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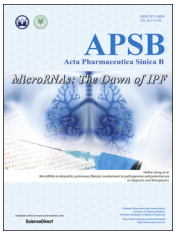

REVIEW

The fate of medications evaluated for ischemic stroke pharmacotherapy over the period 1995–2015

Xiaoling Chen[a], **Kewei Wang**[a,b,*]

[a]*Department of Molecular and Cellular Pharmacology, State Key Laboratory of Natural and Biomimetic Drugs, Peking University School of Pharmaceutical Sciences, Beijing 100191, China*
[b]*Department of Pharmacology, Qingdao University School of Pharmacy, Qingdao 266021, China*

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KEY WORDS

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Abstract Stroke is a brain damage caused by a loss of blood supply to a portion of the brain, which requires prompt and effective treatment. The current pharmacotherapy for ischemic stroke primarily relies on thrombolysis using recombinant tissue plasminogen activators (rt-PAs) to breakdown blood clots. Neuroprotective agents that inhibit excitatory neurotransmitters are also used to treat ischemic stroke but have failed to translate into clinical benefits. This poses a major challenge in biomedical research to understand what causes the progressive brain cell death after stroke and how to develop an effective pharmacotherapy for stroke. This brief review analyzes the fate of about 430 potentially useful stroke medications over the period 1995–2015 and describes in detail those that successfully reached the market. Hopefully, the information from this analysis will shed light on how future stroke research can improve stroke drug discovery.

Abbreviations: ADP, adenosine diphosphate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASIC1a, acid-sensing ion channel 1a; BDNF, brain-derived neurotrophic factor; CFDA, the China Food and Drug Administration; CNTF, ciliary neurotrophic factor; GDNF, glial cell line–derived neurotrophic factor; iGluRs, ionotropic glutamate receptors; MHRA, Medicine and Healthcare Products Regulatory Agency; NBP, butylphthalide/3-*n*-butylphthalide; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartate; rt-Pas, recombinant tissue plasminogen activators; TCM, traditional Chinese medicine; TRP, transient receptor potential; TRPC, transient receptor potential canonical; TRPM, transient receptor potential melastatin; TRPV, transient receptor potential vanilloid

*Corresponding author at: Department of Molecular and Cellular Pharmacology, State Key Laboratory of Natural and Biomimetic Drugs, Peking University School of Pharmaceutical Sciences, Beijing 100191, China.
E-mail addresses: wangkw@bjmu.edu.cn, wangkw@qdu.edu.cn (Kewei Wang).

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1. Introduction

Stroke is the leading cause of death and long-term disability in China with a population of stroke patients over 7 million[1,2]. With the rise in prevalence and trend towards younger patients, stroke prevalence in China varies from 260 to 719 per 100,000 people for all ages[3]. According to the Report on Chinese Stroke Prevention released in 2015, approximately 15% of people over 40 are at high risk of stroke with a comprehensive standardized prevalence of stroke between 2011 and 2013 of about 2% and an 8.1% rise in prevalence[1,4]. The prevalence of stroke patients in urban areas is higher than in rural areas and people in the North of China have a higher prevalence than those in the South[1,5]. On the basis of World Bank Data, China will have 31.77 million stroke patients by 2030 costing the country as much as $40.0 billion per year.

Stroke is classified into either ischemic stroke affecting approximately 87% of patients or hemorrhagic stroke affecting the other approximately 13%[6]. Ischemic stroke is caused by a reduction in cerebral blood supply, whereas hemorrhagic stroke results from the rupture of a blood vessel in the brain causing bleeding into the brain or subarachnoid space. For hemorrhagic stroke, neurosurgery is required to treat the bleeding. For ischemic stroke, current interventional treatment regimens mainly include blood pressure management, catheter-based interventions, thrombolytic therapy, anticoagulation therapy, defibrinogen therapy and pharmacotherapy to improve cerebral blood circulation. This review is limited to drug therapy of ischemic stroke, which aims to restore blood flow.

In an effort to gain insight into what makes a stroke drug succeed in reaching the market, we have examined the fate of about 430 potential stroke drugs evaluated over the past twenty years (1995–2015). The analysis was based on data reported from the Addis Insight Database deposited by December 25, 2015. We found that approximately 300 drug candidates (70%) were discontinued, about 70 (17%) are undergoing preclinical assessment, 40 (9%) are in various phases of clinical trials and only 19 (4%) have reached the market (Fig. 1).

The 430 drug candidates can be divided into two main categories based on their mechanism of action: thrombolytics and neuroprotective agents. Thrombolytic therapy aims at removing the thrombus blockage and includes drugs that act as plasminogen activators, antithrombotic agents and platelet aggregation inhibitors. Neuroprotective agents aim to halt the ischemic cascade and prevent secondary injuries or at least decrease the loss of vulnerable neurons in the ischemic penumbra[7,8]. Neuroprotective agents act by various mechanisms including as antioxidants, neuron stimulants, calcium channel antagonists and free radical scavengers.

2. Drugs discontinued in clinical trials

Analyzing the 300 drug candidates that did not reach the market reveals several interesting aspects. First, 72 (24%) drugs were thrombolytics and included inhibitors of thrombin, factor Xa, platelet aggregation and serine endopeptidase (Fig. 1). Of the remaining 228 failed drugs, 74 (32%) were central nervous system neuroprotective agents with putative ability to either limit the toxicity of the major excitatory neurotransmitter glutamate[9] or act as calcium channel antagonists. An example of the latter is the atypical analgesic ziconotide (trade name Prialt), derived from the toxin of the cone snail as the synthetic form of an ω-conotoxin peptide. It was originally launched by Elan Corporation for the treatment of severe chronic pain where it acts as a selective N-type voltage-gated calcium channel blocker[10]. Phase III clinical trials

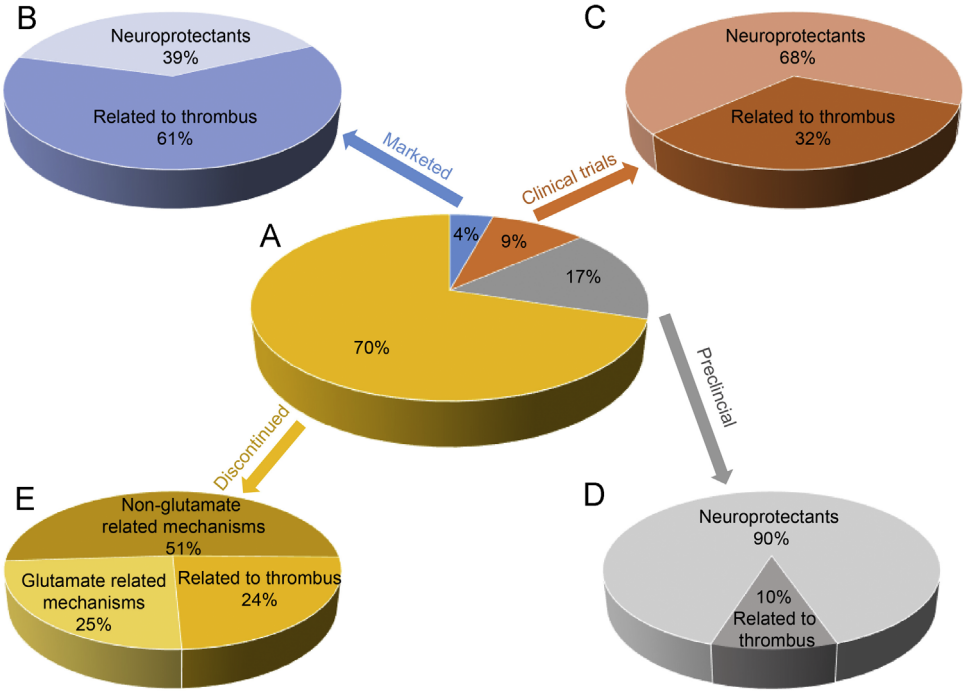

Figure 1 The landscape of ischemic stroke drug discovery and therapy over the period 1995–2015. (A) The classification of 430 drug candidates by pie chart based on the mechanism of action: (B) the 4% of drugs on the market; (C) the 9% undergoing clinical trials; (D) the 17% undergoing preclinical evaluation and (E) the 70% of failed drug candidates.