Pharmacological Strategies for Enhancing Cognition in Schizophrenia

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Abstract Researchers have long recognized that individuals with schizophrenia experience challenges in a wide range of cognitive domains, and research on cognitive impairment in schizophrenia is not a recent phenomena. However, the past 10–20 years have seen an increasing recognition of the central importance of cognition to understanding function and outcome in this illness (Green et al. in Schizophr Bull 26:119–136, 2000), an awareness that has shifted the emphasis of at least some work on schizophrenia. More specifically, there has been a rapidly growing body of work on methods of enhancing cognition in schizophrenia, as

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a means to potentially facilitate improved outcome and quality of life for individuals with this debilitating illness. The current chapter reviews the results of a range of studies examining adjunctive pharmacological treatments to enhance cognition in schizophrenia using a range of designs, including single-dose studies, open-label repeated dosing studies, and double-blind parallel group and crossover designs with repeated dosing. Although many of the single-dose and open-label studies have suggested positive cognitive effects from a range of agents, few of the larger-scale double-blind studies have generated positive results. The current state of results may reflect the need to identify alternative molecular mechanisms for enhancing cognition in schizophrenia or the need to reconceptualize the ways in which pharmacological agents may improve cognition in this illness, with a concomitant change in the traditional clinical trial study design used in prior studies of cognitive enhancement in schizophrenia.

Keywords Cognition · Control · Executive control · Improvement · Pharmacological · Schizophrenia · Working memory

1 Introduction

Researchers and theorists as far back as Bleuler and Kraeplin have recognized that abnormalities in cognitive function are a key component of schizophrenia, one of the most debilitating psychiatric disorders (Bleuler 1950; Kraeplin 1950). There are some data to suggest that the degree of impairment in certain aspects of cognition predicts the subsequent onset of schizophrenia (Cornblatt et al. 1999; Niendam et al. 2003; Sorensen et al. 2006). Further, individuals who share unexpressed genetic components of vulnerability to schizophrenia also experience impairments in cognitive function (Delawalla et al. 2006; Seidman et al. 2006; Snitz et al. 2006; Toulopoulou et al. 2003). In addition, some evidence suggests that the stronger the genetic risk, the greater the impairment in cognitive function in first-degree relatives (Glahn et al. 2003; Tuulio-Henriksson et al. 2003). As such, the attempt to understand the specific nature and sources of cognitive deficits in this disorder has a long and well-established history in the schizophrenia literature. However, in many ways, the last two decades have witnessed a relative explosion of research on cognition in schizophrenia, much of it couched within the framework of understanding the cognitive neuroscience of schizophrenia. There are at least two major forces driving the current wave of research on the psychological and neurobiological mechanisms that give rise to cognitive deficits in schizophrenia. One of these forces is the fact that over the past 20 years, the field of basic cognitive neuroscience has generated a wealth of new information on the neural systems that support specific processes involved of a range of cognitive functions, including the domains of working memory (WM), episodic memory (EM), and other aspects of

"executive" control. As such, clinical scientists have been able to use this information to guide the search for the neural mechanisms that give rise to cognitive deficits in schizophrenia and a wealth of information is now available about the neurobiological abnormalities associated with a range of cognitive impairments in schizophrenia (Barch 2005; Minzenberg et al. 2009; Tamminga 2006).

A second force is that a growing body of research suggests that cognitive function in schizophrenia is one of the most critical determinants of social and occupational function in schizophrenia, potentially more so than the severity of other aspects/symptoms of schizophrenia such as hallucinations, delusions, or even negative symptoms (Cervellione et al. 2007; Gold et al. 2002; Green et al. 2000; Heinrichs et al. 2008; McClure et al. 2007; Williams et al. 2007). Such findings have led even the most applied of researchers and clinicians to become more invested in understanding the nature and source of cognitive deficits in schizophrenia, as such information may help to identify the treatment approaches that may be most effective in ameliorating such cognitive deficits in schizophrenia. This renewed emphasis on understanding cognitive impairment in schizophrenia has contributed to a rapidly growing body of work on methods of enhancing cognition in schizophrenia, as a means to potentially facilitate improved outcome and quality of life for individuals with this debilitating illness. This work has included major initiatives within the field designed to improve the measurement of cognition in schizophrenia during the conduct of clinical trials, such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program (Marder and Fenton 2004) and the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) program (Carter and Barch 2007), as well as major initiatives to identify and test novel pharmacological and behavioral approaches for improving cognition and functional outcome in schizophrenia (Buchanan et al. 2007a; Floresco et al. 2005; Stover et al. 2007a, b).

The goal of the current chapter is to provide an overview of the current status of results from treatment trials conducted to investigate the ability of pharmacological agents to enhance cognitive function in schizophrenia. This review focuses on studies that were either open-label, single-blind, or double-blind studies of adjunctive therapy (not monotherapy) designed to improve cognition in schizophrenia, with the obvious hope that such improvement would translate into improved life function and outcome in this illness. For good or for bad, the wealth of different neurobiological abnormalities identified in individuals with schizophrenia and which have been associated with cognitive impairment provides a wealth of potential targets for enhancing cognitive function in schizophrenia. This "embarrassment of riches" is not necessarily positive, as it suggests that the complexity of the neurobiology of cognitive impairment in schizophrenia may hamper the potential effectiveness of agents targeting a single mechanism, and that more creative approaches may be necessary for this complex disorder. Nonetheless, the MATRICS Neuropharmacology Committee identified a number of promising targets for the treatment of cognitive impairment in schizophrenia, including cholinergic, dopaminergic, and glutamatergic agents (Buchanan et al. 2007a). The field has been pushing forward with a range of clinical trials using

agents targeting these mechanisms as well as many others, and there are now over 70 published studies of trials of examining pharmacological enhancement of cognitive function in schizophrenia.

2 Cholinergic Agents

A large body of human and animal research has highlighted the critical role that acetylcholine plays in a range of cognitive functions. Much of the animal work has focused on its role in memory (Gold 2003, 2004; Hasselmo 2006; Power et al. 2003), as research has demonstrated that impairing the septohippocampal and nucleus basalis of Meynert cortical cholinergic projections can impair memory function (Mandel et al. 1989). Further, supplementing the cholinergic system pharmacologically (e.g., via physostigmine administration) can help reverse the impairments causes by the disruption of these pathways through lesions, other pharmacological agents, or even aging (Arendt et al. 1990; Kamei et al. 1990; Mandel et al. 1989). Further, much research points to a consistent impairment in the cholinergic system in dementias such as Alzheimer's disease that involve impairments in memory as well as other cognitive functions (Schliebs and Arendt 2006). Not surprisingly, drugs that enhance the function of the cholinergic system have been a major focus of treatment for Alzheimer's disease and other neurological disorders involving memory impairment (Birks et al. 2009; Cincotta et al. 2008; Mohan et al. 2009; Razay and Wilcock 2008; Reingold et al. 2007).

The pattern of cognitive impairment in schizophrenia is not identical to that found in Alzheimer's disease and there is not the same type of evidence for cholinergic impairments in schizophrenia as there is in Alzheimer's. Nonetheless, there are studies suggesting a range of impairments in the cholinergic system in schizophrenia, including alterations in choline acetyltransferase (Powchik et al. 1998), and both nicotinic and muscarinic receptors (Breese et al. 2000; Crook et al. 1999, 2000, 2001; Deng and Huang 2005; Griffith et al. 1998; Scarr et al. 2009) in the brains of individuals with schizophrenia (for reviews, see Adams and Stevens 2007; Berman et al. 2007; Martin and Freedman 2007; Terry 2008).

There are a number of pathways by which one could attempt to enhance or regulate cholinergic function in schizophrenia. These include the use of acetylcholinesterase inhibitors (a focus for dementia work) that serve to inhibit acetylcholinesterase, the primary enzyme serving to break down acetylcholine in the synaptic cleft. Blocking the function of acetylcholinesterase should enhance cholinergic function by making more acetylcholine available for both nicotinic and muscarinic receptors in a nonspecific fashion (Buchanan et al. 2007a). An alternative would be to use direct nicotinic and muscarinic agonists that could target a range of receptor types that are either thought to be impaired in schizophrenia or involved in cognitive function. Both of these approaches have been tried in individuals with schizophrenia.

2.1 Cholinesterase Inhibitors

The first studies focusing on cholinergic enhancement in schizophrenia used the cholinesterase inhibitor donepezil (trade name Aricept), which is currently approved for the treatment of Alzheimer's disease and has shown evidence of efficacy for stabilizing cognition and functional outcome in this illness (Tsuno 2009). As shown in Table 1, results of these studies in schizophrenia have overall been negative. Several open-label studies found improvements in either memory (Chung et al. 2009) or motor function (Buchanan et al. 2003), and one double-blind crossover study found evidence for improved verbal memory (Erickson et al. 2005). However, the vast majority of the double-blind, placebo-controlled studies have not found any evidence for cognitive enhancement with donepezil compared to placebo in schizophrenia (Akhondzadeh et al. 2008; Fagerlund et al. 2007; Freudenreich et al. 2005; Friedman et al. 2002; Kohler et al. 2007; Tugal et al. 2004), including a recent large-scale multisite study with over 200 patients (Keefe et al. 2008). Keefe et al. offered a number of speculations as to why donepezil may not be effective in schizophrenia, including the hypothesis that a 10-mg dose of donepezil (the final dose in the Keefe et al. study) may be too high and may actually impair cognitive function.

A number of smaller-scale studies have also examined rivastigmine as a cognitive enhancer in schizophrenia Table 2. Rivastigmine is also a cholinesterase inhibitor, but one that leads to longer-lasting inhibition than donepezil, which is considered a short-acting inhibitor (Polinsky 1998). There have been fewer studies with rivastigmine than donepezil and none had the large sample size of the Keefe et al. study. As shown in Table 2, an early open-label study did provide evidence of improvement in memory function among individuals with schizophrenia taking rivastigmine (Lenzi et al. 2003), and two early 12-week, double-blind, parallel group studies provided some trend-level evidence for improved memory and executive control, as well as altered functional brain activity during cognitive task performance in individuals with schizophrenia (Aasen et al. 2005; Kumari et al. 2006). However, three subsequent 24-week double-blind studies did not provide any evidence for cognitive enhancement on any working memory, long-term memory, executive or speed measures (Chouinard et al. 2007; Guillem et al. 2006; Sharma et al. 2006).

In the last 4 years, a number of additional studies have also examined galantamine as a cognitive enhancer in schizophrenia. Like donepezil and rivastigmine, galantamine is a cholinesterase inhibitor (Table 3). However, it is also an allosteric modulator for both α_7 and $\alpha_4\beta_2$ nicotinic receptors (Dajas-Bailador et al. 2003; Schilstrom et al. 2007; Wang et al. 2007). Further, galantamine may indirectly augment dopamine function, which could have beneficial effects on some aspects of cognitive function, though with a risk for psychosis augmentation (Schilstrom et al. 2007; Wang et al. 2007). The studies with galantamine have had mixed results. Of the five double-blind, placebo-controlled, multiweek trials, four have provided some evidence of improvements in cognitive function with galantamine compared to placebo

Table 1 Donepezil studies in schizophrenia

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
Donepezil 5 and 10 mg	Friedman et al. (2002)	36 (18/18); ages 48.8/50.3	Risperidone	Clinically stable; 2+ SD below normal on the CLVT	Spatial Working Memory; CPT-IP: TMT; WCST; DSPT; VF; RAVLT	12-week, double-blind, placebo-controlled, parallel group	No significant improvements on any cognitive measure
Donepezil 5 mg → 10 mg	Buchanan et al. (2003)	15; age 43.1	Olanzapine		P50: RAVLT; BVRT; PEG; Digit Symbol; GDS CPT	6-week, open-label	Significant improvement on PEG
Donepezil 5 mg	Tugal et al. (2004)	12; ages 18–45	Conventional	Duration of schizophrenia or at least 2 years; clinically stable; high school graduate; no anticholinergics	WMS-R Figural Memory, Visual Reproduction, Visual Paired Associates, Logical Memory, and Verbal Paired Associates; VF; TMT; WCST	12-week, double-blind, placebo-controlled, crossover design	No significant improvements on any cognitive measure
Donepezil 5 mg → 10 mg	Freudenreich et al. (2005)	36 (19/17); age 48.7; 80% smokers	Conventional and second generation	Clinically stable; <20 on MMSE; no antipsychotic with strong anticholinergic properties	Digit Span; HVLT-R; TMT; Benton Oral Word Association Test; PEG	8-week, double-blind, parallel group	No significant improvements on any cognitive measure
Donepezil	Erickson et al. (2005)	15; age 43	Conventional and second generation	Stable doses of antipsychotics for at least 4 weeks	RAVLT; TMT	18 double-blind, placebo-controlled, crossover	Significantly improved verbal learning
Donepezil 5 mg → 10 mg	Fagerlund et al. (2007)	11 (7/4); ages 23–43; 71/50% smokers	Ziprasidone	No treatment refractory patients; no anticholinergics	CANTAB; Buschke Selective Reminding; Rey Complex Figure; TMT; Symbol Digit; VF	16-week, double-blind, placebo-controlled, parallel group	Impairments in planning efficiency; No improvement in verbal recall compared to placebo
Donepezil 5 mg	Lee et al. (2007a)	24 (12/12); ages 42.2/44.2; 66.7/50% smokers	Haloperidol	Score between 15 and 24 on K-MMSE	K-MMSE; HVLT; RAVLT; Digit Span; Digit Symbol; Stroop; TMT; VF; Boston Naming Test	24-week, double-blind, placebo-controlled parallel group	Significant improvement in HVLT; Trend-level improvements in K-MMSE, RAVLT; Digit Span
Donepezil 5 mg → 10 mg	Kohler et al. (2007)	26 (13/13); ages 31.7/30.0; 54% smokers	Second generation	Clinically stable; BPRS <35; no anticholinergics	University of Pennsylvania Computerized Neurocognitive Battery	12-week, double-blind, placebo-controlled parallel group	No significant improvements on any cognitive measure

Donepezil 5 mg → 10 mg	Akhondzadeh et al. (2008)	30 (15/15); ages 32.3/33.9	Risperidone	Clinically stable; >19 on MMSE	WCST; WMS-R Figural Memory, Visual Reproduction, Verbal and Visual Paired Associates, Logical Memory: Digit Span; Block Design	12-week, double-blind, placebo-controlled parallel group	No significant improvements on any cognitive measure
Donepezil 5 mg → 10 mg	Keefe et al. (2008)	250 (124/121); ages 40.9/39.7; 73/72% smokers	Second generation	<5 on CGI-S; <81 on PANSS; −0.5 to −2.5 SD on BACS composite; >5th grade reading level on WRAT-3; no anticholinergics or antiparkinsonians	CATIE Neurocognitive Battery: COWAT; Category Instances; HVLT; Digit Symbol; Letter–Number Auditory Working Memory; CPT-IP; PEG; Visual–Spatial Working Memory; WISC-R Mazes	12-week, double-blind, placebo-controlled parallel group	No significant improvements on any cognitive measure
Donepezil 5 mg → 10 mg	Chung et al. (2009)	13; age 36.6; 23% smokers	Second generation	Clinically stable; at least 1 SD below norm on Computerized Neurocognitive Function Test	SCoRS; Computerized Neurocognitive Function Test (Digit span, visual span, auditory and visual CPT; Stroop, Trail Making, verbal and visual learning, hypothesis formation and finger tapping	12-week, open-label	Follow-up testing after 12 weeks of donepezil showed improved backward digit span, CVLT performance; Trail Making Performance (both A and B)

CPT-IP Continuous Performance Test – Identical Pairs, *COWAT* Controlled Oral Word Association Test, *DSPT* Digit Span Distraction Test, *GDS CPT* Gordon Diagnostic System Continuous Performance Test, *HVLT* Hopkin's Verbal Learning Test, *K-MMSE* Korean Mini-Mental Status Exam, *MMSE* Mini-Mental Status Exam, *PEG* Grooved Pegboard, *RAVLT* Rey Auditory Visual Learning Test, *SCoRS* Schizophrenia Cognition Rating Scale, *TMT* Trail Making Test, *VF* Verbal Fluency, *WMS-R* Wechsler Memory Scale-Revised, *WCST* Wisconsin Card Sorting Test

Table 2 Rivastigmine studies in schizophrenia

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
Rivastigmine 3 mg → 12 mg	Lenzi et al. (2003)	16; age 32	Second generation	Clinically stable; at least 2-year duration of schizophrenia	MMSE; CPT; WMS	12-month, open-label	Significant improvement in MMSE, WMS
Rivastigmine 3 mg → 12 mg	Aasen et al. (2005)	20 (11/9); age 42.6	Second generation	Clinically stable; <41 errors on the NART; −0.5 to −2 SDs below normal on CVLT	CPT with fMRI	12-week, double-blind, parallel group	Trend for more correct responses in rivastigmine group in control condition of CPT; increase in cerebellar activity
Rivastigmine 3 mg → 12 mg	Kumari et al. (2006)	21 (11/10); 73 and 90% smokers	Second generation	Medication Stable; no anticholinergics; 1–2 SDs below normal on CVLT	N-back task (0-, 1-, and 2-back) with fMRI	12-week, double-blind, parallel group	Trend for accuracy improvement across loads in rivastigmine group; increased occipital gyrus activation in rivastigmine group
Rivastigmine 3 mg → 18 mg	Guillem et al. (2006)	18 (9/9); ages 32.7/25.1; Fagerstrom 3.8/3.9	Second generation	<90 on RBANS composite	Continuous face recognition task with ERPs	24-week, crossover, comparing rivastigmine + antipsychotic to antipsychotic alone	No significant improvements in cognitive data, some significant modulation of various ERP components
Rivastigmine 3 mg → 12 mg	Sharma et al. (2006)	21 (11/10); ages 42.6/46.8; some overlap with prior studies	Second generation	Clinically stable; no anticholinergics; >41 errors on NART; −1 to −2 SD on CVLT	CVLT; NART; WCST; TMT; Digit Symbol; Dot Test; CPT-IP; Finger Tapping	24-week, double-blind parallel group	No significant improvements on any of the cognitive measures
Rivastigmine 3 mg → 12 mg	Chouinard et al. (2007)	20 (9/11); ages 32.7/25.7; 55/82% smokers	Conventional or second generation	<75 on the immediate or delayed memory indices of the RBANS	CANTAB Paired Associates Learning, Reaction Time, Rapid Visual Processing; Stockings of Cambridge; Spatial Working Memory	24-week, crossover, comparing rivastigmine + antipsychotic to antipsychotic alone	No significant improvements on any of the cognitive measures

BACS Brief Assessment of Cognition Scale, *CPT-IP* Continuous Performance Test – Identical Pairs, *DSPT* Digit Span Distraction Test, *GDS CPT* Gordon Diagnostic System Continuous Performance Test, *HVLT* Hopkin's Verbal Learning Test, *K-MMSE* Korean Mini-Mental Status Exam, *MMSE* Mini-Mental Status Exam, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *RAVLT* Rey Auditory Visual Learning Test, *SCoRS* Schizophrenia Cognition Rating Scale, *TMT* Trail Making Test, *WMS-R* Wechsler Memory Scale-Revised, *WCST* Wisconsin Card Sorting Test

on both total battery scores and measure of memory and processing speed (Buchanan et al. 2008; Lee et al. 2007b; Noren et al. 2006; Schubert et al. 2006). One of these was a relatively large-scale study (86 patients) that found greater improvements on galantamine versus placebo for Digit Symbol and California Verbal Learning Performance, though more improvement on placebo for a Continuous Performance Test measure (Buchanan et al. 2008). However, one was a very small study (only 12 patients) which did not conduct formal statistical tests and provided only qualitative evidence for the benefits of galantamine (Noren et al. 2006). The most recent double-blind study was of a shorter duration (8 weeks) than the majority of the previous studies (12 weeks), and found that instead of improving cognitive function, galantamine impaired Continuous Performance Test – Identical Pairs (CPT-IP) performance, Stroop Interference, and some aspects of working memory (Dyer et al. 2008). This last study also used a higher dose of galantamine than prior studies (32 mg compared to 24 mg). As discussed by the authors of this negative galantamine study (Dyer et al. 2008), the mechanism of action of galantamine also differs at lower versus higher doses. At lower doses, galantamine acts as an allosteric modulator of α_7 and $\alpha_4\beta_2$ nicotinic receptors, increases burst-firing activity of dopamine cells in the ventral tegmental area (VTA), and increases prefrontal dopamine (Schilstrom et al. 2007; Wang et al. 2007). At higher doses, galantamine primary acts primarily as a cholinesterase inhibitor. Thus, the positive results at lower doses may reflect the allosteric modulatory effects and the dopaminergic effects. In contrast, the negative results at higher doses of galantamine are consistent with the generally negative results with donepezil and rivastigmine, both of which primarily operate as cholinesterase inhibitors.

Taken together, the results of the studies with donepezil, rivastigmine, and galantamine suggest that cholinergic agents that primarily act as cholinesterase inhibitors (which would include high-dose galantamine) are not particularly effective at improving cognitive function in schizophrenia. However, the somewhat more positive results with lower dose galantamine, which operates as an allosteric modulator of α_7 and $\alpha_4\beta_2$ nicotinic receptors and which has dopaminergic effects as well, suggest that an alternative mechanism for modulating cholinergic function in schizophrenia may have more positive effects of cognition. This latter suggestion is consistent with the body of evidence implicating abnormalities in the α_7 receptor as a potential pathophysiological mechanism in schizophrenia, and thus as a potential treatment target, as discussed in more detail in the next section.

2.2 Nicotine, Nicotinic Receptor Agonists, and Muscarinic Receptor Agonists

This body of work implicating nicotinic receptor abnormalities includes evidence that individuals with schizophrenia and their relatives show a failure to inhibit or filter responses to sensory stimuli, as evidenced by reduced P50 suppression

Table 3 Galantamine studies in schizophrenia

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
Galantamine 8 mg → 24 mg	Schubert et al. (2006)	16 (8/8); ages 48.3/46.8); 94% smokers	Risperidone	No anticholinergics	RBANS; Conner's CPT; Object Matching Memory Test; Tower of Toronto Puzzle	8-week, double-blind, placebo-controlled, parallel group	Significant improvement in RBANS total with galantamine
Galantamine 8 mg → 16 mg	Lee et al. (2007b)	24 (12/12); ages 39.5/41.5	Conventional	18–24 on K-MMSE	K-MMSE: HVLT: RCFT; Digit Span; Digit Symbol; Stroop; TMT; VF; Boston Naming Test	12-week, double-blind, placebo-controlled parallel group	Significant improvement in RCFT recognition for galantamine compared to placebo
Galantamine 8 mg → 24 mg	Noren et al. (2006)	12 (9/3)	Second generation		RAVLT; TMT; Letter–Number Sequencing; Vocabulary; WCST	12-week, parallel group comparing galantamine + antipsychotic to antipsychotic alone	No formal statistical tests conducted
Galantamine 0, 4, and 8 mg doses	Sacco et al. (2008)	21; 9 nonsmokers, 6 satiated, and 6 nonsatiated smokers; ages 44.7/47.0/48.6	Conventional and second generation	Deficits in Visual–Spatial Working Memory	CPT; TMT; Stroop; Digit Span; Simple Auditory Attention	Acute dose, double-blind, placebo-controlled	No significant improvements on any cognitive measure
Galantamine 8 mg → 24 mg	Buchanan et al. (2008)	86 (42/44); ages 49.9/49.5	Second generation other than clozapine	Clinically stable; <90 on RBANS; no anticholinergic medications	WAIS-III Letter–Number Sequencing; BACS number sequencing; CVLT; Brief Visual Memory Test; PEG; Digit Symbol; GDS CPT	12-week, double-blind, placebo-controlled, parallel group	Galantamine improved Digit Symbol and CVLT more than placebo, placebo improved GDS CPT more than galantamine

Galantamine 8 mg → 32 mg	Dyer et al. (2008)	18 (9/9); ages 44.3/50.5	Second generation	No anticholinergic medications	CPT-IP; Stroop; WAIS-III Letter–Number Span; PEG	8-week, double-blind, placebo-controlled, parallel group	Galantamine impaired CPT-IP, Stroop Interference, and LNS without reordering

BACS Brief Assessment of Cognition Scale, *CPT-IP* Continuous Performance Test – Identical Pairs, *DSPT* Digit Span Distraction Test, *GDS CPT* Gordon Diagnostic System Continuous Performance Test, *HVLT* Hopkin's Verbal Learning Test, *K-MMSE* Korean Mini-Mental Status Exam, *MMSE* Mini-Mental Status Exam, *PEG* Grooved Pegboard, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *RAVLT* Rey Auditory Visual Learning Test, *RCFT* Rey Complex Figure Test, *SCoRS* Schizophrenia Cognition Rating Scale, *TMT* Trail Making Test, *VF* Verbal Fluency, *WMS-R* Wechsler Memory Scale-Revised, *WCST* Wisconsin Card Sorting Test

(Adler et al. 1998; Cullum et al. 1993; Griffith et al. 1998; Waldo et al. 1995; Young et al. 1996). Animal work suggests that activation of α_7 nicotinic receptors is critical for the presence of sensory gating in P50 paradigms (Luntz-Leybman et al. 1992). Further, there is evidence for the reduced expression of the α_7 nicotinic receptors in the hippocampus (Freedman et al. 1995) and cingulate cortex (Marutle et al. 2001) in postmortem brains of individuals with schizophrenia. The smoking behavior of individuals with schizophrenia has also been interpreted as evidence for nicotinic receptor abnormalities in this illness, as a high percentage of individuals with schizophrenia smoke (Smith et al. 2006), and when they smoke, they tend to extract more nicotine than a smoker without schizophrenia (Olincy et al. 1997). Consequently, a number of researchers have interpreted the smoking behavior in schizophrenia from a "self-medication" perspective, suggesting that nicotine may have positive effects on both symptoms and cognitive function in schizophrenia (Kumari and Postma 2005; Leonard et al. 2007).

The hypothesis that smoking may improve cognitive function in schizophrenia has led to the conduct of a number of controlled trials of nicotine in schizophrenia. As shown in Table 4, these studies have used the nicotine patch, nicotine spray, and nicotine gum in both smoking and nonsmoking individuals with schizophrenia to examine a range of cognitive functions. All of the studies have essentially been single-dose studies examining the acute effects of nicotine on cognitive function, typically following withdrawal of some length if the individuals were smokers. The vast majority of these studies found some positive benefit of nicotine on some aspect of cognitive function, including faster reaction times in a range of tasks (AhnAllen et al. 2008; Barr et al. 2008; Hong et al. 2009; Jubelt et al. 2008; Levin et al. 1996; Smith et al. 2002, 2006), as well as improved EM (Jacobsen et al. 2004; Jubelt et al. 2008; Myers et al. 2004; Smith et al. 2002), working memory (Levin et al. 1996; Myers et al. 2004; Smith et al. 2006), and attentional/executive control functions (AhnAllen et al. 2008; Barr et al. 2008; Depatie et al. 2002; Harris et al. 2004; Hong et al. 2009; Smith et al. 2006). This was true for both smokers and nonsmokers, and for individuals taking both conventional and second-generation antipsychotics. Although nicotine has had relatively consistent positive effects across studies, these effects should be considered modest in that nicotine did not improve every measure examined in each study and the magnitude of the effects are not large. Further, nicotine as a therapeutic agent may be limited by tachyphylaxis. For example, a 6-mg nicotine gum dose improved the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) attentional index in nonsmokers, but impaired it in smokers. However, in this study, smokers were only required to be abstinent for 2 h prior to testing, as compared to overnight in many of the other studies. The authors suggest that this relatively short withdrawal period may have meant that the agonist effects of nicotine were still subject to tachyphylaxis and that longer periods of abstinence may be necessary to reinstate positive agonist effects in smokers (Harris et al. 2004). However, taken together, the results of these studies do suggest some benefit of nicotine on cognitive function in schizophrenia, consistent with a self-medication hypothesis.

Table 4 Nicotinic and muscarinic receptor agonist studies in schizophrenia

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
Nicotine							
Nicotine patch (0, 7, 14, 21 mg/day) combined with haldol	Levin et al. (1996)	15; age 38.9; 100% smokers	Haldol starting at 2 mg/day and incremented at 2 mg every 2–3 days until bradykinesia detected; high/med/lose doses of haldol	Smoker	Automated Neuropsychological Assessment Metrics (reaction time, verbal, and visual memory)	Before smoking each day, given patch of 0, 7, 14, and 21 mg of nicotine in randomized counterbalanced design	Nicotine significantly improved reaction time, delayed match to sample performance in medium- and high-dose haldol. Quadratic effects of nicotine on CPT reaction time
Nicotine nasal spray (10 mg/ml) and research cigarettes (0.1 vs. 1.9 mg)	Smith et al. (2002)	31; age 40.8; 100% smokers	Conventional and second generation	Smoker	Automated Neuropsychological Assessment Metrics (reaction time, verbal, and visual memory); Verbal Memory from RANDT; VF	Single-dose, double-blind, crossover (following abstinence)	Nasal spray significantly improved verbal memory; higher dose nasal spray (2 puffs) improved two-choice reaction time and spatial rotation accuracy
Nicotine patch (14 mg)	Depatie et al. (2002)	15; age 36.7	Conventional and second generation	Smoker; FSIQ > 80	CPT-IP; Visually guided saccades and antisaccades; Smooth pursuit	Single-dose, double-blind, placebo-controlled, crossover study	Nicotine increased hits in on CPT, decreased antisaccade errors, and increased gain in no-monitoring condition compared to placebo
Nicotine nasal spray (1.0 mg)	Myers et al. (2004)	29 (15 smokers, 14 nonsmokers); ages 39.4/41.6	Conventional and second generation		Delay recognition task; Working memory task	Single-dose, crossover design, no drug versus nasal spray in randomized order at least 1 h apart	Recognition and d′ was significantly better for smoking individuals with schizophrenia with nicotine than in the control condition

(*continued*)

Table 4 (continued)

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
Nicotine gum 6 mg	Harris et al. (2004)	20 (10 smokers, 10 nonsmokers); ages 44.5/43.1	Conventional and second generation		RBANS	Single-dose, double-blind, placebo-controlled, crossover study (after 2 h withdrawal)	Smoker by nicotine interaction for the RBANS attention index, such that nonsmokers got better on nicotine and smokers got worse
Nicotine patch 28 or 35 mg depending on BMI	Jacobsen et al. (2004)	13; age 42.9; 100% smoker	Conventional and second generation	Smoker	N-back (1- and 2-back), with either monaural or binaural presentation (high selective attention demand) with fMRI	Single-dose, double-blind, placebo-controlled, crossover study (after 15 h withdrawal)	On dichotic 2-back, higher plasma nicotine concentration was associated with better accuracy; greater activity in left insula and right putamen at high memory load under nicotine; greater activity in right thalamus, right globus pallidus and left lingual gyrus with high attention demand under nicotine
Nicotine nasal spray	Smith et al. (2006)	27; age 37.6	Conventional and second generation	Smoker; male	Conner's CPT; Spatial Rotation Test; Dot Memory Test; Verbal Memory from RANDT	Double-blind, placebo-controlled (active or placebo) nicotine spray on each of 2 days	Nicotine reduced CPT reaction time, reduced difference in error between immediate and delay memory on Dot

Nicotine patch 14 mg	Barr et al. (2008)	28; age 47.7	Conventional and second generation	Nonsmoker; >35 on WRAT	CPT-IP; Stroop; Letter–Number Sequencing; PEG	Single-dose, double-blind, placebo-controlled, crossover study	Nicotine reduced reaction time, SD of hit RT and random and commission errors on CPT-IP, reduced interference score on Stroop
Nicotine patch	AhnAllen et al. (2008)	22; age 47.59; 100% smokers	Conventional and second generation		Attention Network Test	Baseline, withdrawal and patch rescue conditions	Executive network function and overall reaction time improved on patch compared to baseline
Nicotine patch 14 mg	Jubelt et al. (2008)	10; age 46; 0% smoker	Second generation	Nonsmoker; <35 on WRAT-3	Source Monitoring Task	Single-dose, placebo-controlled, crossover study	Nicotine reduced false alarm rates and reaction times for new items
Nicotine patch 21 or 35 mg depending on smoking level	Hong et al. (2009)	20; age 35; 100% smoker	Second generation	Smoker	Rapid Visual Information Processing Task with fMRI	Single-dose, double-blind, placebo-controlled, crossover study	Nicotine improved hit rate and reduced reaction time; increased BOLD in a range of regions on nicotine
DMXB-A							
DMXB-A 75 mg (+37.5 mg) and 150 mg (+75 mg)	Olincy et al. (2006)	12; ages 20–58	Conventional and second generation	Nonsmoking	RBANS; P50	Single-dose, placebo-controlled, double-blind, crossover	Low-dose DMXB-A improved total RBANS compared to placebo and increased P50 suppression
DMXB-A 75 and 150 mg	Freedman et al. (2008)	31; 22–60	Conventional and second generation	Clinically stable; nonsmoker	MCCB (no social cognition): P50	4-week (for each arm), double-blind, placebo-controlled, crossover	No differential improvement with either DMXB-A dose compared to placebo on full analysis. In first arm only, attention

(*continued*)

Table 4 (continued)

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
							and working memory significantly improved with DMXB-A, but not with placebo
Xanomeline							
Xanomeline 75 mg → 225 mg	Shekhar et al. (2008)	20 (10/10); ages 34.4/42.1	Unmedicated	Total PANSS score > 60	CPT-IP; Stroop; WMS; WAIS; TMT; Word list memory and recall; COWAT; Shipley Vocabulary Test; Finger Tapping	4-week, double-blind, placebo-controlled, parallel group	Significant improvements on xanomeline for List Learning, Story Recall and Delayed Memory

BACS Brief Assessment of Cognition Scale, *CPT-IP* Continuous Performance Test – Identical Pairs, *COWAT* Controlled Oral Word Association Test, *DSPT* Digit Span Distraction Test, *GDS CPT* Gordon Diagnostic System Continuous Performance Test, *HVLT* Hopkin's Verbal Learning Test, *K-MMSE* Korean Mini-Mental Status Exam, *MCCB* MATRICS Consensus Cognitive Battery, *MMSE* Mini-Mental Status Exam, *PEG* Grooved Pegboard, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *RAVLT* Rey Auditory Visual Learning Test, *RCFT* Rey Complex Figure Test, *SCoRS* Schizophrenia Cognition Rating Scale, *TMT* Trail Making Test, *VF* Verbal Fluency, *WMS-R* Wechsler Memory Scale-Revised, *WCST* Wisconsin Card Sorting Test

Given the potential therapeutic benefit of nicotinic receptor modulation, researchers have also been exploring the development of α_7 nicotinic receptor agonists as a treatment for cognitive impairment in schizophrenia. One such drug is 3-[(2,4-dimethoxy)benzylidene]anabaseine (DMXB-A) developed by the Kem laboratory (Kem et al. 2004; Walker et al. 2006). At lower concentrations, DMXB-A is an α_7-selective partial agonist, though at higher doses it is also a weak antagonist at $\alpha_4\beta_2$ receptors (Kem et al. 2004). As shown in Table 4, the first study with DMXB-A was a single-dose proof-of-concept study with two doses of DMXB-A in individuals with schizophrenia who were nonsmokers. The low dose improved total RBANS scores and increased P50 suppression (Olincy et al. 2006). The fact that the high dose did not improve the RBANS may be an indication of tachyphylaxis or the involvement of other receptors besides α_7 (Olincy et al. 2006). However, despite this initial positive proof-of-concept study, the subsequent 4-week, double-blind placebo-controlled, crossover study did not provide clear evidence for cognitive benefits of DMXB-A over and above placebo, though there was an significant though modest improvement in negative symptoms at the high dose (Freedman et al. 2008). This second study with DMXB-A used the MATRICS Consensus Cognitive Battery (MCCB), and one of the issues raised by the authors was the presence of unexpected practice effects in some of the MCCB domains. For example, speed of processing showed a significant effect of testing session, and a trend-level repetition effect was found for the attention/vigilance domain. Thus, the authors compared only the first arm of the study for each individual, providing essentially a small-sample size parallel-group design. Both the attention/vigilance and working memory domain scores showed either a significant or trend-level improvement with both doses of DXMB-A and not placebo, and numerically the visual learning and reasoning domains showed the same pattern. However, the opposite trend was apparent for speed of processing and verbal learning, with numerically more improvement under placebo than under either DXMB-A dosage.

In sum, the work on nicotine effects on cognitive function in schizophrenia suggests that this is a potentially promising avenue for cognitive enhancement, though clearly nicotine itself will not be an effective approach due to tachyphylaxis. The initial trials with DMXB-A suggest some promise for selective α_7 nicotinic receptor agonists, though the support is not strong at this point. There is also additional positive evidence from a study with Tropisetron (Koike et al. 2005), which is a strong 5-HT3 antagonist that is also a high-affinity partial agonist for α_7 nicotinic receptors (Koike et al. 2005). Tropisetron improved P50 suppression among individuals with schizophrenia, though only in nonsmokers. Thus, while modulation of nicotinic receptors remains a viable approach for cognitive enhancement in schizophrenia, the extent studies suggest that issues related to dosing, tachyphylaxis, and sustainability of response will need careful attention.

Although much of the attention in terms of cholinergic function in schizophrenia has focused on nicotinic receptors for the reasons outlined earlier, acetylcholine also acts at muscarinic receptors that would also be a potential cognition-enhancing target. Further, modulation of muscarinic receptors can also modulate dopamine

function (Gomeza et al. 1999, 2001; Zhang et al. 2002). Xanomeline is a selective M1 and M4 muscarinic agonist that exerts functional dopamine antagonism without having affinity for any dopamine receptor (Shekhar et al. 2008). In a recent 4-week double-blind, placebo-controlled, parallel-group study in unmedicated individuals, xanomeline improved total Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Symptom Scale (PANNS) scores more than placebo, and improved a number of measures of EM (see Table 4). However, this was a small-scale study, and further work will be needed to determine whether agents such as xanomeline are effect cognition either as primary treatments or as adjunctive treatments for cognitive impairment in schizophrenia.

3 Glutamatergic Agents

Glutamate is the primary neurotransmitter mediating excitatory neurotransmission in the human brain and as such plays a role in numerous cognitive functions. Glutamate can exert its excitatory effects through either ionotropic or metabotropic receptors. The ionotropic glutamate receptors include NMDA, AMPA, and kainite receptors, and there are at least three classes of metabotropic glutamate receptors, with one group (mGluR1 and mGluR4) serving to strengthen presynaptic glutamate release and postsynaptic NMDA neurotransmission. In contrast, the other two groups limit glutamate release (Buchanan et al. 2007a; Meldrum 2000). Much of the attention in terms of schizophrenia has focused on the NMDA receptor, given the fact that NMDA receptor antagonists such as PCP or ketamine can induce psychosis and some aspects of cognitive impairment (Javitt and Zukin 1991; Newcomer et al. 1999; Newcomer and Krystal 2001). This has led to an NMDA receptor-hypofunction hypothesis for schizophrenia (Olney et al. 1999).

3.1 Glycine Allosteric Modulators

NMDA receptors have a number of different binding sites. Given that direct agonism of the glutamate-binding site can cause excitotoxicity (Camon et al. 2001), much of the research on cognitive enhancing effects has focused on the glycine allosteric modulatory site (Buchanan et al. 2007a). In terms of cognitive function, studies have mainly focused on the amino acids glycine and D-serine, as well as D-cycloserine, an antituberculosis drug that easily crosses the blood–brain barrier and has partial agonist properties in a specific dose range (Goff et al. 1995). A number of early small-sample studies have provided evidence for a positive effect of glycine on negative symptoms (Table 5). (Heresco-Levy et al. 1996, 1998, 1999, 2004). In addition, several studies have found evidence for improvements in negative symptoms when D-cycloserine was added to conventional antipsychotics (e.g., Goff et al. 1999), though not when added to clozapine (e.g., Goff et al. 1996).

Despite these initial positive results in regards to negative symptoms, neither glycine nor D-cycloserine has proven to have any consistent positive benefits on any aspects of cognitive function as assessed by a formal test. Table 5 outlines all of the glycine and D-cycloserine studies in schizophrenia that have used cognitive measures, and only one out of seven studies found any positive benefit. The 1995 dose-finding study by Goff et al. (1995) found improved reaction time on the Sternberg Item Recognition test, but only at the 50-mg dose. However, this finding was not replicated in subsequent larger-scale studies with patients taking either conventional neuroleptics (Goff et al. 1999) or clozapine (Goff et al. 1996). These null results cannot readily be explained by factors such as type of antipsychotic medication, trial length, dosage, or baseline negative symptom levels, as the majority of the studies have required individuals to have significant negative symptoms, have studied patients on both conventional and second-generation medications, and have used a range of trial lengths. The largest trial – The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST) study – directly compared glycine and D-cycloserine to placebo in individuals taking any antipsychotic but clozapine and did not find any overall significant improvements in either negative symptoms or cognition as a function of either adjunctive treatment (Buchanan et al. 2007b). One concern with the CONSIST study and the prior ones is that daily dosing of agents such as D-cycloserine can be subject to tachyphylaxis, which would limit effectiveness. Thus, Goff and colleagues also explored the efficacy of once-weekly D-cycloserine. However, although there was some improvement in Logical Memory thematic recall after 1 week, there were no significant improvements on any cognitive measure compared to placebo after 8 weeks (Goff et al. 2008a). Taken together, the consistent negative findings for cognitive function with either glycine or D-cycloserine suggest that these are not promising pathways for cognitive enhancement in schizophrenia.

3.2 AMPA Receptor Modulators

Although activation of the glycine allosteric modulatory site has not yet proven effective at enhancing cognitive function in schizophrenia, there are other approaches being examined for enhancing glutamate function. One such alternative is to modulate AMPA receptors rather than NMDA receptors. Although much of the focus on glutamate dysfunction in schizophrenia has been on NMDA receptor abnormalities, there is also evidence for decreased AMPA receptor density in the hippocampus of individuals with schizophrenia (Meador-Woodruff and Healy 2000). AMPA plays an important role in learning and memory via its impact on long-term potentiation. Activation of AMPA receptors facilitates a level of depolarization that eliminates the magnesium block in NMDA channels, allowing activation of NMDA receptors and setting in motion intracellular processes that induce LTP and changes in genetic expression that are thought to facilitate memory processes. Goff et al. (2001, 2008b) (see Table 5) have used CX516, which they

Table 5 Glutamatergic modulation studies in schizophrenia

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
Glycine							
Glycine 60 g	Evins et al. (2000)	27 (14/13); ages 52/58	Olanzapine or risperidone	Clinically stable	Stroop; WAIS Vocabulary, Information, digit span, and block design; CVLT, JOLO	8-week, double-blind, placebo-controlled, parallel group	No significant effects on any cognitive measure
D-*cycloserine*							
D-cycloserine 5, 15, 50, and 250 mg	Goff et al. (1995)	9; age 43	Conventional	Stable medication dose for at least 4 months	SIRP	Consecutive 2-week trials of placebo, 5, 15, 50, and 250 mg D-cycloserine	Significantly improved reaction times on the SIRP at the 50 mg dose
D-cycloserine 5, 15, 50, and 250 mg	Goff et al. (1996)	10; age 40.4	Clozapine	Meet primary deficit syndrome criteria	SIRP	Consecutive 2-week trials of placebo, 5, 15, 50, and 250 mg D-cycloserine	No significant effects on Sternberg
D-cycloserine 50 mg	Goff et al. (1999)	47 (23/24)	Conventional	Meet primary deficit syndrome criteria; stable dose of conventional narcoleptic for 4 weeks; 30+ on SANS	SIRP; Stroop; Miller-Selfridge; VF; Digit Span; Finger Tapping	8-week, double-blind, placebo-controlled, parallel group	No significant effects on any cognitive measure
D-cycloserine 5, 15, 50, and 250 mg	Evins et al. (2002)	10; age 42	Risperidone	Meet primary deficit syndrome criteria; 30+ on SANS	Word List Generation; Finger Tapping; Digit Span and Stroop	Consecutive 2-week trials of placebo, 5, 15, 50, and 250 mg D-cycloserine	No significant effects on any cognitive measure
D-cycloserine 50 mg	Goff et al. (2005)	55 (27/28); only 26 completed; ages 45.9/47	Conventional monotherapy	40+ on SANS	CVLT; Vocabulary; Information; Digit Span; Block Design; ANART; Stroop; Category Fluency; Finger Tapping and WCST	6-month, double-blind, placebo-controlled, parallel group	No significant effects on any cognitive measure

D-cycloserine 50 mg	Buchanan et al. (2007b)	157 (52/53/52); ages 42.6/44.4/43.4	Any antipsychotic but clozapine	Persistent moderate to severe negative symptoms; BRPS positive symptoms >19; Simpson–Angus EPS <9	WAIS Digit Symbol; WAIS Digit Search; Phonemic and Category Fluency; CPT; RAVLT; Brief Visual–Spatial Memory Test; Letter–Number Span; WAIS Letter–Number Sequencing; Visual–Spatial Working Memory; WCST	16-week, double-blind, double-dummy, placebo-controlled, parallel group	No significant effects on any cognitive measure
D-cycloserine 50 mg (1× per week)	Goff et al. (2008a)	38 (19/19); ages 50.1/48.0	Any antipsychotic but clozapine	Stable dose of antipsychotic for 4 weeks	NAART; HVLT; WCST: TMT Part B; Phonemic and Category Fluency; WMS Face Memory; Letter–Number Span; WAIS Letter–Number Sequencing; Logical Memory	8-week, double-blind, placebo-controlled, parallel group	D-cycloserine improved thematic recall on Logical Memory at 1 week; no significant effects on any cognitive measure at week 8
Ampakine							
CX516 (Ampakine) 2,700 mg	Goff et al. (2001)	13 (8/5); age 39.8	Clozapine	Stable medication dose for at least 6 months	RANDT 5-item acquisition; WCST; Rey/Taylor Figure; GDS CPT; TMT (B); VF; Finger Tapping	4-week, double-blind, placebo-controlled, parallel group	No formal statistical tests; large positive effect size for CX516 on WCST, RANDT 5-item acquisition and moderate positive effects on GDS CPT, VF, and Rey/Taylor Figure

(*continued*)

Table 5 (continued)

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
CX516 (Ampakine) 2,700 mg	Goff et al. (2008b)	95 (54/51); ages 43.7/42	Clozapine, olanzapine, or risperidone	At least 6 months on stable dose of antipsychotic	Degraded Stimulus CPT; CVLT; WCST; TMT; Letter–Number Span; Grooved Peg Board; Phonemic and Category Fluency	4-week, double-blind, placebo-controlled, parallel group	No significant effects on any cognitive measure
Lamotrigine							
Lamotrigine 50 mg → 400 mg	Goff et al. (2007)	Study 1: 209; age 41 Study 2: 212; age 41.6	One or more of clozapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone	Persistent positive symptoms for at least 3 months; >4 CGI; stable optimal dose of antipsychotic for at least 1 month	BACS + delayed verbal recall; Stroop	14-week, double-blind, placebo-controlled, parallel group	In study 2, but not study 1, the BACS composite score improved more in the lamotrigine group than in the placebo group
Sildenafil							
Sildenafil 50 and 100 mg	Goff et al. (2009)	15; age 49.7	Conventional or second generation	Stable dose of all medications for 4 weeks	HVLT; Logical Memory; Letter–Number Sequencing; Digit Symbol; Category Fluency; CPT-IP; Spatial Span	Double-blind, placebo-controlled, random-order, single-dose crossover design (placebo 50 and 100 mg)	No significant effects on any cognitive measure
Memantine							
Memantine 5 mg → 20 mg	Krivoy et al. (2008)	7; ages 20–56	Conventional or second generation	Stable antipsychotic dose for at least 6 weeks	Neurobehavioral Cognitive Scale Examination; Clock Drawing Test	6-week, open-label	No significant effects on any cognitive measure

Memantine 5 mg → 20 mg	Lieberman et al. (2009)	138 (70/68); ages 40.9/40.1	Second-generation monotherapy	>25 on BPRS; >3 on at least one BRPS psychosis symptom; stable antipsychotic dose for 4 weeks	BACS	8-week, double-blind, placebo-controlled, parallel group	No significant effects on any cognitive measure

CPT-IP Continuous Performance Test – Identical Pairs, *COWAT* Controlled Oral Word Association Test, *DSPT* Digit Span Distraction Test, *GDS CPT* Gordon Diagnostic System Continuous Performance Test, *HVLT* Hopkin's Verbal Learning Test, *JOLO* Judgment of Line Orientation, *K-MMSE* Korean Mini-Mental Status Exam, *MMSE* Mini-Mental Status Exam, *RAVLT* Rey Auditory Visual Learning Test, *SCoRS* Schizophrenia Cognition Rating Scale, *SIRP* Sternberg Item Recognition Performance Task, *TMT* Trail Making Test, *VF* Verbal Fluency, *WMS-R* Wechsler Memory Scale-Revised, *WCST* Wisconsin Card Sorting Test

refer to as an "Ampakine." CX516 binds to an allosteric site of the AMPA receptor. This enhances depolarization by prolonging channel opening in the presence of glutamate (Goff et al. 2008b). The first small-sample size study did not conduct formal statistical tests, but did see positive effects of CX516 on a number of cognitive measures, as well as on negative symptoms (Goff et al. 2001). Unfortunately, however, a relatively large sample size follow-up study did not find any positive benefits for CX516 on either cognitive function or symptoms in the overall analysis. This was true even when subjects taking clozapine were examined separately from those taking either olanzapine or risperidone (Goff et al. 2008b). The authors suggest that at least three factors could have influenced this null result, including too small of a dose (though this dose did produce insomnia and fatigue), too short of a trial (although fast effects were seen in animal studies), practice effects under placebo (though these were small), and potentially negative interactions with antipsychotics. Further, the authors note that the negative results with CX516 should not be taken as evidence again the potential effectiveness of any pathway toward modulating AMPA receptors, as there are a number of alternative mechanisms that might be more efficacious (Goff et al. 2008b).

3.3 Phosphodiesterase 5 Inhibitors

As another potential option for enhancing glutamate function, Goff et al. (2009) have also explored the use of phosphodiesterase 5 (PDE5) inhibitors. These agents increase cyclic guanosine monophosphate (cGMP) that would augment an NMDA–nitric oxide synthase (NOS)–cGMP pathway thought to be involved in long-term potentiation. Goff et al. (2009) used a PDE5 inhibitor called *sildenafil* that has been approved for the treatment of erectile dysfunction. There were no positive effects of single doses of either 50 or 100 mg of sildenafil on any cognitive measure in individuals with schizophrenia taking either conventional or second-generation antipsychotics (Goff et al. 2009). However, this was a small-sample size study and it is possible that repeated dosing is necessary for individuals with schizophrenia to experience a cognitive benefit from a PDE5.

3.4 NMDA Receptor Antagonists

In a different approach to regulating glutamate function in schizophrenia, Goff and colleagues have also examined the effects of lamotrigine, an anticonvulsant thought to inhibit excessive glutamate release related to impaired inhibitory feedback from GABAergic interneurons (Anand et al. 2000). The logic behind the use of lamotrigine is as follows. There is evidence that ketamine produces symptoms analogous to schizophrenia by blocking NMDA receptors on GABAergic

inhibitory interneurons. This results in excessive glutamate release at non-NMDA glutamate receptors, as the blockage of the NMDA receptors on the gamma-aminobutyric acid (GABA) interneurons reduces inhibitory feedback that would normally serve to limit glutamate release. If this mechanism of action is at play for NMDA-mediated glutamatergic function in schizophrenia, as suggested by Olney et al. (1999), then blocking excessive glutamate release resulting from chronic NMDA hypofunction could enhance cognition and reduce negative symptoms in schizophrenia. Goff and colleagues reported on two separate large-scale clinical trials with this agent. Lamotrigine did not have any greater benefit than placebo on any clinical measure in either study. In one study, but not the other, the composite score from the Brief Assessment of Cognition Scale (BACS) improved more with lamotrigine than with placebo. However, the magnitude of this effect was relatively small, and in study 1 there were more cognitive responders on placebo than on lamotrigine (Goff et al. 2007). To test a similar hypothesis, several groups have also examined the effectiveness of memantine as an adjunctive treatment for cognitive impairment in schizophrenia (see Table 5). Memantine is currently licensed for use in Alzheimer's and is a noncompetitive low-affinity NMDA receptor antagonist. In an initial small-scale open-label study, memantine improved negative symptoms, but did not alter cognitive function (Krivoy et al. 2008). However, in a subsequent much larger placebo-controlled double-blind study, memantine did not improve either clinical symptoms or cognitive function (Lieberman et al. 2009).

In sum, the extent studies examining a variety of mechanisms designed to enhance or regulate glutamate function in schizophrenia as a means of improving negative symptoms and cognitive function have not shown much positive evidence for efficacy in either regard. This is particularly disappointing given the range of different mechanisms studied to date and the fact that a number of the trials had relatively large samples and good power to detect clinically relevant effects. This is not to say that we should give up hope for mechanisms that might enhance cognitive function via modulation of the glutamate systems. As recently reviewed by Javitt (2008), glycine transport inhibitors might represent a promising pathway to augment NMDA receptor activation. In addition, as noted by Goff, other means of modulating AMPA receptor function that differ from the mechanism of action of CX516 might very well end up being more effective at regulating glutamate function and enhancing cognition in schizophrenia.

4 Gamma-Aminobutyric Acid Modulating Agents

In recent years, much interest has also centered on the role of GABA dysfunction in the pathophysiology of schizophrenia, due in large part to the work of David Lewis and colleagues (Hashimoto et al. 2008; Konopaske et al. 2006; Lewis and Hashimoto 2007; Lewis et al. 2005; Lewis and Moghaddam 2006) (see chapter, this text). Lewis and others have shown that mRNA for GAD67 interneurons is reduced in postmortem brains of individuals with schizophrenia (Volk et al. 2000, 2001).

These GABA neurons express the calcium-binding protein parvalbumin (Lewis and Moghaddam 2006). These parvalbumin-expressing neurons include chandelier neurons whose axons terminate on the axon initial segments of pyramidal neurons (Melchitzky and Lewis 2003). Importantly, animal research has demonstrated that GABA neurons in prefrontal cortex are critical for intact working memory function, potentially because inhibitory GABA interneurons help to regulate gamma-activity in cortical pyramidal neurons, a mechanism that may serve to support working memory representations (Barr et al. 2009; Farzan et al. 2009). Individuals with schizophrenia showed reduced gamma-band activity in prefrontal cortex during cognitive control tasks, a finding which Lewis and colleagues have hypothesized to be related to altered GABAergic function in prefrontal cortex in this illness (Cho et al. 2006).

To test this hypothesis, Menzies and colleagues (see Table 6) examined the influence of lorazepam (a GABA agonist for the benzodiazepine receptor site that allosterically enhances postsynaptic inhibitory effects) and flumazenil (antagonist or partial inverse agonist at the GABA receptor benzodiazepine site) on working memory and functional brain activation as measured by fMRI. The task used was an N-back working memory task with multiple memory loads (0-, 1-, 2-, and 3-back). As hypothesized, lorazepam impaired working memory performance in schizophrenia, though not in controls. This effect was significant in individuals with schizophrenia at the 1-back (with a trend at the 2-back load). In contrast, flumazenil improved working memory performance at both the 1- and 2-back condition in patients, though not in controls (Menzies et al. 2007).

In a subsequent study (see Table 6), Lewis et al. (2008) conducted a 4-week small-sample double-blind placebo-controlled study with MK-0777. MK-0777 is a benzodiazepine-like drug with selective activity at GABA receptors containing α_2- or α_3-subunits. The logic of targeting these subunits is that it would avoid the negative cognitive effects and sedation that occur with GABA receptors containing α_1- or α_5-subunits are activated (Lewis et al. 2008). The authors used a number of different cognitive measures in this study, including the RBANS and both the N-back and the AX-CPT, as well as using EEG to measure γ-activity during a cognitive control task. On the RBANS, only the delayed memory subtest showed a positive effect of MK-0777 over placebo. However, on the AX-CPT, there was a trend for improvement in the discriminability index, and some trends for improved N-back performance and γ-activity during cognitive control performance. The effect sizes were relatively large, but the small-sample size precluded clear statistical interpretations of the results. However, a subsequent larger-scale study with a very similar design (4-week, double-blind, placebo-controlled) using either a 6- or 16-mg dose failed to replicate these results (Buchanan et al. 2010). Specifically, the Buchanan et al. study did find any significant positive effects of MK-0777 on the MCCB battery (total score or subscale scores) or on either the AX-CPT or the N-back. Thus, although the approach of targeting GABA receptors has received some positive support in small-scale and single-dose study, the more recent larger study was not supportive and additional work is needed to establish the efficacy of this or related approaches.

Table 6 GABAergic modulation studies in schizophrenia

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
Lorazepam 2 mg and flumazenil 0.9 mg	Menzies et al. (2007)	12; age 44.4	Second generation	Male; no anticholinergics or benzodiazepines	N-back (0-, 1-, 2-, and 3-back) working memory with fMRI	Single-dose, double-blind, placebo-controlled	Lorazepam impaired d′ (at 1-back) and flumazenil improved d′ (at 1- and 2-back)
MK-0777 6 mg → 16 mg	Lewis et al. (2008)	15 (6/9); ages 24–50	Second generation	Clinically stable; unemployed; IQ > 79; RBANS composite < 90	RBANS; N-back (0-, 1-, and 2-back); AX-CPT; Preparing to Overcome Prepotency (POP) Task	4-week, double-blind, placebo-controlled, parallel group	On RBANS, only delayed memory index showed MK-0777-related improvement; MK-0777 improved POP task performance, trend for d′-context on AX-CPT
MK-0777 6 and 16 mg	Buchanan et al. (2010)	60 (19/21/21); ages 43.3/44.9/40	Second generation	Clinically stable; BPRS Hallucinatory Behavior or Unusual Thought Content > 6; Conceptual Disorganization > 5; SAS > 7; CDS > 11; Maximum MCCB performance below 1.0 SD from perfect; HVLT < 32; >4th grade on WTAR	MCCB; AX-CPT; N-back (0-, 1-, and 2-back)	4-week, double-blind, placebo-controlled, parallel group	No significant effects on any cognitive measure

AX-CPT AX Continuous Performance Test, *BPRS* Brief Psychiatric Rating Scale, *MCCB* MATRICS Consensus Cognitive Battery, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status

5 Dopaminergic Agents

Early and simple forms of the dopamine hypothesis of schizophrenia – focused primarily on enhanced subcortical dopamine function – are no longer considered tenable. However, there continues to be evidence that dopamine is critically involved in the pathophysiology of schizophrenia, but that the nature of dopaminergic abnormalities is much more complex than originally thought. Current theories focus on a dysregulation of the dopamine system that involves both disrupted phasic dopamine function in subcortical regions, as well as hypodopaminergic function in prefrontal cortex (Lisman et al. 2008). It has been hypothesized that the heightened dopamine neurotransmission in subcortical regions contributes to the positive psychotic symptoms of schizophrenia, while hypoactive dopamine neurotransmission in cortical regions contributes to negative symptoms and cognitive impairment (Toda and Abi-Dargham 2007).

Further, there is a wealth of work implicating the dopamine system in many of the cognitive domains that are impaired in schizophrenia with the most evidence in regards to working memory and cognitive control (Goldman-Rakic et al. 2000). For example, working memory function is impaired in nonhuman primates following 6-hydroxydopamine lesions in PFC (Brozoski et al. 1979), or administration of dopamine antagonists (Sawaguchi and Goldman-Rakic 1994). In addition, administration of low-dose DA agonists can improve working memory in monkeys (Williams and Goldman-Rakic 1995), especially those with impaired performance (Arnsten et al. 1994; Cai and Arnsten 1997; Castner et al. 2000). Current models of the role of dopamine in working memory emphasize the important interactions between multiple dopamine receptors (e.g., D1 vs. D2) as well as interactions with other neurotransmitter systems (Gonzalez-Burgos et al. 2005; Seamans and Yang 2004).

There is also growing evidence that the administration of dopamine agonists can improve cognition in humans, including working memory. Methylphenidate (Clark et al. 1986; Elliott et al. 1997; Mehta et al. 2000), amphetamine (Mattay et al. 1996, 2000), bromocriptine (Kimberg et al. 1997; Luciana and Collins 1997; Luciana et al. 1992, 1998), and pergolide (Kimberg and D'Esposito 2003; Muller et al. 1998) have all been shown to improve working memory in healthy human participants. Interestingly, there is also research to suggest that dopamine agonists may be particularly effective for those individuals with the worst performance in the absence of drug (Kimberg and D'Esposito 2003; Kimberg et al. 1997; Mattay et al. 2000, 2003; Mehta et al. 2001). For example, individuals with the high-activity form of the COMT gene (leading to more catabolism of dopamine) have worse working memory performance than individuals with the low-activity form of the COMT gene (Egan et al. 2001; Malhotra et al. 2002), and also show the greatest positive benefit of amphetamine (Mattay et al. 2003). Although several of these agents are not selective for dopamine, and it is likely that all of these drugs influence neurotransmitter systems other than the dopamine system, such results are generally consistent with the hypothesis that administration of dopamine agonists can improve working memory. Further, there is evidence that levodopa can improve working memory and related

cognitive functions in individuals with impaired dopamine function, such as those with Parkinson's disease (Cools et al. 2002; Cooper et al. 1992; Costa et al. 2003; Kulisevsky et al. 1996, 2000; Lange et al. 1995).

5.1 Indirect Dopamine Agonists

Given these lines of evidence suggesting a role for dopamine in cognitive function in schizophrenia, a number of studies have examined the influence of various dopaminergic agents in schizophrenia, though most have not been in the form of a traditional clinical trial (see Table 7). These studies have provided evidence that individuals with schizophrenia taking haloperidol show improved performance on the Wisconsin Card Sorting Task with the administration of amphetamine, despite minimal or no exacerbation of positive symptoms (Daniel et al. 1991; Goldberg et al. 1991). In more recent work, Barch and Carter found that individuals with schizophrenia on stable doses of haloperidol or fluphenazine showed improvement in a number of cognitive domains following a single dose of amphetamine (0.25 mg/kg), including increased accuracy and faster reaction times on spatial working memory, increased language production, and decreased reaction time on the Stroop (with no loss of accuracy). These cognitive improvements occurred without an exacerbation of the positive symptoms of psychosis. The interpretation of these results has been that cognition is improved in schizophrenia with the coadministration of haloperidol and amphetamine because treatment with a typical antipsychotic blocks D2 receptors in subcortical regions. This blockage is thought to prevent a negative impact of dopamine agonists of positive symptoms, leaving D1 receptors in regions such as prefrontal cortex free to benefit for enhanced cholinergic transmission (Goldberg et al. 1991).

Further, individuals with schizotypal personality disorder also show improved performance on the Wisconsin Card Sorting Task, on a spatial working memory task, and on reaction time in an antisaccade task with the administration of amphetamine (Kirrane et al. 2000; Siegel et al. 1996; Wonodi et al. 2006), even in the absence of stable treatment with an antipsychotic. In contrast, one additional study used methylphenidate in young individuals with schizophrenia, once off medication and once after the patients were stabilized on medication (Szeszko et al. 1999). These researchers found that this indirect dopamine agonist reduced word production, increased redundant errors on a verbal fluency tasks, and increased disorganization symptoms, both when patients were on medication and when they were off medication (Szeszko et al. 1999).

5.2 Atomoxetine and Amantadine

Two additional agents that have been used in schizophrenia are also thought to have at least an indirect effect on increasing dopamine function (see Table 7). One such

Table 7 Dopaminergic modulation studies in schizophrenia

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
Dextroamphetamine							
Dextroamphetamine 0.25 mg/kg	Goldberg et al. (1991)	21; age 32	Haldol		WCST; VF; Selective Reminding Test; CTP; Stroop; Understanding Communication Test; Finger Tapping; TMT (B)	Double-blind, single-dose, placebo-controlled, crossover	Amphetamine significantly improved motor speed on Trails and Finger Tapping, trend-level improvement in correct responses on WCST and on Understanding Communication Test
Dextroamphetamine 0.25 mg/kg	Daniel et al. (1991)	19; ages 20–40	Haldol		WCST and Sensorimotor Control with SPECT	Double-blind, single-dose, placebo-controlled, crossover	Amphetamine improved number of correct responses and percentage of conceptual-level responses on WCST; Amphetamine increased DLPFC activity during WCST
Dextroamphetamine 0.25 mg/kg	Siegel et al. (1996)	9; age 43	Unmedicated	Schizotypal personality disorder	WCST	Double-blind, single-dose, placebo-controlled, crossover	Fewer errors on amphetamine compared to placebo, after controlling for placebo performance
Dextroamphetamine 30 mg	Kirrane et al. (2000)	12; age 39	Unmedicated	Schizotypal personality disorder;	DOT Test of Spatial Working Memory	Double-blind, single-dose, placebo-	Improved delay condition

				medication free for at least 2 weeks; low monoamine diet for 3 days prior to testing		controlled, crossover	performance on the DOT
Dextroamphetamine 0.25 mg/kg	Barch and Carter (2005)	10; age 36.6	Stable dose haldol or prolixin	Clinically stable	Spatial Working Memory; Language Production; Category Monitoring CPT; Stroop	Double-blind, single-dose, placebo-controlled, crossover	Amphetamine increased accuracy and speeded RT on spatial working memory, increased language production, and decreased RT on the Stroop (with no loss of accuracy)
Dextroamphetamine 30 mg	Wonodi et al. (2006)	11; age 34.8	Unmedicated	Schizophrenia spectrum personality disorder no lifetime exposure to antipsychotic medications	Antisaccade Task	Double-blind, single-dose, placebo-controlled, crossover, with two amphetamine sessions and one placebo session	Amphetamine reduced antisaccade latency, but not errors
Methylphenidate							
Methylphenidate 0.5 mg/kg	Szeszko et al. (1999)	11; age 24.5	Unmedicated at active phase	<12 weeks of lifetime antipsychotic exposure; 4 or more on at least one psychotic symptom of SAPS	Word Production	Pre- and postmethyl -phenidate perfusion at unmedicated baseline and after treatment stabilization criteria met for 8 weeks	Methylphenidate reduced word production and increased redundant word production

(*continued*)

Table 7 (continued)

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
Atomoxetine							
Atomoxetine 40 mg → 80 mg	Friedman et al. (2008)	20 (10/10)	Second generation	Stable antipsychotic doses for at least 4 weeks	BACS; N-back (0-, 2-, and 3-back) with fMRI	4-week, double-blind, placebo-controlled, parallel group	No significant improvements on any cognitive measure
Atomoxetine 0, 40, and 80 mg	Sacco et al. (2009)	12 (3/4/5)	Conventional and second generation	Smoker; must have deficit in visuospatial working memory	Attention; Cognitive Switching; Working memory; COWAT; Fine Motor; Learning and Memory	1-week, double-blind, placebo-controlled, crossover, with two doses of atomoxetine and placebo	Individuals in 80 mg group showed improvement in Visual–Spatial Working Memory, and COWAT compared to placebo, but no changes were statistically significant
Amantadine							
Amantadine 100 mg	Fayen et al. (1988)	9; age 30	Conventional	Required antiparkinsonian daily for 4 weeks	RAVLT	6-week, double-blind, crossover design, amantadine versus trihexy-phenidyl	First four trials of RAVLT significantly better on amantadine compared to trihexyphenidyl; trends for recognition to be better as well

Amantadine 200 mg	Silver and Geraisy (1995)	26; age 36.7	Conventional or second generation	Stable medication doses for at least 2 months	BVRT; WMS; MMSE	2-week, double-blind, crossover design, amantadine versus biperiden	Logical Memory and visual reproduction from the WMS significantly better on amantadine versus biperiden
Amantadine 200 mg	Silver et al. (2005)	29; age 36.86	Conventional or second generation	Stable medication dose for at least 1 month	WAIS Digit Span; DOT Test; Finger Tapping; BVRT; MMSE; Abstraction Inhibition and Working Memory Task; Penn CPT; Penn Face Memory Test; Visual Object Learning Test; JOLO	3-week, double-blind, placebo-controlled, parallel group	No significant improvements on any cognitive measure
Dihydrexidine							
Dihydrexidine 20 mg	George et al. (2007)	13; age 39.45	Conventional and second generation	PANSS score >50 but less than 90, at least one PANSS negative item >4; stable antipsychotic dose for at least 2 weeks	TMT; HVLT; COWAT	Double-blind, single-dose, placebo-controlled, crossover	No significant improvements on any cognitive measure

CPT-IP Continuous Performance Test – Identical Pairs, *COWAT* Controlled Oral Word Association Test, *DSPT* Digit Span Distraction Test, *GDS CPT* Gordon Diagnostic System Continuous Performance Test, *HVLT* Hopkin's Verbal Learning Test, *JOLO* Judgment of Line Orientation, *K-MMSE* Korean Mini-Mental Status Exam, *MMSE* Mini-Mental Status Exam, *RAVLT* Rey Auditory Visual Learning Test, *SCoRS* Schizophrenia Cognition Rating Scale, *SIRP* Sternberg Item Recognition Performance Task, *TMT* Trail Making Test, *VF* Verbal Fluency, *WMS-R* Wechsler Memory Scale-Revised, *WCST* Wisconsin Card Sorting Test

agent is atomoxetine, which is a selective norepinephrine reuptake inhibitor that also serves to increase extracellular dopamine in prefrontal cortex (Friedman et al. 2008), but not in subcortical regions (Bymaster et al. 2002). Neither study found evidence for statistically significant improvements in cognitive performance on atomoxetine among individuals with schizophrenia (Friedman et al. 2008; Sacco et al. 2009), though Sacco et al. (2009) reported relatively large effect size improvements that did not reach statistical significance given the small-sample size. Several additional studies have also examined the effects of amantadine, which has both NMDA antagonist properties and indirect dopamine agonist properties. Two of these studies compared amantadine to an anticholinergic medication, and found better memory performance on amantadine versus either biperiden (Silver and Geraisy 1995) or trihexyphenidyl (Fayen et al. 1988). However, given the absence of a placebo condition, it is difficult to tell whether this reflected actual benefits of amantadine, or impairments due to the anticholinergic medications. A third study did compare amantadine to placebo, but did not find any significant improvements in cognitive performance associated with amantadine, though it did improve visual motor coordination (Silver et al. 2005).

5.3 Selective Dopamine Agonists

As described earlier, single-dose studies of an indirect dopamine agonist have provided evidence of cognitive improvements among individuals with schizophrenia taking stable doses of high-potency antipsychotics, and among individuals with schizotypal personality disorder not taking any medication. However, concerns about amphetamine sensitization and the potential negative effects of more global enhancement of dopamine availability even among medicated patients with schizophrenia have really prevented agents such as amphetamine or methylphenidate from being seen as viable long-term adjunctive treatments for the enhancement of cognitive function in schizophrenia. To be specific, this is because indirect (and nonselective) dopamine agonists will enhance dopamine function in both subcortical and cortical regions, and will modulate neurotransmitters other than dopamine, making it more likely to generate negative effects alongside any potential positive effects. As such, much interest has centered on the possibility of developing selective dopamine agonists that target receptors thought to mediate the positive effects of dopamine on cognitive function in prefrontal cortex, such as D1 receptors. One such agent is dihydrexidine (DAR-0100), which is the first full D1 agonist (Zhang et al. 2009). This agent has been used in a single-dose crossover design, which found that DAR-0100 increased perfusion in prefrontal cortex, as well as in temporal and parietal regions (Mu et al. 2007). However, DAR-0100 did not produce any significant positive effects on cognition, though the sample size was clearly too small to have any power to detect significant effects, and no means or standard deviations were presented that would allow computation of an effect size (George et al. 2007). Nonetheless, the

field remains optimistic that agents similar to DAR-0100 may end up providing evidence of cognitive enhancement in the absence of psychosis exacerbation, should it become clinically feasible to conduct a larger-scale, longer-term studies with a direct D1 agonist.

6 Modafinil

Although the choice of many agents as potential cognitive enhancers in schizophrenia has been driven by theoretical considerations of potential pathophysiological mechanisms and ways to target these mechanisms, some choices have been based on more practical considerations of proven efficacy in other disorders. For example, a number of studies have examined the use of modafinil as a potential cognitive enhancing agent in schizophrenia. Modafinil has the trade name Provigil and has been approved for use in various sleep disorders (Didato and Nobili 2009; Kumar 2008). Modafinil can improve cognition as well as mood and fatigue in sleep-deprived individuals, and there is evidence for beneficial effects on cognition even in nonsleep-deprived individuals (Kumar 2008; Minzenberg and Carter 2008). It is not yet clear exactly how modafinil works. Many hypotheses about the effects of modafinil on cognitive function have centered on dopamine. However, modafinil is structurally different than amphetamine, and it is clear that modafinil has effects on many neurotransmitter systems (Minzenberg and Carter 2008), including the ability to inhibit the function of both the dopamine transporter and the norepinephrine transporter, leading to functionally higher levels of both dopamine and norepinephrine. An additional hypothesis is that modafinil can act as a hypocretin/orexin agonist with excitatory influences on locus coeruleus adrenergic system (Minzenberg et al. 2008; Morein-Zamir et al. 2007).

Given that modafinil had good efficacy as a cognitive enhancer in sleep-deprived and even healthy individuals, as well as positive evidence for cognitive enhancement with modafinil in a number of psychiatric disorders (Turner 2006; Turner et al. 2003, 2004a), a number studies have examined its effects on cognitive and brain function in schizophrenia (see Table 8). Early studies using a single-dose design provided evidence for improvement in either cognition (Turner et al. 2004b) or brain function (Hunter et al. 2006; Spence et al. 2005) and a 4-week open-label study also showed evidence for some cognitive improvement among individuals with schizophrenia (Rosenthal and Bryant 2004). However, despite this early promise, subsequent longer-term, double-blind, placebo-controlled studies have not provided any consistent evidence for cognitive enhancement in schizophrenia as a function of modafinil (Freudenreich et al. 2009; Pierre et al. 2007; Sevy et al. 2005). Though these more recent studies are not encouraging, Freudenreich et al. (2009) have suggested that more definitive larger-scale studies are still needed, particularly if they examine the effects of modafinil on a range of cognitive, motor, and fatigue parameters in patients treated with different types of antipsychotics.

Table 8 Modafinil studies in schizophrenia

Agent and dose	Authors	Sample size	Antipsychotics	Inclusion/exclusion criteria	Cognitive assessment	Design	Outcome
Modafinil 200 mg	Turner et al. (2004b)	20; age 43	Conventional and second generation	Clinically stable; stable doses of neuroleptics; >25 on MMSE	CANTAB: Digit Span; PRM; DMTS; SWM; SSP; NTOL; IDED; STOP	Double-blind, placebo-controlled, single-dose, crossover	Modafinil improved Digit Span forward and backward, extradimensional shift performance on the IDED, but slowed response latency on NTOLS
Modafinil 100 mg → 200 mg	Rosenthal and Bryant (2004)	11; age 38.8	Conventional and second generation	Illness duration of at least 2 years; stable doses of antipsychotics for at least 1 month; a maximum score of 4 on no more than 1 PANSS positive item	WAIS-III Letter–Number Sequencing	4-week, open-label	Significant improvement on raw Letter–Number Sequencing scores
Modafinil 200 mg	Sevy et al. (2005)	20 (10/10); 35.9/38.9	Conventional and second generation	Stable doses of antipsychotics for at least 1 month; 4+ on CGI fatigue	CPT-IP; Oculomotor Delayed Response Task; DMTS; COWAT; RAVLT	8-week, double-blind, Placebo-controlled, parallel group	No significant improvements on any cognitive measures
Modafinil 100 mg	Spence et al. (2005)	21; age 37.7	Conventional and second generation	>70 NART; >2 on at least one SANS item; no prominent positive symptoms	2-Back working memory task with fMRI	Double-blind, placebo-controlled, single-dose, crossover	No significant improvement on cognitive measures; significantly greater working memory-related activity in anterior cingulated on modafinil

Modafinil 100 mg	Hunter et al. (2006)	12; age 37	Conventional and second generation	>70 NART; >2 on at least one SANS item; no prominent positive symptoms	VF with fMRI; Sheffield Activity in Time Task	Double-blind, placebo-controlled, single-dose, crossover	Modafinil associated with increased left dorsolateral PFC activity; Worse letter fluency performance at baseline associated with greater increase in activity
Modafinil 100 mg	Pierre et al. (2007)	20 (10/10); ages 49.8/48.7	Conventional and second generation	Stable doses of antipsychotics for at least 1 month; <15 on BRPS Psychosis; >19 on SANS total and >1 on either affective flattening or alogia	TMT; Degraded Stimulus CPT; CVLT	8-week, double-blind, Placebo-controlled, parallel group	No significant improvements on any cognitive measures
Modafinil 100 mg → 300 mg	Freudenreich et al. (2009)	35 (19/16); ages 44.2/46.4; 50/75% smoker	Clozapine	Clinically stable; clozapine for at least 6 months	NAART; Degraded Stimulus CPT; HVLT; WMS-III Faces and Family Pictures; WCST; TMT; WAIS-III Letter–Number Sequencing; VF; PEG	8-week, double-blind, Placebo-controlled, parallel group	No significant improvements on any cognitive measures

CPT-IP Continuous Performance Test – Identical Pairs, *COWAT* Controlled Oral Word Association Test, *DSPT* Digit Span Distraction Test, *GDS CPT* Gordon Diagnostic System Continuous Performance Test, *HVLT* Hopkin's Verbal Learning Test, *K-MMSE* Korean Mini-Mental Status Exam, *MMSE* Mini-Mental Status Exam, *PEG* Grooved Pegboard, *RAVLT* Rey Auditory Visual Learning Test, *SCoRS* Schizophrenia Cognition Rating Scale, *SIRP* Sternberg Item Recognition Performance Task, *WMS-R* Wechsler Memory Scale-Revised, *WCST* Wisconsin Card Sorting Test, *DMTS* Delayed Match to Sample Size, *SWM* Spatial Working Memory, *SSP* Spatial Span Performance, *NTOL* One-Touch Tower of London, *PRM* Pattern Recognition Memory, *IDED* Intradimensional/Extradimensional Shift Task, *STOP* Stop Signal Task, *VF* Verbal Fluency

7 Other Agents

In addition to the different classes of agents described in the sections earlier, there are a number of additional novel approaches that have been tried in only one or two studies each (Table 9). For example, two studies have examined the influence of mirtazapine on cognition in schizophrenia. Mirtazapine is a dual-acting antidepressant that has antagonist effects at the α_2-adrenergic, 5-HT_2 and 5-HT_3 receptors, as well as indirect agonist effects at the 5-HT_{1a} receptor. The logic for the use of this drug as a potential enhancer of cognition in schizophrenia stems from the argument that clozapine (which may also have adrenergic and serotonin effects) has shown evidence of enhanced efficacy for negative symptoms in schizophrenia (Berk et al. 2009; Delle Chiaie et al. 2007). The first open-label study with mirtazapine showed beneficial effects on RBANS total scale scores as well as immediate and delayed memory scores (Delle Chiaie et al. 2007). However, a subsequent 6-week double-blind placebo-controlled study did not replicate the initial positive findings of the open-label study, failing to find any significant improvement as a function of mirtazapine in any cognitive measure among individuals with schizophrenia.

One study has also examined mifepristone (RU-486), which is a progesterone receptor antagonist and an antagonist of glucocorticoid receptors at high doses. The logic behind the use of mifepristone is that there is evidence that chronic elevations of endogenous cortisol levels (as is found in Cushing's syndrome) are associated with cognitive impairment (Gallagher et al. 2005) and the fact that HPA axis dysfunction may play a role in schizophrenia (Walker and Diforio 1997). However, a 1-week double-blind, placebo-controlled crossover study did not find any significant positive effects on any cognitive measures in schizophrenia. There has also been one study examining the potential benefits of pregnenolone, a neurosteriod shown to have beneficial effects on learning and memory in animal models (Marx et al. 2009). However, a small-sample 8-week, double-blind, placebo-controlled, parallel-group study did not find any significant improvements on either the BACS or the MCCB, though it did show significant improvements on SANS negative symptom scores compared to placebo (Marx et al. 2009). In addition, increases in serum pregnenolone levels predicted improvements in BACS scores at the end of the trial. Thus, although this small study did not find positive overall effects on the BACS or MCCB, it may be that with appropriate dosing, more positive effects might be found. Lastly, one additional study examined minocycline, a tetracycline. Minocycline has reduced cognitive impairments induced by PCP in animal models (Levkovitz et al. 2010). It has a number of effects and its mechanism of action in regards to cognitive enhancement is currently unclear. These effects include an ability to block nitric oxide-induced neurotoxicity, its influence on dopamine neurotransmission, and its influence on microglia that may impact apoptosis (Levkovitz et al. 2010). Interestingly, this 24-week, single-blind, placebo-controlled study showed positive benefits on SANS negative symptom ratings as well as positive effects on a number of cognitive measures, including an executive function

Table 9 Mixed or unique agent studies in schizophrenia

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
Mirtazapine 30 mg	Delle Chiaie et al. (2007)	15; age 32.3	Clozapine	Clinically Stable	RBANS	8-week, open-label	Significant improvement on RBANS immediate memory, delayed memory and total scale
Mirtazapine 30 mg	Berk et al. (2009)	38 (18/20); ages 37.8/35.9	Second generation	Clinically Stable	Digit Span; Word Learning; TMT and VF	6-week, double-blind, placebo-controlled, parallel group	No significant effects on any cognitive measure
Mifepristone 600 mg	Gallagher et al. (2005)	19; age 43.1	Conventional and second generation	Clinically stable	CANTAB Spatial Working Memory; RAVLT; CANTAB Spatial Span; WAIS Digit Span; CANTABN Pattern and Spatial Recognition Tasks; VF; CPT	1-week, double-blind, placebo-controlled, crossover	No significant effects on any cognitive measure
Pregnenolone 500 mg	Marx et al. (2009)	18 (9/9); ages 52.7/49/4	Second generation	Stable antipsychotic doses for at least 4 weeks	BACS and MCCB	8-week, double-blind, placebo-controlled, parallel group	No significant effects on any cognitive measure

(*continued*)

Table 9 (continued)

Agent and dose	Authors	Sample size	Antipsychotics	Additional criteria	Cognitive assessment	Design	Outcome
Minocycline 200 mg	Levkovitz et al. (2010)	54 (36/18); ages 24.7/25.1	Risperidone, olanzapine, quetiapine, or clozapine	Within 5 years of diagnosis; had not received antipsychotics for 6 months prior to current symptom exacerbation; had been initiated on treatment 14 days before	CANTAB Psychomotor Speed; Rapid Visual Processing; Pattern Recognition Memory; Spatial Recognition Memory; Spatial Working Memory; ID/ED; Stockings of Cambridge	24-week, single-blind, placebo-controlled, parallel group	Significant positive effects of minocycline on executive functioning composite score, Spatial Recognition Memory, ED errors, Spatial Working Memory

CPT-IP Continuous Performance Test – Identical Pairs, *COWAT* Controlled Oral Word Association Test, *DSPT* Digit Span Distraction Test, *GDS CPT* Gordon Diagnostic System Continuous Performance Test, *HVLT* Hopkin's Verbal Learning Test, *K-MMSE* Korean Mini-Mental Status Exam, *MMSE* Mini-Mental Status Exam, *RAVLT* Rey Auditory Visual Learning Test, *SCoRS* Schizophrenia Cognition Rating Scale, *SIRP* Sternberg Item Recognition Performance Task, *WMS-R* Wechsler Memory Scale-Revised, *WCST* Wisconsin Card Sorting Test, *VF* Verbal Fluency

composite score, spatial recognition memory, extradimensional shift errors, and spatial working memory (Levkovitz et al. 2010). These initial positive results suggest a need for a more definitive double-blind placebo-controlled study to more fully delineate the potential cognitive enhancing effects of this novel agent.

8 Conclusions

The studies reviewed earlier represent a concerted effort on the part of the field to identify adjunctive treatments that could potentially improve cognitive function in schizophrenia, with the hope that such cognitive improvement would subsequently lead to enhancements in social, occupational, and educational achievement. The various studies represent diverse approaches that span many different neurotransmitter systems thought to be impaired in schizophrenia, as well as different mechanisms for modulating the function of those systems. Many single-dose and open-label studies have shown promising positive effects of a number of different agents on cognitive function in schizophrenia. In particular, many of the single-dose studies with nicotine and the single-dose studies with amphetamine have shown relatively consistent positive effects on measures of both accuracy and reaction time, though it is not always clear that these effects are of a clinically significant magnitude. However, the holistic view of the results of the more definitive or larger-scale studies is not nearly so encouraging. Specifically, relatively few large-scale, well-controlled, double-blind studies have shown any robust evidence for improvement in any domain of cognitive function in schizophrenia. This is true regardless of whether the individuals in the study were limited to those taking conventional antipsychotics, second-generation antipsychotics, or even limited to clozapine alone. The studies with galantamine are perhaps overall the most encouraging, but even galantamine has at least one null result in a double-blind study (Dyer et al. 2008), and a mixed result in another (Buchanan et al. 2008).

There are two responses one could have to the observation that few large-scale studies have generated positive evidence for cognitive enhancement effects in schizophrenia. One response is that we have just not yet found the right agent or mechanism, and that with continued drug development, we will hone in on an effective approach. It is certainly true that there are many theoretically motivated attractive targets that are currently in development. As described earlier, although glycine agonists or partial agonists have not been effective, glycine transporter inhibitors are another alternative approach to enhancing glutamate function (Javitt 2008). Although DMXB-A, an α_7-selective partial agonist, did not reveal positive results in its first double-blind study, xanomeline (a muscarinic agonist) did show positive effects and there are other approaches to muscarinic and nicotinic receptor activation that may be more effective, including targeting M_1 or $\alpha_4\beta_2$ receptors (Lieberman et al. 2008). In addition, another potential target is the histamine H_3 receptor (Esbenshade et al. 2008). In particular, H_3 receptor antagonists are attractive because of the fact that they regulate the release of many other neurotransmitters

relevant for cognition, including dopamine, acetylcholine, and norepinephrine, and have shown positive effects on a range of cognitive functions in animal models (Esbenshade et al. 2008). Thus, H_3 antagonists may be able to modulate multiple neurotransmitter systems simultaneously in a way that may end up having more efficacy than mechanisms that focus on a single neurotransmitter system, although many such putatively selective agents also result in modulation of additional neurotransmitter systems.

A corollary to the above argument is that we may also need more predictive animal models in order to identify promising agents with a higher hit rate. Many of the drugs that come to early clinical trials have shown some evidence of improving cognitive function in animal studies, typically with rodents. These studies have used paradigms thought to capture core aspects of the cognitive functions impaired in individuals with schizophrenia or individuals with other cognitive disorders. However, many of these animal models lack construct validity, in the sense that they may not be tapping into the same cognitive or neurobiological processes operating in humans (Geyer 2008), because of species differences both in behavioral repertoires and in neural systems. Such rodent models are attractive for their ease of use and practicality, but these qualities become less helpful if the results of such studies lack predictive utility for knowing how drugs will influence cognition in humans. Thus, either the development of rodent models of cognition with more construct validity for human cognition, and/or the greater use of primate models that may have better predictive utility may be necessary advancements in order to move the field forward.

An alternative response, however, is to suggest that the approaches we have been using to test the ability of various agents to enhance cognition in schizophrenia are part of the problem, and that novel approaches are needed. The primary approach has been to simply add some type of potentially procognitive molecule to ongoing antipsychotic treatment, and then to test individuals prior to the start of the trial and at the end (as well as at some intermediate points in various studies). This approach assumes that the procognitive effects of the molecule will occur via relatively fast acting changes in neurotransmission that may or may not remain stable over the course of the trial. However, the logic for targeting many of the neurotransmitter systems upon which we have focused is their role in plasticity, learning, and memory. Individuals with schizophrenia may have experienced impairments in the wiring or developmental connectivity of various neural systems in the brain because of long-standing impairments in one or more of these neurotransmitter systems. As such, it may not be reasonable to expect that administration of a drug over a matter of weeks or months will be sufficient to reverse this damage or to help "rewire" the systems that support many cognitive functions that are impaired in schizophrenia. Instead, it may be that a combination of pharmacological enhancements with systematic and potentially intensive cognitive rehabilitation or training may be necessary to engender more robust and potentially longer-lasting change. Obviously, this may not be true for all molecules or for all cognitive functions. However, it is not unreasonable to expect that truly clinically significant cognitive change may require more than just either pharmacological enhancement or cognitive

rehabilitation alone, but rather a combination of approaches that use the scaffolding provided by regulation of impaired neurotransmitter systems to engender plasticity and learning in a way that leads to more profound cognitive change among individuals with schizophrenia. This is of course an empirical question, and such studies are clearly time consuming and costly. However, such efforts will be well worth the cost should they reveal new avenues for robust, clinically significant and long-lasting cognitive change in schizophrenia, particularly if this translates into enhanced life function for individuals with this illness.

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