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(CNS and Neurological Disorders)

Editor:
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(Volume 12)

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PREFACE

Brain disorders are a major public health and economic concern. The causes of these disorders are heterogeneous, and so as the treatment options. State-of-the-art advances in scientific techniques, evolving clinical observations, and diagnostic accuracies to study the neurobiology of different diseases are very illuminating, and assist in not only deciphering the physiology of brain disorders but also the mechanisms that make people more vulnerable to these disorders.

As our understanding is evolving, our knowledge is expanding, and so is our book series *Frontiers in Clinical Drug Research - CNS and Neurological Disorders*. The organization and content of volume 12 of our book series like its predecessors sets the physiology of the brain by outlining the pathology of neurodegenerative disorders, the role of neuroinflammation in neurological disorders, aging in brain tumors, comorbidities in epilepsy as well as placebo effect based on available empirical evidence by actively formulating, synthesizing, and analyzing these pieces of evidence. The relationships between these medical illnesses are complex, multifactorial, and bidirectional.

Since the aim of the series is to include current advancements in the field, rather covering the materials exhaustively, this volume also precisely educates readers about the salient examples of the latest advancement happening in the translational research of various brain aliments, encompassing neurodegenerative disorders and neurological disorders. The volume also contextualizes the engaging and accessible introduction to drug repurposing for neurological disorders. The last chapter of the volume also discusses the organophosphorus poisoning or intoxication emergency, a very scarcely discussed topic, with reference to neuroactive drugs that can be used to treat it.

Briefly, **Chapter 1** highlights the current approaches used for tracking the new drugs by reviewing recent drugs tested in clinical trials for the treatment of Alzheimer's and Parkinson's diseases. **Chapter 2** summarizes an intellectual and conceptual framework for understanding the neurobiology of placebo by interpreting its evolutionary origin, meanings, mechanisms, monitoring, and implications from therapeutics' perspective. **Chapter 3** discusses the role of gut microbiota in neuroinflammation and neurological disorders. **Chapter 4** glances the role of age in pediatric tumors of the central nervous system. **Chapter 5** comprehensively and critically assesses the current knowledge about epilepsy when it is comorbid with the full range of medical disorders with reference to drug repurposing in clinical trials. **Chapter 6** reviews the progress on the development of oxime derivatives as a potential antidote for organophosphorus poisoning.

Therefore, each chapter in the book very ostensibly introduces beginners in the basic science to the primary as well as advanced knowledge in the field. At the same time, these chapters are equally valuable not just for other mental health professionals, and psychiatrists but also for a wide range of medical specialists as well. Besides, it offers researchers, postdoctoral fellows, and students in diverse fields of neurobiology, neurology and neuroscience the tools they need to obtain a fundamental background in the major neurodegenerative, and neurological disorders. In conclusion, the volume provides a glimpse into the future that we are moving toward by exploring a greater understanding of the common pathways that mediate neuropathological illnesses, symptoms, and the relevant pathophysiological and neurophysiological phenomenon.

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CHAPTER 1

Recent Drugs Tested in Clinical Trials for Alzheimer´s and Parkinson´s Diseases Treatment: Current Approaches in Tracking New Drugs

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Abstract: Affecting more than 50 million people worldwide and with high global costs annually, neurological disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) are a growing challenge all over the world. Globally, only in 2018, AD costs reached an astonishing $ 1 trillion and, since the annual costs of AD are rapidly increasing, the projections estimate that these numbers will double by 2030. Considering the industrial perspective, the costs related to the development of new drugs are extremely high when compared to the expected financial return. One of the aggravating factors is the exorbitant values for the synthesis of chemical compounds, hindering the process of searching for new drug candidates. In the last 10-year period, an average of 20 to 40 new drugs were approved per year, representing a success rate of less than 6%. However, the number of referrals for new drug orders and/or applications remained at approximately 700 each year, reinforcing the difficulty in the process of identifying and developing novel drugs. Regarding neurodegenerative diseases, the FDA (USA) approved 53 new therapies in 2019, including 48 new molecules and, from these, three are medicines and two are vaccines. The main drugs recommended for the treatment of these disorders are included in the following classes: Dopamine supplement (Levodopa), Monoamine oxidase (MAO) inhibitor (Selegiline, Rasagiline), Dopamine agonist (Apomorphine, Pramipexole), and Acetylcholinesterase inhibitor (Donepezil, Rivastigmine, Galantamine). Additionally, the current pharmacological treatments are not able to cure these patients and considering the etiological complexity and the prevalence of neurological disorders, scientists have a

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great challenge in exploring new therapies and new molecules to find an adequate and viable treatment for these diseases. Clinical trials are essential in this process and thus, this chapter describes the most important drugs that were targets of phase III and IV clinical studies in the last five years, associated with the most common neurological disorders worldwide, AD and PD. Information about mechanisms of action, experimental studies in other diseases that support their use, and chemical structure of the drugs are included in this chapter. Additionally, nature as a source of valuable chemical entities for PD and AD therapeutics was also revised, as well as future advances in the field regarding tracking new drugs to get successful results and critical opinions in the research and clinical investigation.

Keywords: Acetylcholinesterase inhibitor, Clinical trials, FDA, Neurological disorders.

INTRODUCTION

Neurological diseases (ND) are a heavy burden carried by patients, their families, communities, and governments [1]. As the world population grows old, especially in developed nations, the combined annual costs of ND are rapidly rising [2]. In the United States, the social burden of ND is up to $ 800 billion, and disorders like Parkinson's disease (PD), Alzheimer's disease (AD), and other dementias represent more than one-third of these ND [2]. For elderly, ND can dramatically increase health care costs due to other associated comorbidities, such as Idiopathic Parkinson's Syndrome (IPS) disease and fall-related fractures [3]. It is estimated that about 61% of the IPS patients will have at least one fall during the course of the disease, and 39% will suffer multiple falls, generating high disease-specific costs [3]. In 2015, German data showed that IPS patients' treatment cost was more than € 3.2 billion, which amounted to about 1% of Germany's total annual medical expenses [3]. Projections estimate that by 2050 only AD dementia will have a devastating impact, affecting 131 million people worldwide [4]. In 2018, AD costs were nearly $ 1 trillion and, since the annual costs of AD are rapidly increasing, the projections estimate that these numbers will double by 2030 [4].

To reduce this social burden related to ND as a whole, not only for AD and PD, a global effort towards discovering new drug therapies that may reduce these costs is welcome. That is a concern mainly because many ND still have poorly defined or even undefined etiopathogenesis [5]. In addition, many ND present subjective and context-dependent clinical manifestations, making the sample selection for treatment trials, using clinical criteria, inevitably heterogeneous [5]. Due to this heterogeneity, the inclusion criteria for the studies are often more rigorous, adding to the time, cost, and risk to the drug development process [6]. All these aspects, when combined, reflect the success rates of new drugs for ND, which are the lowest for any therapeutic area [6]. For example, in the early 2010 decade, less

than 10% of the potential drugs that started clinical testing reached the market, and from the compounds that eventually moved on to phase III testing, less than 50% got approval [6]. This scenario explains why clinical research programs for ND tend to be longer and more complex than those for other diseases [6].

In 2008, Pharmaceutical Research and Manufacturers of America (PhRMA) presented a report that contained more than five hundred drugs for neurological disorders, which were still in the development stage [6]. When analyzed in detail, the reports data demonstrated that the research and development (R&D) pipeline contained previously known drugs, undergoing repurposing processes, *i.e.*, tested for new indications [6].

Regarding the pipeline of drugs and biologics in clinical trials for the treatment of AD, a recent study that has utilized a survey of annual pipeline reports of the past five years provided a longitudinal insight into clinical trials and drug development for AD [4]. According to the Common Alzheimer's and Related Dementias Research Ontology (CADRO) for classifying treatment targets and mechanisms of action, the results revealed that, in 2020, there were 121 agents in clinical trials to treat AD [4]. Among them, there were 29 agents in phase 3, 65 in phase 2, and 27 in phase I trials. Also, the data showed testing of twelve agents in trials targeting cognitive enhancement, twelve intended to treat neuropsychiatric and behavioral symptoms, and 97 agents in disease modification trials [4]. For example, compared to the 2019 pipeline, these data showed a growth in the number of disease-modifying agents targeting pathways other than the amyloid or the tau pathways [4]. Finally, the clinical trials' data from the last five years showed a progressive emphasis on non-amyloid targets. Those candidate treatments aim at targets involving mechanisms like inflammation, synapse, neuronal protection, vascular factors, neurogenesis, and interventions on epigenetics [4]. Also, data revealed significant growth in the repurposed agents' pipeline as well [4].

In recent years, several drugs with the potential to modify the disease and with neuroprotective effects are being evaluated in preclinical and clinical studies. The United States stands out for conducting the largest number of phase III and phase IV clinical studies, both for AD and PD Fig (**1**). Thus, this chapter summarizes the most important drugs that were targets of clinical studies from 2015 to 2020, associated with the most common neurological disorders worldwide: AD and PD. The approached clinical studies are related to phase III and IV studies registered on *clinicaltrials.gov*. Data like mechanisms of action, experimental studies in other diseases that support their use, and chemical structure of the drugs are included in this chapter. Also, a revision focused on nature as a source of valuable chemical entities for PD and AD therapeutics is also reported. Finally, future adv-

CHAPTER 2

Neurobiology of Placebo: Interpreting its Evolutionary Origin, Meaning, Mechanisms, Monitoring, and Implications in Therapeutics

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Abstract: Placebo is defined as the therapeutic response to inert treatment. However, this is a bit simplistic because comprehending the biological basis of the placebo effect requires understanding the entire therapeutic context and the patient immersed in it. Placebo does not cure the disease but alleviates symptoms. The placebo impact must be seen in the context of the recipients' cultural milieu, psychosocial background, the tone and tenor of the accompanying verbal communication (caring, indifferent, unfriendly), therapeutic rituals (*e.g.*, tablet, injection, or a procedure, including diagnostic tests), symbols (white coat, syringe, the diagnostic paraphernalia), and its meanings to the patient (past experiences and personal hope). Placebo is the inert treatment juxtaposed against the broad context of the accompanying sensory and sociocultural inputs that signal benefit. It could also be the harm in the case of nocebo. A major objective of a standard clinical trial is to eliminate or at least minimise the influence of placebo. Many methods have been devised to measure and eliminate placebo responders in the trial populations. The neurological basis of the placebo effect is complex and must have an evolutionary basis because the susceptibility to placebos may be traced back to animals and birds. The placebo effect probably owes its evolutionary origin to signalling sickness and the ability to draw comfort from winning sympathetic attention and care from conspecifics. Pain being a complex sensory experience with a strong affective component, the neuronal pathways that reflect both sensory experience and the affective components have been explored in the study of the placebo effect. Placebo research, having expanded from psychology to neurology, presently involves research tools that include pharmacology, brain imaging, genetics, animal models, *etc.* This review will discuss multiple dimensions of the placebo effect, including evolutionary, cultural, psychosocial, and neurological aspects, in addition to providing cues for transformational implications in clinical trials and therapeutic modalities that benefit

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society. Contemporary medicine is demonising placebo because it is a confounder in clinical trials. It would be much more useful if the healthcare system can harness the therapeutic potential of the placebo effect by manipulating the therapeutic context.

Keywords: Cognition, Evolutionary biology, Neurobiology, Placebo.

INTRODUCTION

The urge to heal is intrinsic to all forms of life. The enduring recuperative drive, the *sine qua non* for survival, is mostly unconscious and innate, and begins at the molecular level -- even the DNA is equipped with the technology for self-repair. The most primitive parts of the brain handle the most fundamental life-sustaining functions, demonstrating its evolutionary antiquity as well as the minimal need for 'intelligent' interventions by the conscious mind. The healing power of physicians, until recently, rested mostly on the results of the placebo effect [1]. This is self-evident today because we know that many of the pre-World War remedies were either useless or positively harmful. There is a scandalous account of how Calvin Coolidge Jr died, quite possibly from the treatment he received for infection [2]. Despite so many ineffective and hazardous remedies, the medical profession has consistently enjoyed society's awe and trust for thousands of years. Voltaire probably had the placebo effect in mind when he famously said, "The art of medicine consists of amusing the patient while nature cures the disease" [3].

There is a growing tendency to attribute the combined role of mind and body in fighting and recovering from illnesses [4]. Studies suggest that subjective perceptual states such as mindsets and expectations influence human physiology. For instance, young adults could improve their vision when exposed to a mindset patterned to suit pilots and athletes. For instance, vision improved when subjects learned to read the Snellen Eye Charts in reversed progression [5]. Those who were scared of catching the flu in winter actually expressed more real flu symptoms. This is consistent with the idea that the brain influences metabolic and endocrine regulation based on environmental challenges, appropriate to the context of available resources. Such a scheme has an evolutionary advantage because expectations prepare the body to cope better with an anticipated event.

The many case records of miraculous cures reinforce the value of subjective interventions. For instance, at the famous healing shrine of Lourdes, literature reports 176 cases of cancer that regressed without treatment [6]. Considering that people of different religious faiths experienced such cures, success appears to have depended more on the patient's state of mind than religious faith. On the other hand, these cures do not violate the laws of nature. They merely hasten the

normal reparative process [7]. 'No one has grown a new limb or an eye at Lourdes', quotes a review on placebo!

The Context of Health and Disease: The Mind-Body Continuum

A recent study by Harvard University threw up a surprise [8]. When diabetics were asked to drink the same sweetened beverage from different bottles, with labels declaring different sugar contents, the rise in blood sugar in each individual was proportionate to the labelled sugar content, not the actual sugar content in what was consumed. In another study by the same department, they employed manipulated 'fast' and 'slow' clocks to modify the perception of time in type 2 diabetics. Interestingly, a fall in blood sugar correlated with the perceived time interval, not the actual time interval. In other words, the metrics of the environment must be meaningful to the mind; subjective perception can control the metabolic trajectory.

The role of the mind in metabolic regulation is not limited to diabetic subjects [9]. Women who were conditioned to consider work as a kind of exercise achieved greater weight control and a fall in BMI (body mass index). In another study, the ghrelin levels in subjects consuming milkshakes depended on the labelled calorific value rather than the true calorific value [10]. Yet another study showed that just believing to follow a low-calorie diet (while actually on an energy-balanced diet) can help reduce body mass. Endocrine regulation, as well as its potential disruption, is influenced by the conscious mind [11].

There is an evolutionary advantage in such perceptual neuroendocrine controls. Consciously anticipated events can potentially prepare the body to become future-ready. Maintaining the time course of blood sugar must have been much more difficult in the food-insecure primitive environment. In corollary, an evolutionary mismatch can explain the recent surge in metabolic disorders.

Placebo and the Therapeutic Context: the Evolutionary Backdrop

While the placebo effect is the response to inert treatment, the placebo phenomenon, in its totality, is a lot more complex [12]. PE constitutes a number of diverse variables/ entities that create the therapeutic context as a whole. The words uttered by the physician during encounters at the hospital, the body language of physicians, nurses and bystanders, the therapeutic rituals of diagnosis and treatment, the seemingly trivial, but ominous symbols and signals, such as white coats, stethoscopes, the smells of antiseptics, signboards notifying say, 'Cancer Hospital', (possibly a 'death sentence'), *etc*., combine to create the therapeutic context. Every accompanying sensory/social stimulus that signal benefit, along with all the procedural rituals of therapeutic interventions, merges

CHAPTER 3

Role of Gut Microbiota in Neuroinflammation and Neurological Disorders

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Abstract: The prevalence of neurological diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Multiple sclerosis (MS) are growing in the world, but their pathogenesis is unclear and effective treatment does not exist. Neuroinflammation is associated with many neurodegenerative mechanisms involved in neurodegenerative diseases. The human gut microbiota is an aggregate of microorganisms that live in the gastrointestinal tract (GIT) that plays a crucial role in maintaining human health and the pathogenesis disease condition. The microbiota can affect neuronal function through neurotransmitters, vitamins, and neuroactive microbial metabolites like short-chain fatty acids. The change in gut microbiota architecture causes increased permeability of the intestine and immune system activation, contributing to systemic inflammation, neurological injury, and eventually neurodegeneration. Available data suggest that the microbiota send signals to the central nervous system (CNS) by activating afferent neurons of the vagus nerve *via* neuroendocrine and neuroimmune pathways. The molecular interaction between the gut/microbiome and CNS is complex and bidirectional, ensuring gut homeostasis and proper digestion. Evidence suggests that dysfunction of the gut-brain axis could be a significant factor leading to many disorders of CNS. In this chapter, we explore how the gut microbiome may affect brain function and the development of neurological disorders. In addition, we are also trying to highlight the recent advances in improving neurological disease by supplemental probiotics and faecal microbiota transplantation *via* the concept of the gut-brain axis to combat brain-related dysfunction.

Keywords: Alzheimer's disease, Central nervous system, Parkinson's disease, Gastrointestinal tract, Microbiota, Multiple sclerosis, Neuroinflammation.

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INTRODUCTION

The human microbiome comprises bacteria, viruses, archaea and eukaryotic organisms that live in and on our bodies. These microbes potentially affect human physiology, both in health and illness conditions [1]. The human microbiota is estimated to include 10^{13}–10^{14} microbial cells, with a microbial cell-to-human cell ratio of about 1:1. The varied gut microbiota comprises bacteria classified as Firmicutes, Bacteroidetes, and Actinobacteria [2]. This diverse and complex microbiome functions as a functional extension of host genomes, with an estimated 50–100-fold increase in gene count compared to the host. These additional genes have resulted in various enzymatic proteins that were not previously encoded by the host and serve a vital function in aiding host metabolism and therefore contribute to the control of host physiology [3]. The microbiota helps the host in many ways, including improving gut integrity and shaping the intestinal epithelium, harvesting energy, protecting against pathogens, and regulating host immunity. However, these processes may be disturbed due to changed microbial composition, a condition known as dysbiosis. However, these processes may be concerned due to altered microbial composition, a condition known as dysbiosis. With the development of more sophisticated techniques for profiling and characterizing complex ecosystems, it has become increasingly clear that the microbiota plays a role in a wide variety of intestinal and extra-intestinal illnesses [4].

COMPOSITION AND STRUCTURE OF THE HUMAN GI MICROBIOTA

The human gastrointestinal tract is a complicated system that starts at the oesophagus and ends at the anus, with most data collected to date from the distal colonic microbiota owing to specimen collecting practicalities. Significant physiological factors like as pH, bile content, and transit time change throughout the GI tract, contributing to the existence of different microbial populations in the upper and lower GI tracts [5]. The gut microbiota is not as varied as bacteria found in other body parts and has a high degree of functional redundancy. A comprehensive inventory of the human gut microbiome's functional capability was recently acquired, with 9879896 genes discovered using a combination of 249 newly sequenced and 1018 previously published samples. The study identified country-specific microbial signatures, suggesting that environmental factors, such as diet, shape gut microbiota composition, and possibly also by host genetics [6]. However, it is noted that microbiotas with varying designs may exhibit some functional redundancy, resulting in comparable protein or metabolite profiles. This knowledge is crucial for developing treatment therapeutic strategies to modify and shape the microbial community in disease. It is critical to evaluate

cognition, hearing, vision, and speech first to interpret examination results accurately.

INTERACTION OF GUT AND NERVOUS SYSTEM, GUT-BRAIN-AXIS

The gut-brain connection was identified for the first time by Gershon American physicist at the end of the 19th century. The gut-brain axis communicates in two directions between the brain and the gut. For instance, the CNS influences gut function in reaction to psychological and physical stresses, altering motility, secretion, and immunological reactivity, while alterations in the gut microbiota may result in behavioral and neurochemical changes [7]. The microbiota-gut-brain axis control the GI tract and CNS through the vagus nerve, hypothalamic–pituitary–adrenal axis, and various cytokines.

The vagus nerve has been a primary focus in recent studies of the gut-brain axis because it represents a major bidirectional connection between the body and the brain. The vagus nerve is the 10th cranial nerve and serves several GI organs such as the oesophagus, stomach, small intestine, and colon, as well as other digestive organs such as the liver, pancreas, and gallbladder, as well as cardiopulmonary organs such as the heart, lung, trachea, and aortic arch [8]. Sensory (afferent) and motor (efferent) fibres coexist in the vagus nerve, but their cell bodies are located in different places: sensory neurons in the nodose/jugular ganglia adjacent to the jugular foramen and motor neurons in the dorsal motor nucleus of the vagus (DMV) and the nucleus ambiguus in the brainstem. Sensory neurons of the vagus nerve are genetically diverse, with a wide range of molecular machines for sensing stretch, tension, and other chemical signals, as well as connecting with other sensory cells such enteroendocrine cells, neuroepithelia bodies, taste buds, and enteric neurons. The vagus nerve's genetically unique sensory neurons are expected to encode different body information [8].

The gut microbiota controls the gut-brain axis, where brain communication to the GI tract is linked to permeability, motility, secretion, and immunological modulation in the brain's function. The gut-brain axis comprises the immune system, neuroendocrine system, GIT, ENS, ANS, and CNS, controlling afferent and efferent regulation. The GI tract regulates endocrine and exocrine secretions, motility, and microcirculation and is also involved in immunological and inflammatory processes. Numerous brain regions, including the hypothalamus, pituitary adrenal (HPA), and vagus nerve system, regulate metabolic, immunological, and homeostatic functions [9].

Changing the composition of the gut microbiota may disrupt gut homeostasis and affect the CNS and many metabolic diseases such as inflammatory bowel disease (IBD). The health-promoting bacteria concentration is reduced when the

CHAPTER 4

The Role of Age in Pediatric Tumors of the Central Nervous System

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Abstract: Pediatric tumors of the central nervous system (CNS) are the second most common type of solid childhood cancer. As such, they have a major effect on the rates of morbidity and mortality in children. CNS tumors originate from abnormal cells in the brain and/or spinal cord, which can be classified as either benign or malignant. They can be further subdivided into different categories based on several principal aspects, such as tumor location, histopathology, and developmental age. Among these various characteristics, age is one of the most consequential determinants for CNS tumors. Specific groups between 0 and 21 years of age, for instance, have radically divergent landscapes in terms of their tumor incidence and unique biology. Depending on the age of the child, key case features may differ like the clinical evaluation, medical diagnosis and prognosis, recommended therapy and treatment courses, anticipated responses and tolerability to treatment, and management of side effects. Effective teamwork is another crucial component for the successful management of pediatric CNS tumors. In patient-and-family-centered care, ensuring a detailed education of the children and their families, as well as their involvement in the decision-making process where appropriate, is imperative. To determine the best available options for the patient, multidisciplinary medical teams will often deliberate over all of the possible procedures. The holistic care provided by these inter-professional collaborations for this vulnerable population will depend on the age of the child, in addition to the level of patient and family participation. Evidence shows that support and counseling of the patient and their family during the entire treatment process can have a significant impact on outcomes. This chapter will review the essential diagnostic and prognostic considerations of childhood CNS tumors, with special emphasis placed on favorable therapies and treatments, including in-depth discussions around the multi-faceted responses to treatment and the management of its side effects. In particular, this content will highlight the critical role that age, and interdisciplinary healthcare teams play in comprehensive disease management.

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Keywords: Age, Brain, Central Nervous System, CNS, Disease Management, Multidisciplinary, Pediatric, Quality of Life, Spinal Cord, Tumors, Team, Treatment.

INTRODUCTION

2020 was a harrowing year in human health history. For Andrew Kaczynski and Rachel Louise Ensign, it was no different. Six months after then-President Donald Trump declared a state of emergency over COVID-19 in the United States (U.S.), Andrew and Rachel received news that no parent would wish upon another—their six-month-old daughter, Francesca "Beans" Kaczynski, had just been diagnosed with a rare and aggressive brain cancer known as atypical teratoid rhabdoid tumor (ATRT). This type of tumor often manifests in the cerebellum or brain stem, which are largely responsible for coordinating movement and controlling basic body functions, respectively. Symptoms include headaches, nausea, and vomiting, as well as balance loss and an abnormally large head size in infants. Prior to Beans' supervising physician developing a novel treatment protocol at the Dana-Farber Cancer Institute in Boston, Massachusetts, ATRT was effectively a death sentence for kids. Now, the survival rate for children with ATRT over the age of three can be as high as 70%; however, if the child is under one, then their chance of survival plummets to less than 10%. How can merely two years of life account for more than a seven-fold difference in surviving such a pernicious disease? This tragic discrepancy is due in part to treatment protocols not recommending radiation therapy for babies before they reach 12 months. With limited options in the wake of this grim prognosis, Beans passed away just three months later on Christmas Eve [1].

Although this case is fortunately far and few between, pediatric tumors of the central nervous system (CNS) continue to affect families around the nation and across the world every day. While an average of only 60 cases of ATRT are identified in the U.S. each year [2], 500 more children are diagnosed with medulloblastoma [3]. Approximately one in every four American children with a brain tumor has medulloblastoma, making it the most common type among adolescence [4]. Overall, depending on the country, the annual incidence of pediatric brain tumors ranges from 1.15 to 5.14 cases per 100,000 children [5]. These sobering rates translate to tens of thousands of children developing CNS tumors worldwide, wherein the causes are mostly unknown a number do not survive. The survivors encounter immense challenges related to their physical and psychological health, in addition to various social and intellectual obstacles. Nevertheless, children with brain tumors generally have a better prognosis than adults with similar conditions [6]. For all forms of brain tumors, approximately 3 out of 4 children survive for at least 5 years after their diagnosis [7]. Clinical

outcomes for these vulnerable patients have improved tremendously in recent decades, with the implementation of advanced screening measures and the development of targeted treatment strategies [8]. The field of pediatric oncology continues to grow and progress in what is a very active area of research.

This chapter will explore the essential diagnostic and prognostic considerations of childhood CNS tumors, with special emphasis placed on favorable therapies and treatments, including in-depth discussions around the multi-faceted responses to treatment and the management of its side effects. In particular, this content will highlight the critical role that age and multidisciplinary healthcare teams play in comprehensive disease management. The key learning objectives are to:

1. Discuss the procedures for performing a clinical evaluation and rendering medical diagnoses/prognoses of CNS tumors, according to the fundamental features of the case.

2. Examine the suggested, evidence-based treatment and therapy options for CNS tumors in children, depending on the medical diagnosis and prognosis.

3. Investigate the patient response to treatment and management of side effects, given relevant circumstances like developmental age and tumor presentation.

4. Review the importance of enhancing holistic care approaches among multidisciplinary healthcare teams by improving the quality of care for vulnerable pediatric populations affected by childhood CNS tumors.

The ultimate goal of this chapter is to provide a comprehensive summary on how CNS tumors are managed in children of different ages while also emphasizing the role of multidisciplinary team care, from diagnosis to post-treatment. Clinically relevant descriptions are given for the most common tumor types in addition to their overall epidemiology, pathological presentation, clinical diagnosis, and treatment regimens. Tumor classifications are separated by their severity scale, from low- to high-grade, with some genetic data included as well. Although the diagnostic criteria and treatment modalities may be similar for these two broad groups of tumors, their management and outcomes are quite different. Furthermore, despite a degree of standardization in treatment strategies among many practitioners and institutions, a variety of emerging and experimental techniques are also employed on a case-by-case basis. General management principles are described in the context of standard therapy, but other approaches may be considered equally valid. This complete presentation should better inform the reader to the different management options for pediatric CNS tumors.

CHAPTER 5

Drug Repurposing in CNS and Clinical Trials: Recent Achievements and Perspectives Focusing on Epilepsy and Related Comorbidities

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Abstract: Central Nervous System (CNS) disorders are a massive burden on the global health system, including a broad range of clinical conditions, such as epilepsies, depression, dementia, multiple sclerosis, and Parkinson's disease. Permanent efforts are being made to find early, non-invasive, and effective diagnostic methods, as well as efficient and safe drug-based treatments for CNS conditions. Nevertheless, many patients displaying these clinical conditions still face the lack of an effective pharmacotherapy to cure the diseases or at least to properly control the progression of symptoms. Currently, epilepsies present an estimated prevalence of 0.5%–1% worldwide, and around 30% of the patients remain refractory to the available drug treatment. The comorbidities that affect epileptic patients, such as cognitive impairment and depression, are major public health challenges. This scenario highlights the urgent need for approving new therapeutic tools for CNS diseases. A successful development process of a new compound presenting therapeutic potential can range up to 20 years and cost hundreds of millions of US dollars, from the initial characterization of the *in vitro* chemical and biological properties until clinical trials. Additionally, drug development has a low success rate in the case of CNS conditions. In this context, drug repurposing (or drug repositioning, DR) is an alternative way to reduce the cost and accelerate the process of a drug-based treatment approach since it identifies a novel clinical application for an existing compound already approved for a distinct indication. In the present chapter, we aim to describe recent outcomes of DR

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aiming at CNS pathological conditions, especially discussing the recent clinical trials and their impacts on future endeavors in the search for the management of epilepsies and related comorbidities.

Keywords: Central Nervous System, Clinical Trial, CNS Diseases, Cognitive Impairment, Drug Repurposing, Drug Repositioning, Epilepsy, Depression, Pharmacotherapy.

INTRODUCTION

The Drug Repurposing Context

Historically, conventional approaches in relation to investing cost and time in a drug discovery campaign would normally involve millions of dollars and decades as average requirements to achieve the target outcomes and introduce final products into the market. This scenario has not substantially changed in recent years, and apparently, it has no expectations to be far from this pattern in the future. Even considering computational campaigns and further modern strategies to improve the time spent in the first *in silico*, *in vitro* and other preclinical steps, the time required to assure the efficacy and safety of new pharmaceutical entities by clinical studies is mandatory. Furthermore, recent estimation of these data reinforces that the average cost required to bring a new approved compound to clinical use is extremely high, being almost 1 billion dollars. In the specific case of drugs targeting the Central Nervous System (CNS), the mean estimates range from around 500 million to more than 1,8 billion dollars of expenditures. Simultaneously, the percentage of final successful compounds in this high-cost context is considerably low, with clinical trial success rates ranging from only 15% to around 51% [1].

The above-mentioned items that contribute to this scenario are acceptably referred to as top facts that pave the way to the continuing search for less expensive alternatives targeting approved drugs, side-by-side with the urgent pharmacotherapy needs in public health systems. In this context, drug repurposing (or drug repositioning, DR) emerges as one of the most promising pathways.

The main idea of DR is focused on using already approved drugs for new therapeutic applications. The history of DR is relatively recent in therapy, and one of the most representative cases is thalidomide [2]. The drug, which was synthesized in the early 1950s by the company Ciba in Switzerland, has been extensively used for years as an antiemetic agent for pregnant women worldwide [3]. However, the first reports on thalidomide-related congenital malformations were raised in the 1960s [4, 5], and the use of the drug was systematically banned.

Simultaneously, researchers have started investigations on alternative applications for the compound, culminating in surprising and successful applications on lepra skin eruptions [6 - 9] and multiple myeloma, also including thalidomide derivatives in this last case [10 - 13]. Besides thalidomide, other drugs have experienced DR pathways, including the recent and successful administration of systemic dexamethasone in the treatment of patients with COVID-19 [14, 15].

In this chapter, we intend to discuss promising approaches, especially clinical ones, targeting new applications of already approved drugs in the context of CNS disorders. The new applications described here are centered on solving drug-resistant epilepsy and two of its most relevant comorbidities, cognitive impairment and depression.

Drug Repurposing Aiming at Cognitive Improvement and Anticonvulsant Activity in Epilepsy

Epilepsies are chronic conditions mainly characterized by the presence of recurrent seizures. The manifestation of these pathological conditions might occur in different forms, including tonic-clonic convulsions. In terms of biochemical and pathophysiological alterations, epilepsies display modifications in the electrical function of the brain tissue, which might be caused by an imbalance between inhibition and excitation events, resulting in abnormal and excessive neuronal activity [16].

Epileptic seizures present different causes. This etiology scenario ranges from genetic to non-heritable pathological alterations, which might be acquired from other medical conditions. All these possible causes might lead to different types of seizures [17]. In general, the diagnosis pathway of an epileptic patient in clinical practice follows two stages. In this process, the focus of the first stage is based on classifying the seizure type or syndrome, followed by the second stage, which is characterized by the search for the disease's cause. Classifications of epilepsies have been extensively dedicated to the characterization of the first stage. However, the cause of the pathological condition is considered of paramount importance in defining the proper pharmacotherapy, as well as the management of the clinical condition during the patient's life [16].

According to recent data, around 70 million people in the world are diagnosed as epileptic patients, and these numbers suggest a current incidence rate of 61.4 in 100,000 people [18, 19]. Antiepileptic drugs (AEDs) are the first choice in the pharmacotherapy of epilepsies, and approximately 70% of patients properly respond to the treatment by using a monotherapy, while about 20-30% of total patients require polytherapy. Despite the current availability of drugs, about one-

CHAPTER 6

Progress on the Development of Oxime Derivatives as a Potential Antidote for Organophosphorus Poisoning

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Abstract: Nowadays, organophosphorus poisoning is the most common emergency throughout the world. Two functionally different types of drugs are used in common to treat such intoxication cases. The first type includes the reactivators of acetylcholinesterase (AChE)-oximes, which have the capability to restore the physiological function of inhibited AChE. The second type includes anticholinergic, such as atropine that antagonizes the effects of excessive ACh by blocking muscarinic receptors. Alternatively, anticholinergic and reactivators may be co-administered to get synergistic effects. At muscarinic and nicotinic synapses, organophosphorus compounds inhibit AChE release by phosphoryl group deposition at the enzyme's active site very quickly. AChE regenerative process can be accelerated by detaching the OP compound at -OH group of the enzyme. OP compound combines with the AChE enzyme forming a complex and making it inactive. After ageing of the inactive state of AChE, it is difficult to break the complex to regenerate the enzyme resulting in acetylcholine accumulation at synapses. To counter the effect of OP compound, oximes catalyse the reactivation of active AChE by exerting nucleophilic attack on the phosphoryl group. Oximes theoretically remove OP compound from the complex by acting on phosphoryl bond resulting in enzyme reactivation. Reactivation of AChE inhibited by OP compounds through the above mentioned approach poses certain limitations. There is no universal antidote capable of effectively restoring AChE inhibi-

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ted by wide-ranging OP compounds. The oxime reactivators are efficient only when administered before the "ageing" of AChE-OP complex. Anticholinergic drugs, like atropine, are effective only on muscarinic receptors but not on nicotinic receptors (nAChRs).

Keywords: Acetylcholine, Acetylcholinesterase, Atropine, Obidoxime, Butyrylcholinesterase, HI-6, Organophoshosphorus, Poisoning: Oxime, Reactivation, 2-PAM.

INTRODUCTION

History

The history of organophosphate (OP) compounds began in 1800, when Moschnine [1, 2] synthesized a mono ester named tetraethyl pyrophosphate (TEPP). The process was first published in 1854 by de Clermont [3]. Nearly 80 years later in 1934, Dr. Gerhard Schrader, a German chemist, synthesized hundreds of OPs including parathion and tabun (dimethyl phosphoroamidocyanidate), sarin (isopropyl methylphosphonofluoridate), and soman (O-Pinacolylmethylphosphonofluoridate). Schrader later also synthesized a series of fluorine-containing esters including diisopropylfluorophosphate (DFP) and sarin, pyrophosphate esters including TEPP and octamethylpyrophosphortetramide (OMPA), and thio and thiono phosphorus esters including parathion and its oxygen analog paraxon [4, 5] led by observations of Lange and Kruger, who described the synthesis of two OP compounds and noted that their vapour inhalation produced certain health effects, engaged in the exploration of this type of compounds. Their work resulted in the synthesis of parathion; one of the most frequently used OP pesticide in recent decades. After II World War, thousand of OP compounds were synthesized worldwide for various purposes (pesticides, nerve agents in medicine and in chemical warfare, flame retardants and parasiticides in veterinary medicine). Due to the lack of persistence in the environment and in exposed individuals and due to lesser insect resistance development in comparison to organochlorine pesticides, the OP pesticides are today the most commonly used group of pesticides throughout the world. It should be emphasized, that from several points of view (public health and intensive agriculture), their use today is a must and not an option. Although their persistence in environment is relatively low, the extensive use of OP pesticides in modern agriculture has raised several problems regarding environmental and food safety issues [6 - 8].

The OP compounds have a wide variety of applications, hence is a serious threat for occupational hazard, self-poisoning, unintentional misuse, terrorist attack and

threats of warfare use, not only for army rather civilian targets as well. Organophosphates are mainly used for civilian purposes as a pesticides or acaricides, *etc.* but their acute toxicity is comparable to the organophosphonates, developed for military purposes.

OP poisoning has been a frequent cause of admission of people to hospitals and Intensive Care Units (ICU) in developing countries [9]. OP poisoning causes about 3 million acute intoxications annually, 0.3 million of which lead to fatalities [10]. OPs that were developed as chemical warfare nerve agents (CWAs) are all highly toxic and dangerous [11 - 13]. OP nerve agents have been used and are most likely to be used in the future by terrorists and dictators around the world because of their relatively easy synthesis and availability of suitable delivery systems [14]. Warfare and terrorist use of CWAs include the Aum Shinrikyo terrorist attack in the Tokyo subway in 1995, the 1980–1988 Iraq–Iran war where Iraq reportedly used nerve agents against Iranian troops and later on Kurd civilians and the murder of a family member of the North Korea Leader, Kim Jong Nam on February 2017 in Kuala Lumpur [15 - 17]. Despite international efforts aimed at regulating and lessening the use of these environmentally toxic compounds, more than 100 different OP compounds are still being used intensively as pesticides, with only unreliable or sporadic monitoring of the environment and workers involved in their use.

Organophosphorus Compounds

Organophosphorus compounds are esters, amides or thiol derivatives of phosphoric, phosphonic, phosphinic acids, and phosphorothioic or phosphonothioic acids. The phosphonic acid derivatives are more toxic than the phosphoric acids (Inchem.org) whose oxygen atom can be substituted by sulphur or nitrogen atoms [18]. In other words, it is an organic compound that contains phosphorus as an integral part of the molecule and formed by the reaction of alcohol and phosphoric/phosphonic/phosphinic acids.

General Structure Of An OP

The basic structure of an OP compound consists of the following;

a. A central phosphorus atom (P).
b. P is double bonded to either oxygen or sulphur.
c. A leaving group which is specific to the individual organophosphorus. It is a labile acyl residue (halide, cyano, phenol, or thio group).
d. R_1 and R_2 groups which are ethyl or methyl, alkyl, alkoxy, alkylthio or amino group.

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ZAREEN AMTUL

Prof. Amtul due to her background in clinical psychiatry and neurodegenerative disorders, brings expertise in neuroanatomy, pathophysiology, drug development, and diagnosis of brain disorders. Prof. Amtul's main area of research has been chemical biology and medicinal bioinorganic chemistry. Prof. Amtul has extensively researched the biochemical, molecular, and behavioural substrates of memory impairment in Alzheimer's disease, vascular cognitive impairment, stroke, depression, epilepsy, and frontotemporal dementia-related disorders using biochemistry, structural biology, optogenetics, decoy, and Trojan horse technologies, bioinformatics, and computational biology. She is a recipient of several national and international awards in basic and SoTL research including the J. William Fulbright award from the USA, the Alexander von Humboldt-Stiftung award from Germany, the Ontario Mental Health Foundation, and the CIHR Strategic Training awards from Canada, as well as a few international traveling grants. She is also the recipient of the Pasha Begum Best Mentor Award from the American Society of Science, Engineering, and Technology (ASSET), USA.