Advances in drug discovery and development in geriatric psychiatry

Drug discovery for disorders of the central nervous system is a long and challenging process, with a high attrition rate from the preclinical stages through to marketing a compound. In geriatric psychiatry, the heterogeneous nature of these disorders and their origins, makes finding effective treatments that work across larger numbers of patients challenging. Additional issues are the large amount of comorbid diagnoses, and the often lack of relevant animal models of these disorders.

The initial discoveries of pharmacological agents that could alter psychiatric diseases were often found by serendipity and were a result of the disease model that started with the behavior, while understanding how these agents affected cortical mechanisms was a secondary concern. However, following this period, there has been limited success in developing effecting new compounds for neuropsychiatric disorders. This decrease is driven in part by the fact that all the easy or straightforward targets for pharmacologic modulation have all been investigated, so the new approaches have needed to be more systematic than the earlier approaches to identify potential targets. These new methodologies are being aided by a greater understanding of the cortical underpinnings of these disorders, as well as technological advancements. One advantageous approach is the use of induced pluripotent stem cell cultures or immortalized cell lines from patients. These cell cultures have enabled lead targets to be tested on disease-specific tissues, which increases the likelihood of identifying a compound with high efficacy.

There have been several promising new targets for the development of drugs for geriatric psychiatric disorders and we focus on a number in this article. We look at drugs specifically targeting protein kinases and myeloid cells. Also, we describe the intricate mechanisms of new agents including multi-target compounds, allosteric modulators of synaptic or presynaptic receptors, epigenetic drugs and the repurposing of approved drugs.

Myeloid cells are bone marrow-derived cells found in the central and peripheral nervous systems and include many support cells such as microglia and macrophages. Myeloid cells make an attractive target for new agents as they are involved in the cortical immune system and inflammation. Drugs affecting protein kinases have been used in cancer, but they are also increasingly the targets of neuropsychiatric drug discovery. This is because they act as mediators of phosphorylation of other lipids, proteins, and sugars. By targeting protein kinases, researchers aim to modulate cellular metabolism, thereby affecting downstream cortical processes.

A strategy to overcome the multimorbidity and heterogenous nature of geriatric psychiatric disorders is to utilize multi-target drugs. By combining two or more agents together, these new compounds may be more effective at treating multiple symptoms, while reducing the potential for drug-drug interactions. Allosteric modulators of synaptic receptors do not bind to the primary (orthosteric) binding site of the receptor but rather to other sites on the receptor. Positive or

negative allosteric modulators are only active when the target neurotransmitter is also binding at the primary site, which reduces the possibility of side effects or off-target effects, a problem which has plagued the development of orthosteric agents in the past. Epigenetic drugs, such as DNA methylation inhibitors, aim to alter or reverse maladaptive epigenetic mechanisms that can have downstream effects on the cortical processes, possibly resulting in a slowed or halted disease progression. Finally, there has been an increase in the repurposing of approved compounds for new disorders. This represents a cost-effective way of addressing symptomatology.

In a field rife with failure, there is hope that these new pharmacological agents, designed with a focus on systems pharmacology, offer the potential to produce disease-modifying effects in geriatric psychiatric disorders.

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