overall probability of achieving seizure freedom in 2015, with over 25 antiepileptic drugs (AEDs) available in the market, is in the order of about 70%, and only marginally greater compared with the early 70s when physicians had only a handful of AEDs to choose from [2]. The newer drugs have improved outcomes for people with epilepsy, but this improvement relates mostly to a reduced toxicity burden and fewer adverse drug interactions, with overall no more than 10–15% of patients refractory to older drugs achieving sustained seizure freedom with the newer agents [3,4].

The fact that about one third of people with epilepsy cannot be fully controlled with available AEDs is a major unmet need, and represents the most important motivation for investing into development of newer, more effective agents [5,6]. There are, however, other shortcomings in currently available treatments which could be addressed by introduction of innovative therapies. First, none of the existing AEDs is free from troublesome side effects and adverse drug interactions, to the extent that quality of life in people with pharmacoresistant epilepsy is often impacted more by the adverse effects of medications than by the seizures themselves [7]. Development of safer and better tolerated AEDs may not only improve quality of life by reducing the burden of side effects, but could also lead to improved seizure outcomes by allowing use of larger, non-toxicity limited, doses [8]. Second, AEDs are currently prescribed based primarily on consideration of seizure type(s), comorbidities and co-medications, and there are no reliable tools to predict clinical responses in the individual patient [4]. The introduction of newer, biomarker-guided pharmacological therapies targeting the mechanisms underlying seizure generation in a given patient could allow truly rational drug selection, and avoid the trial-and-error approach presently used to identify the best treatment for an individual. Lastly, currently available AEDs have purely symptomatic effects, i.e., they suppress seizures but they do not affect the underlying disease [1]. Development of disease-modifying antiepileptogenic agents, capable of preventing or curing epilepsy or its

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progression, or even prevent epilepsy-related comorbidities, would provide a truly revolutionary advance [9,10].

Current understanding of the mechanisms underlying epileptogenesis, seizure generation and seizure spread is advancing at an unprecedented pace, paving the way to the design and identification of compounds which have the potential of improving in a major way clinical outcomes [1,11]. This will imply a shift in the approaches used for drug discovery, and will also require a review of the methodology currently used in clinical development [12]. This article will provide a brief overview of the barriers that still limit efficient AED development, and discuss possible approaches to bring to fruition much needed innovative treatments for epilepsy.

2. Hurdles to new drug development: facts and misperceptions

Despite the existence of many unmet needs, investment into development of new treatments for epilepsy has declined somewhat in recent years, similarly to other central nervous system areas [13]. There are many reasons for this, and it is important for them to be properly evaluated and addressed because they are partly based on misperceptions.

2.1. The market value for epilepsy drugs is small and crowded

The value of therapeutic drug sales for epilepsy in the 8 major markets (US, Canada, France, Germany, Italy, Spain, the UK and Japan) is projected to reach U.S. $4.5 billion by 2019 [14]. While such market may be regarded as relatively small compared to size of the epilepsy population (2.3 million people in the U.S. alone), it is by no means a negligible market. In fact, a large fraction of AED sales is accounted for by inexpensive older medications and generic products, and the share of the market value that can be captured by a newly introduced medication can be substantial. For example, the sales of lacosamide, an AED introduced in 2008, are projected to reach U.S. $ 1.2 billion by 2020, which would place it within the 30 most profitable drugs overall [15]. The latter example also demonstrates that the presence of a crowded AED market is no barrier to the penetration of a relatively successful drug. It can be easily envisaged that a well tolerated drug, superior to existing agents in terms of seizure freedom rates or in terms of ability to influence the underlying disease, could achieve a huge success in the market place.

The attractiveness of developing truly innovative medications for epilepsy is reinforced by other considerations. First, new markets for pharmaceuticals are rapidly expanding, with emerging markets gaining increasing access to recently developed medicines. Second, experience has taught us that many medications developed for epilepsy can find successful applications in other therapeutic areas, such as mood disorders, migraine, and neuropathic pain [16]. In fact, it has been estimated that a new AED with additional approved indications in bipolar disorder and neuropathic pain might have a potential market size three times larger than that of epilepsy alone [16].

2.2. Developing AEDs that are superior to existing agents is an elusive target

Although the introduction of any new AED brings incremental value to the pharmacological armamentarium, it remains a fact that none of the AEDs developed in the last two decades impacted greatly on the probability of achieving freedom from seizures, and that overall recently developed AEDs are not more efficacious than older agents [1,6]. Based on this consideration, some scientists within the pharmaceutical industry have become disillusioned about the feasibility of developing truly superior epilepsy treatments.

In fact, careful assessment of available evidence challenges the perception that second generation AEDs have not improved clinical outcomes for people with epilepsy. Apart from significant tolerability advantages, including a lower potential to cause adverse drug interactions, newer AEDs do allow full seizure control to be achieved in a small, but not negligible, proportion of patients refractory to older agents [17]. Moreover, although overall newer AEDs may not be more efficacious than older treatments, there can be specific syndromes for which a new AED has clearly superior antiseizure activity, the most notable example being vigabatrin for infants with epileptic spasms associated with tuberous sclerosis [18].

More importantly, the limited impact of newer generation AEDs in reducing the problem of drug resistance can be explained by the fact that these drugs, with very few exceptions, were discovered using traditional animal models [1,19]. Recent advances in knowledge now permit substantial revision of the drug discovery paradigms which have been in use for over 70 years, leading to completely innovative approaches such as the design of treatments which target the mechanisms of drug resistance, correct the molecular defects known to cause epilepsy in specific individuals, or possess disease modifying rather than purely symptomatic effects [1,9]. Further discussion on how the process of AED discovery can be improved is provided in Section 3 of this article.

2.3. Epilepsy is a highly heterogeneous disease, which implies that a single drug is unlikely to benefit broadly all patients

Epilepsy encompasses many syndromes and subsyndromes with a vast array of causes and different underlying mechanisms [20]. However, there are common mechanisms of seizure generation and propagation that can be successfully targeted by a single pharmacological agent. Valproic acid and benzodiazepines, for example, are broadly effective across all seizure types and epilepsy syndromes, even though there are patients who are resistant to these drugs across the entire seizure spectrum [4]. It has to be acknowledged, however, that novel treatments more specifically targeted at a precise etiological mechanism are more likely to have their efficacy restricted to those patients in whom that mechanism is operating.

In fact, the heterogeneity of the epilepsies represents an opportunity for the pharmaceutical industry, rather than a limitation. Many epilepsies frequently associated with drug resistance and for which unmet needs are greatest fulfil the criteria for an orphan disease, and therefore the development of a treatment for these indications can benefit from facilitated regulatory pathways [13,21,22], availability of data sharing programs [23] and in some settings also from financial incentives from governmental agencies or other sources [13]. Major breakthroughs are being made in understanding the molecular defects underlying many of these syndromes, including several epileptic encehalopathies of childhood, making it possible to rationally design highly efficacious compounds precisely targeting the underlying etiological mechanisms [24,25]. Importantly, for some of these syndromes no licensed treatments exist, and therefore any new compound that has shown any degree of efficacy in a controlled trial in such indications would enjoy virtual exclusivity in terms of regulatory approval. This combination of factors makes drug development in less common severe epilepsy syndromes quite attractive not only to large pharmaceutical industry, but also to small and medium-size enterprises.

It should be noted that a superior efficacy profile is not necessarily dependent on achieving complete seizure control in a high proportion of patients. Superiority may derive from the