

COMMENTARY

The Mind Bending Quest for Cognitive Enhancers

E Arce¹ and MD Ehlers²

Adequate cognitive functioning is essential for daily activities. When there is an insult to the brain, cognitive abilities can suffer, which, in turn, produce substantial medical and functional impairment. Advances in neurobiology, circuit neuroscience, and clinical assessment technology are converging in a manner that holds promise for the development of new pharmacological agents for cognitive enhancement in neuropsychiatric disease.

Whether coca leaves, Ginkgo Biloba, nicotine, or caffeine, the use of psychoactive compounds to “improve” cognition is ancient and universal. Major advances in the modern pharmacology of cognitive enhancers occurred in the 1960s, including the work of the Romanian psychologist and chemist Corneliu Giurgea who synthesized piracetam and referred to compounds that enhance learning and memory as nootropics. Deriving its name from the Greek words for mind (νοῦς) and bend or turn (τρεπεῖν), the subsequent half century has seen a continued effort to find the perfect mind bender to improve cognition in health and disease.

As human beings, we rely on cognitive processes to guide us through life. While we drive to work, we remember to pick up the dry cleaning that we dropped off last week, we maintain a conversation with a family member while we do the dishes, or lay out a step-by-step plan to save for retirement. The cognitive abilities that allow us to perform these and other daily activities involve attention, memory, executive planning, and social cognition, among

others. These complex cognitive processes arise from coordinated neural activity of discrete brain circuits whose function is governed by developmental stage, aging, disease state, and neurochemical status. When there is an insult to our brain, neural processing that directs specific cognitive domains can be impacted, and thus our ability to autonomously navigate daily activities is put at risk.

Several neurological and psychiatric diseases present with deficits in cognition that are fundamental to the disease process and often manifest prior to the syndromic illness. Alzheimer’s disease, a cortical dementia that initiates in the temporal lobe, is characterized by prominent amnesia as well as deficits in attention, language, semantic knowledge, and executive functioning. On the other hand, subcortical dementias, such as Parkinson’s disease, and Huntington’s disease are typified by slowness of thought, impaired attention, and poor planning along with visuoperceptual and constructional deficits. In schizophrenia, cognitive symptoms are severe and include problems with attention and working memory, processing speed,

learning, executive functioning, and social cognition, which remain throughout its course and are strongly correlated with functional outcome. In major depressive disorder (MDD), poor concentration, distorted cognitive processing (i.e., inaccurate perceptions of the world), as well as objective and subjective cognitive control (i.e., ability to adapt moment to moment depending on current goals rather than remaining rigid and inflexible) are often present.

Currently, approved drugs to improve disease-related deficits in cognition provide modest efficacy and have been limited primarily to neurodegenerative disorders, predominantly Alzheimer’s disease. These include cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate (NMDA) glutamatergic receptor blocker memantine, which target classical neurotransmitter systems with an aim to augment the function of specific subclasses of neuronal synapses. Many drugs with diverse mechanisms have been tested in cognitive impairment associated with schizophrenia without success.¹ Gamma-aminobutyric acid_A receptor agonists have been explored in humans as a target to improve working memory with mixed results. No definite success has been found with AMPA modulators, glycine site NMDA receptors agonists, or glycine reuptake inhibitors. Despite the wealth of data pointing at deficits in NMDA receptor function in schizophrenia, glutamate receptor agonists or modulators of various types have failed to show improvement in cognition. Most drugs used to treat schizophrenia block dopamine D2 receptors to improve the classic positive symptoms of hallucinations and delusions, but have failed to demonstrate beneficial effects in cognition. Yet, patients with schizophrenia manifest dysfunction in dopamine-related corticostriatal processes, such as executive

¹Neuroscience Research Unit, Pfizer Inc., Cambridge, Massachusetts, USA; ²Biogen, Cambridge, Massachusetts, USA. Correspondence: MD Ehlers (michael.ehlers@biogen.com)

doi:10.1002/cpt.524

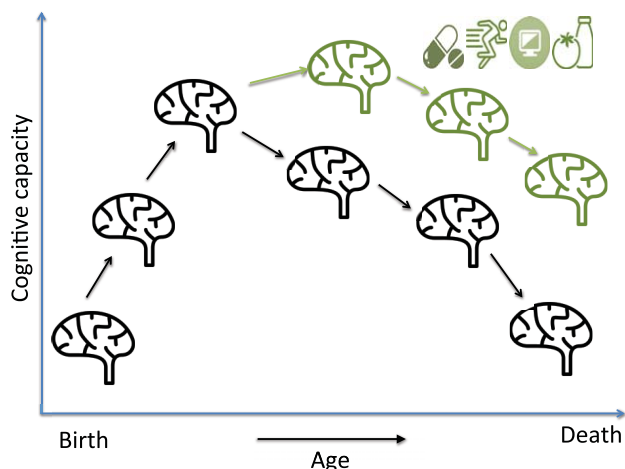


Figure 1 Preservation of cognitive capacity over the lifespan requires a combination of cardiovascular health, cognitive exercise, healthy eating habits, and pharmacological interventions in certain disease states.

function, working memory, and attention. The apparent lack of effect of D2 receptor blockade remains a paradox. The debilitating negative symptoms (e.g., anhedonia, apathy, poverty of speech, and social withdrawal) and cognitive impairment in schizophrenia have been hypothesized to be the result of diminished dopamine activity in the prefrontal cortex but to date there is little understanding of precisely why D2 antagonist treatment is ineffective.

In the early 1990s, the seminal work of Sawaguchi and Goldman-Rakic² led to the proposal of a promising target, the D1 dopamine receptor. Over the ensuing 20 years, a definitive clinical test of selective D1 receptor activation on cognition has been elusive as chemistry caught up with biology. Initial efforts have relied on the D1 agonist compound dihydrexidine. Recently, published work demonstrated improvements in working memory in nonhuman primates but not in humans, which was attributed to dihydrexidine's poor pharmacokinetic profile and exposure,³ features that have plagued all D1-selective ligands discovered to date.

Changing the low success rate in developing cognitive treatments will require a confluence of new science and collaboration among regulators, scientists, and clinicians. Agreement must be achieved regarding what constitutes a treatment target and an appropriate metric because the most appropriate instruments and clinical measures of cognition remain hotly debated. In schizophrenia,

the development of the MATRICS Consensus Cognitive Battery (MCCB) represents such an endeavor, although to date no drug has been approved based on results using the MCCB.⁴ Cognitive impairment is not a *sine qua non* symptom for MDD diagnosis; however, attentional, memory, and executive deficits are highly prevalent, and, thus, several mechanisms are currently being tested. The US Food and Drug Administration (FDA) has historically considered cognition as a “pseudospecific” target in MDD. However, in a recent meta-analysis, MDD was reliably associated with impaired performance on cognitive measures of executive function, beyond deficits in motor and processing speed.⁵ Two pivotal trials of vortioxetine showed improvement on the digit symbol substitution test, a measure of processing speed for which clinically meaningful change has yet to be established. The FDA issued a complete response letter despite a favorable advisory panel vote and European regulatory approval.⁶ Rapastinel, an i.v. formulation of a novel NMDA receptor partial agonist currently in phase III development for adjunctive MDD, has been reported to present antidepressant and procognitive properties in rodents (as opposed to the ketamine-induced psychotomimetic and hallucinogenic side effects), although clinical testing has been limited. In a similar population, a nasal formulation of esketamine, which acts primarily as a non-competitive NMDA receptor antagonist,

but is also a dopamine reuptake inhibitor, improved subjective symptoms of cognitive impairment in treatment-resistant depression.⁷ It will be important to understand the underlying neural circuit mechanisms and ultimate clinical impact of these drugs, as well as develop clear connections between improvement in cognitive domains and practical clinical benefit.

In humans, both disease-related decline in cognitive abilities and treatment-induced improvements are measured through standardized neuropsychological tests. These tools are administered predrug and postdrug exposure in order to evaluate changes attributable to the treatment of interest. One psychometric property that can jeopardize detecting true changes is low test-retest reliability. That is, results can be contaminated by the effects of performing the same test more than once due to learning (i.e., if learning the stimuli improves performance), familiarity effects (i.e., if it takes several tries to learn the expectation behind the test), and strategy (i.e., finding a shortcut or heuristic). Using alternate versions of a test solves the first issue but not the latter two. Circumventing familiarity effects and the engineering of alternative strategies remains a challenge for clinical trials that awaits development and deployment of high-resolution clinical assessment technologies that provide “real-time” data about continuous cognitive function. The emergence of more robust, real world, objective, data-rich, quantitative assessments of cognitive domains will be critical to bring about a more promising era of cognitive-enhancing drugs.

Clinical studies of efficacy often include placebo as a “nonactive” comparator to demonstrate statistical separation from the treatment of interest. In the case of clinical measures of cognition, it is notable just how large and common the beneficial effect of placebo can be, confounding experimental efforts to isolate the treatment effect of novel pharmacology, and emphasizing the complexity of highly adaptive nervous systems. A recent example is the case of encenicline, a selective partial agonist of the $\alpha 7$ nicotinic receptor, in which a high placebo response was noted in the context of two recent negative phase III trials designed to demonstrate its efficacy as a procognitive treatment in schizophrenia.⁸ Efforts to mitigate the high

placebo response rates in cognition studies include the use of novel study designs, such as placebo run-in or the sequential parallel comparison design.⁹ Despite positive results in phase II, the latter method did not ultimately result in a positive outcome after its implementation in the ALKS 5461 pivotal program.¹⁰

Humans possess a highly sophisticated brain, with dramatic expansion of cortical areas relevant to cognition relative to rodents or even evolutionarily proximate primates. These differences are most apparent in the prefrontal cortex, and, thus, it is perhaps not surprising that animal models of disease-related cognitive deficits and pro-cognitive therapeutic efficacy often do not translate to humans. Human biology and circuit neuroscience are paramount to bridge such gaps and shed light on the complex circuitry comprising cognition in humans in health and disease.

If the translational hurdle of the biology of cognitive circuits and clinical assessment were not enough challenge, it is important to point out that demonstrating a difference from placebo on a test of cognitive function is typically not sufficient to achieve drug approval for any disease even where cognitive impairment is central. A co-primary outcome of overall clinical function must show separation between treatment and placebo (or active comparator), to demonstrate that cognitive laboratory measurements are a valid reflection of practical clinical benefit. A link must be established between a measurable feature of brain activity (i.e., cognitive test performance) and “functional” outcome.

The nervous system is unique among organ systems in its primary role in representing, navigating, and adapting to the external world. Cognitive processes are the link between sensory input, experience, forward representation, and motor output. Preserving or augmenting cognitive

function may ultimately require a combination of neurobehavioral, neuromodulatory, and pharmacological approaches. Both classical and popular cognitive interventions have historically not been subject to rigorous double blind placebo-controlled studies characteristic of drug trials. The efficacy of cognitive interventions will become increasingly important as the medical impact of cognitive disorders soars. What exactly are the best routes to achieve brain health? Evidence to date suggests that successful brain training must integrate complexity, novelty, and experiential diversity. Brains with greater cognitive reserve are able to camouflage damage and retain functional capacity over the course of neuropsychiatric and neurodegenerative disease. Cardiovascular health, low stress, and healthy eating habits are themselves neuroprotective agents. Yet, contemporary neuroscience holds promise by defining molecular mechanisms that augment neural plasticity, restore network function, and target synaptic health (**Figure 1**).

Although cognition will never boil down to measuring serum low-density lipoprotein, hemoglobin A1C, cardiac ejection fraction, or tumor volume, rapid advances in neurobiology, circuit neuroscience, and clinical assessment technology presage a coming era of new smart drugs for brain disorders.

CONFLICT OF INTEREST

EA is an employee and stakeholder of Pfizer, Inc. MDE is an employee and shareholder of Biogen

© 2016 The Authors Clinical Pharmacology & Therapeutics published by Wiley Periodicals, Inc. on behalf of The American Society for Clinical Pharmacology and Therapeutics

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

1. Goff, D.C., Hill, M. & Barch, D. The treatment of cognitive impairment in schizophrenia. *Pharmacol. Biochem. Behav.* **99**, 245–253 (2011).
2. Sawaguchi, T. & Goldman-Rakic, P.S. D1 dopamine receptors in prefrontal cortex: involvement in working memory. *Science* **251**, 947–950 (1991).
3. Girgis, R.R. *et al.* A proof-of-concept, randomized controlled trial of DAR-0100A, a dopamine-1 receptor agonist, for cognitive enhancement in schizophrenia. *J. Psychopharmacol.* **30**, 428–435 (2016).
4. Green, M.F., Harris, J.G. & Nuechterlein, K.H. The MATRICS consensus cognitive battery: what we know 6 years later. *Am. J. Psychiatry* **171**, 1151–1154 (2014).
5. Snyder, H.R. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol. Bull.* **139**, 81–132 (2013).
6. FiercePharma. In surprise decision, FDA blocks crucial cognitive claim for Takeda's Brintellix. <<http://www.fiercepharma.com/regulatory/surprise-decision-fda-blocks-crucial-cognitive-claim-for-takeda-s-brintellix/>> (2016). Accessed 9 September 2016.
7. Singh, J.B. *et al.* Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. *Biol. Psychiatry* **80**, 424–431 (2016).
8. Drugs.com. FORUM Pharmaceuticals Inc. Provides update on encenicline phase 3 clinical trial program in cognitive impairment in schizophrenia. <https://www.drugs.com/clinical_trials/forum-pharmaceuticals-inc-provides-update-encenicline-phase-3-clinical-trial-program-cognitive-17063.html> (2016). Accessed 9 September 2016.
9. Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks. <<http://www.action.org/static/action12/Fava.pdf>> (2016). Accessed 9 September 2016.
10. Business Wire. Alkermes announces topline results of FORWARD-3 and FORWARD-4, two phase 3 studies of ALKS 5461 in major depressive disorder. <<http://www.businesswire.com/news/home/20160121005348/en/Alkermes-Announces-Topline-Results-FORWARD-3-FORWARD-4-Phase>> (2016). Accessed 26 August 2016.