Original article

Pharmacological treatment of cognitive deficits in nondementing mental health disorders

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Evidence for pharmacological remediation of cognitive deficits in three major psychiatric disorders—attention deficit-hyperactivity disorder (ADHD), schizophrenia, and depression—is reviewed. ADHD is effectively treated with the stimulant medications methylphenidate and d-amphetamine, as well as nonstimulants such as atomoxetine, implicating cognitive enhancing effects mediated by noradrenaline and dopamine. However, the precise mechanisms underlying these effects remains unclear. Cognitive deficits in schizophrenia are less effectively treated, but attempts via a variety of neurotransmitter strategies are surveyed. The possibility of treating cognitive deficits in depression via antidepressant medication (eg, selective serotonin reuptake inhibitors) and by adjunctive drug treatment has only recently received attention because of confounding, or possibly interactive, effects on mood. Prospects for future advances in this important area may need to take into account transdiagnostic perspectives on cognition (including neurodegenerative diseases) as well as improvements in neuropsychological, neurobiological, and clinical trial design approaches to cognitive enhancement.

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Introduction

This important topic can be considered with either a narrow or broad focus. If, for example, the position is taken that most psychiatric symptoms can be understood as impairments of cognition, or of cognition interacting with emotional or motivational factors (ie, so-called "hot" cognition), then we would be discussing the whole remit of pharmacological treatment in psychiatry. If on the other hand, we consider specifically the deficits in "cold" cognition, for example, memory and attention, that accompany such diagnoses as schizophrenia and depression and most other neuropsychiatric disorders, then we are dealing with a much narrower spectrum. Whilst it is now acknowledged that cognitive dysfunctions play a major role in mental health disorders, and that describing these and their neural basis, and identifying possible pharmacological treatments for them, have been important research objectives, it must also be admitted that there have been rather few clinical successes to date.

The search for new cognitive treatments may be aided by recognizing apparently similar cognitive dysfunctions in what otherwise appear to be very different neuropsychiatric phenotypes. In other words, a memory or attentional impairment in schizophrenia could possibly be treated with a similar medication as in attention deficit-hyperactivity disorder (ADHD). This strategy accepts that the enormous capacity for comorbidity in psychiatry may also extend to the cognitive dimensions. Such considerations mean that the treatment of cognitive impairments associated with neuro-

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degenerative diseases that are not generally considered as "mental health disorders" may also be germane. Neurodegenerative disorders such as Alzheimer disease, Lewy body disease, and frontotemporal dementia have deficits in major, although somewhat distinct, areas of cognition as their defining characteristics, although they are not usually defined as mental health disorders. Parkinson disease and Huntington disease, although classically categorized as movement disorders, of course show clinically significant impairments in the domains of affect and cognition. It can hardly be claimed that pharmacological treatment of cognitive disorders in these conditions has also yet been crowned with success, but this experience may also prove to be informative. In this review, I will focus initially on the status of well-established pharmacological treatments for cognitive impairments in ADHD before considering the present, less clear, status of treatment for cognitive deficits in schizophrenia and depression. I will also be considering some future prospects for treating cognition with pharmacological agents in these disorders. *Table I* provides a "roadmap" for this brief survey, indicating the main drugs used for treating cognition in these three psychiatric disorders (only a few of which are licensed), and incidentally illustrating the diversity and wide range of mechanisms of these compounds.

> Many psychiatric disorders such as autism exhibit impairments in social cognition that are core to the disorder and may require novel neurobiological initiatives and methodological approaches

Attention deficit-hyperactivity disorder

ADHD in either juveniles or adults is generally thought to exemplify so-called "executive" deficits in cognition, which comprise such components as working memory and planning, cognitive control (including inhibitory response control and cognitive flexibility)—although some authors consider that the impairments extend to broader domains such as other aspects of memory.[1] Classically, ADHD also presents with major impairments of sustained attention and distractibility, which have been demonstrated to be related to loss of prefrontal gray matter, not only in individuals with ADHD, but also in their first-degree relatives, suggesting a neurobehavioral endophenotype of the disorder.[2] ADHD is generally considered to be one of the few success stories in treatment in psychiatry. The more severe forms of this disorder are generally treated, apparently paradoxically, with stimulant drugs such as methylphenidate or d-amphetamine, which boost catecholamine function (ie, dopamine [DA] and noradrenaline [NA]) partially as a consequence of their blockade of the DA and NA transporters. Other nonstimulant drugs affecting primarily noradrenergic function are also employed; such as atomoxetine and guanfacine. Meta-analyses indicate that the stimulants exert respectable (medium to large) effect sizes on reducing symptoms

ADHD	SCHIZOPHRENIA	DEPRESSION
Methylphenidate	D-cycloserine	Vortioxetine
Amphetamine	AMPA-R agonists	Modafinil
Atomoxetine	Memantine	
Guanfacine	Donepezil	
Bupropion	Alpha7 nicotinic agonists	
Modafinil	Amphetamine	
	Modafinil	

Table I. Drugs used in the treatment of cognitive dysfunction in three psychiatric disorders. ADHD, attention deficit-hyperactivity disorder; AMPA-R, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

in both juvenile[3] and adult[4] ADHD. Nonstimulants such as atomoxetine, bupropion, and guanfacine are also effective, although with relatively smaller effect sizes. Some analyses suggest that amphetamine is also more effective than methylphenidate, perhaps because of its DA-releasing action.[5] A large recent meta-analysis[6] based on teachers' and clinicians' ratings as the main outcome measures largely confirmed the earlier results, the main recommendation being to employ methylphenidate in children with ADHD and amphetamine in adult ADHD. These impressive effects are mitigated to some extent by tolerability and side effects of these drugs and the (presently largely unsupported) fear of possible stimulant drug-use disorder.

However, there is also some evidence that long-term treatment with stimulants can have a protective effect against the development of psychiatric disorders such as depression, disruptive behavior, or anxiety, and there was less likelihood of repeating the same school grade.[7] Such effects would suggest some improvement in academic performance following stimulant medication, however, this is controversial. In a controlled study, Elia et al[8] found that both d-amphetamine and methylphenidate allowed adolescents with ADHD to attempt more mathematics and reading tasks, although only d-amphetamine improved accuracy of solving maths problems. On the other hand, Loe and Feldman[9] did not find convincing evidence of improved academic outcomes such as reading ability after long-term treatment in juvenile ADHD. Arnold et al[10] have conducted a more recent meta-analysis of effects of treatment using 176 studies of achievement tests (for information learned) and academic performance in juvenile ADHD. Improvement was found to be more prevalent on achievement tests than on academic performance per se for juvenile ADHD following stimulant drug medication, although the best effects were shown with multimodal treatment, also including nonpharmacological approaches.

In parallel to these promising effects on behavioral and cognitive outcomes, Nakao et al[11] reported from another meta-analysis the remarkable result that long-term stimulant medication appeared to be associated with a normalization of the reduced gray matter volume of basal ganglia structures commonly found in ADHD - possibly eliminating the "developmental delay" often postulated in this disorder.

These clinical findings on cognition are in general consistent with considerable evidence that these drugs improve performance on laboratory tests of working memory, sustained attention, and inhibitory response control (thus ameliorating impulsivity) in both juveniles and adults with ADHD.[12] On the other hand, it has also been reported that although, for example, decision-making cognition may be rendered less "risky" by methylphenidate, the drug may also fail to improve adjustment of risk in the face of changing contingencies.[13] This makes it clear that the concept of a general "cognitive enhancer" may be inappropriate; cognitive benefits may also be accompanied by cognitive costs. This consideration is also relevant to the well-known inverted U-shaped function that often determines effects of drugs on cognition—in its simplest form that optimal effects may be obtained by intermediate dose. However, it may also be the case that different behavioral and cognitive tasks require different doses for optimal effects. Evidence for this comes from studies of the effects of L-Dopa on cognition in Parkinson's disease; functions such as spatial working memory and cognitive flexibility may be improved but at the cost of risky decision making and impaired reversal.[14,15] For ADHD, Sprague and Sleator[16] showed that a family of inverted U-shaped functions may explain why doses producing optimal objectively measured behavioral effects of stimulants may not necessarily correspond to teachers' or parents' ratings of efficacy.

A major concern is that despite the relatively successful use of anti-ADHD medications, there is still no definitive understanding of how they produce their cognitive enhancing effects.[17] Although the molecular actions of stimulant drugs are quite well understood (eg, their actions on the catecholamine transporters), it is still not known, for example, which of the two catecholamine neurotransmitters, DA or NA (or both in combination) is responsible for their therapeutic actions, or where in the brain, for example, in the prefrontal cortex or striatum they most effectively operate. Research findings in both experimental animals and humans indicate that both DA and NA may play a role in executive functions, such as working memory, response inhibition, and different aspects of attention in the case of DA potentially at either prefrontal or striatal DA receptors and for NA especially, though not exclusively, in the prefrontal cortex.[18] However, there are suggestions from some predominantly preclinical studies that NA may be more implicated in the control of impulsive behavior[19,20] and selective attention[21,22] whereas DA plays important roles in working memory and sustained attention.[23-25]

Precisely how these neurotransmitter modulations serve to improve cognitive performance may depend on their ability to enhance information processing by various actions on signal-to-noise processing in the prefrontal cortex.[18] However, it is intriguing to consider the possibilities that these mechanisms may reflect processes of elevated arousal or even reward-related motivational effects; that the cognitive enhancing effects result from interactions between such processes and information processing. Stimulant drugs are widely known to combat fatigue and drowsiness, but the proposal here is that these modulations of arousal can directly affect cognition even in the non-sleep-deprived subject.

These research findings and hypotheses have not in general yet been tested or translated to human patients with ADHD. Another complication is that many of the cognitive benefits observed in ADHD have also been shown in laboratory studies of healthy individuals.[26,27] This raises an important issue; whether the drugs are acting to restore a neurochemical deficit associated with the disorder, or whether they are simply producing their cognitive enhancing effects by interacting with largely intact systems to compensate for dysfunctioning neural networks, caused for example by gray matter loss or deficits in functional connectivity.

Although stimulant drug medication for ADHD has been a qualified success, there is still considerable interest in the search for superior drugs without the possible stigma of being drugs of abuse (although fears of possible stimulant drug dependence in ADHD individuals appear to be largely groundless). The atypical stimulant modafinil has been considered in this context,[27,28] as it is not thought to have drug abuse liability but retains many of the cognitive benefits of drugs such as methylphenidate. Its neurochemical action is complex; whilst it acts as a weak blocker of catecholamine transporters, it has several other actions that distinguish it from typical stimulant drugs, including possible indirect actions on glutamate and acetylcholine.[28,29] However, modafinil has not been licensed to date for ADHD medication and it is not thought be as clinically effective as the classical stimulants.[6]

Schizophrenia

It has only been relatively recently accepted that schizophrenia can be associated with profound cognitive deficits, for example, in executive function and memory, which are a barrier to effective rehabilitation even if the psychotic symptoms are controlled. This is a little surprising as it can perhaps be argued that virtually the entire expression of schizophrenia, including the positive symptoms such as delusions and hallucinations, can be thought of as cognitive in nature, albeit in the case of negative symptoms, as an interaction between motivational and cognitive mechanisms. Only the positive symptoms are effectively treated, with both typical, "first-generation" antipsychotics which block DA D_2 receptors (-R) and atypical ("second-generation") antipsychotics which additionally block 5-HT2A-R, amongst others. The psychological mechanisms of these antipsychotic effects are largely unknown but may work again to affect information processing in the striatum and neocortex. There is clearly a potential indirect benefit to be had on general cognitive processing if the disruptive positive symptoms are blunted, but it is in fact controversial whether there is any residual cognitive benefit, indirect or direct. Indeed, there is evidence from studies, both of nonhuman primates[30] and humans[31,32] that chronic treatment with so-called "first-generation" antipsychotics acting as D2-R antagonists may eventually impair normal cognition.

The CATIE trial[33] failed to find any advantage of the "second-generation" agents such as risperidone, quetiapine, and olanzapine compared with a typical antipsychotic agent perphenazine, although most of the drugs produced small but significant improvements in a composite cognitive measure. The recent study by Veselinovic et al[32] similarly showed small-to-moderate effect size improvements in some cognitive tests following treatment with second-generation agents aripiprazole, olanzapine, and quetiapine. Whether these improvements (over baseline and when compared with first-generation drugs) are direct effects on cognitive function is perhaps more questionable. It is possible for example that the first-generation drugs, as part of their detrimental effects on cognition, also impair practice effects, unlike the second-generation drugs which have fewer adverse effects and produce a greater sense of well-being. Furthermore, not all studies have found a superiority of second-generation over first-generation compounds. A large study of effects on computerized reversal learning and attentional set-shifting found that those first-episode patients treated with atypical neuroleptics such as olanzapine and risperidone actually did worse than patients on typical antipsychotic medication, in well-matched groups.[34]

Medications specifically targeting cognitive deficits and usually added to antipsychotic treatment have not been very effective on the whole. A recent meta-analysis by Sinkeviciute et al[35] of 93 trials involving 5630 patients categorized cognitive enhancing effects in terms of the principal neurotransmitter affected. The most effective treatments were glutamatergic, especially α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R) agonists for working memory, which had a small positive effect. Agents acting at the glycine site of the NMDA receptor such as D-cycloserine and the glutamatergic receptor antagonist memantine showed some signs of improvement that were not significant, perhaps as a consequence of insufficient statistical power. The precise mechanism by which memantine achieves its effects is also unclear. It may appear paradoxical that drugs acting as glutamate receptor agonists or antagonists may both have utility in the treatment of schizophrenia. However, NMDA receptor antagonists can enhance glutamate release in the cortex and some metabotropic glutamate receptor agonists such as the mGluR2/3-R agonist pomaglutemad may normalize high levels of glutamate release via their actions at presynaptic receptors.[36] This action is potentially significant as, following a meta-analysis of several clinical trials, this drug was shown to ameliorate positive symptoms in schizophrenia only within 3 years of the first psychotic episode.[37] This may be consistent with theories that in the early phases of schizophrenia there is heightened activity of cortical pyramidal glutamatergic neurons, which may subsequently subside.[36] Pomaglutemad has not yet been tested for its cognitive enhancing effects in schizophrenia, but this finding would suggest that any possible cognitive enhancing effects would be limited to first-episode patients.

The possible utility of glutamatergic compounds is interesting in view of some evidence that "nootropic" cognitive enhancing compounds such as aniracetam have been shown to have possible positive allosteric modulating activity at AMPA-R (ie, act as "AMPA-kines").[38] Early signs of promise of this class of drug in the treatment of mild dementia[39] have not led to its wholesale use for Alzheimer disease. However, there is some recent evidence that aniracetam treatment was superior to cholinesterase inhibition in a study of 276 patients with "mild dementia."[40] Moreover, an early study showed convincing antagonism of cognitive deficits produced by the cholinergic receptor antagonist scopolamine in healthy volunteers.[41] Perhaps novel nootropic agents which overcome some of the problems associated with aniracetam in terms of bioavailability and pharmacokinetic factors will be worth trying in schizophrenia as an adjunctive treatment to antipsychotic medication.

Cholinergic strategies for schizophrenia run somewhat parallel to those used in the treatment of Alzheimer disease and dementia in Parkinson disease which appear to work mainly on attentional function.[42,43] Cholinergic strategies for schizophrenia have utilised cholinesterase inhibitors such as donepezil and alpha7 nicotinic receptor agonists, with findings of very small positive effect sizes in both cases. For example, Haig et al[44] found a small improvement in nonsmoking patients with schizophrenia in verbal learning, working memory, and attention. On the other hand, a follow-up study by the same group did not confirm these findings.[45]

Sinkeviciute et al[35] found no evidence for efficacy of agents affecting serotonergic, noradrenergic, and γ-aminobutyric acid (GABA)-ergic receptors. However, they pointed out a glaring gap in the use of dopaminergic agents. This may appear to be surprising in view of the therapeutic use of DA D2-R antagonists, but there is substantial preclinical evidence that D1-R agonists may enhance working memory function in the primate prefrontal cortex,[23] as well as attention in rodent studies,[24] which has never been adequately tested clinically. This has been due to existing compounds having poor brain penetration, short half-lives, and also some adverse cardiovascular effects. However, the advent of a new class of D1-R agonists with positive allosteric modulation (PAM) may be worth pursuing in an appropriate clinical trial.

In the current absence of a clinically viable D1-R agonist, other less specific agents, such as those used for ADHD, may also be worth further scrutiny. A considerable complication is the possible induction of psychosis by psychomotor stimulants such as amphetamine. However, it is possible that dopaminergic agents such as methylphenidate or modafinil may have some efficacy if investigated in large-scale trials in suitable groups of patients. In support of this hypothesis, Daniel et al[46] found in an fMRI study of a small sample of patients with schizophrenia that d-amphetamine enhanced blood flow in the dorsolat-

eral prefrontal cortex and improved performance on the Wisconsin Card Sorting Test. Likewise, Barch and Carter[47] found benefit in several aspects of cognition including spatial working memory, language production, Stroop performance, and reaction time in 10 patients receiving d-amphetamine in addition to haloperidol medication. The rationale is that the D1-R action will be unaffected by the antipsychotic D2-R medication which may also block the psychotic effects of the drug. Turner et al[48] showed that modafinil, which has mild catecholaminergic and possible glutamate-enhancing function,[29] also improved performance in high functioning, first episode patients performing some CANTAB tests of fronto-executive function including attentional-set shifting, recognition memory, planning, and response inhibition. However, longer-term treatment with either modafinil (or armodafinil) has so far failed to show significant effects.[35] Nevertheless, a recent study[49] found that the cognitive enhancing effects of acute modafinil in schizophrenia depended to some extent on the sensitivity of the cognitive test battery used, the CANTAB tests being more sensitive than the commonly used MATRICS battery. In general, factors such as this, as well as optimal dosing and the choice of suitable subgroups of patients with schizophrenia, given its heterogeneity, may be necessary to adequately test the efficacy of cognitive enhancers in schizophrenia.

Depression

Some of the major symptoms of depression such as impairments in concentration and decision-making have an obvious cognitive nature. However, these are often overlooked because of the clinician's emphasis on mood disorder. Indeed, cognitive dysfunction in depression has attracted considerable controversy because of the obvious interpretative problem, also relevant in terms of the "negative" symptoms of schizophrenia, of motivational or mood factors in depression that may indirectly influence cognition. It has also been suggested that some of the cognitive difficulties in depression may have resulted from disruptive effects of enhanced responses to negative feedback.[50] This motivational-cognitive interaction may thus be particularly important in depression. Nevertheless, it is now generally accepted that there are neurocognitive impairments in depression that are associated with poorer functional outcome and increased probability of relapse—and which importantly are not completely remediated by current treatments for depression such as antidepressant medication. A recent meta-analysis[51] showed a modest positive effect on functions such as divided attention, executive function, immediate memory, processing speed, recent memory, and sustained attention (though not working memory) for depressed participants. However, this effect was largely limited to the selective serotonin reuptake inhibitors (SSRIs) rather than tricyclic antidepressants (perhaps because of their additional anticholinergic actions). The precise mechanisms underlying these cognitive enhancing effects of SSRIs is unknown. Chronic SSRIs, in addition to producing adaptive changes in serotonergic function may also affect other neurotransmitter systems (eg, DA), and affect neurogenesis in the hippocampus. Prado et al[51] do not rule out the possibility that the effects are indirect effects of mood enhancement. This relative lack of efficacy means that impairments are often still evident in remitted depressed patients. Hence cognition has recently become an important target for treatment in depression.

With this aim in view, McIntyre et al[52] have reported cognitive enhancing actions in depression of 8 weeks of treatment with a novel SSRI antidepressant, vortioxetine on a composite cognition end point comprising the Rey Auditory-Verbal Learning Test and the Digit-Symbol Substitution Test from the Wechsler Adult Intelligence Scale, together with a number of other secondary cognitive test outcomes. Importantly, mediation analyses showed that this cognitive enhancing effect was not associated with its mood-elevating effects, suggesting the possibility of parallel effects on mood and cognition, via serotoninergic actions. Vortioxetine is an SSRI with additional actions at 5-HT3, and 5-HT7 receptors but it is not yet clear whether and how these contribute to cognitive enhancing effects. One suggestion has been that its 5-HT3 action may serve to disinhibit GABA-ergic receptors on interneurons.[53] Further mechanistic studies are indicated in healthy volunteers and in studies with experimental animals.

It may also be feasible to augment treatment of depression with SSRIs by other drugs that have greater cognitive enhancing efficacy. Goss et al[54] found in another meta-analysis that modafinil produced added benefit for cognition when combined with standard antidepressant medication. Kaser et al[55] showed that modafinil did indeed act to improve working memory and episodic memory, but not planning or attention in remitted depressed patients.

Conclusions

There are indications of gradual progress in understanding and treating cognitive deficits in psychiatric disorders, but it is clear that there is much to be accomplished, in terms not only of identifying valid targets but also in the methodology for assessing their effects in clinical trials and in experimental medicine studies. A likely area of advance is in methods of evaluating social cognition and related forms, where emotional processing interacts with cognition (so-called "hot"cognition). For example, many psychiatric disorders such as autism exhibit impairments in social cognition that are core to the disorder and may require novel neurobiological initiatives and methodological approaches, in addition to clinical trials. Attempts to remediate social cognition in autism via intranasal oxytocin represents one such promising direction.[56] Overall, this review has argued that more studies are required to define the mechanistic bases of cognitive enhancement produced by both currently employed and yet-to-be discovered pharmacological agents. ■

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