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The treatment of cognitive impairment in schizophrenia

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1. Introduction

1.1 Cognitive Deficits in Schizophrenia

The field of psychopathology research has increasingly come to recognize the importance of cognitive deficits in understanding etiology, course and outcome in schizophrenia (Green et al., 2000; Keefe, 2008), one of the most debilitating of psychiatric disorders. The range of cognitive impairments in individuals with schizophrenia is broad, with the more robust and replicable deficits typically found in the domains of processing speed, episodic memory, working memory, and executive function. Impairments in these domains are associated with alterations in the neural systems known to support these cognitive functions, including impairments in the function of the medial temporal lobes (Heckers, 2001; Reichenberg and Harvey, 2007), the prefrontal cortex (Minzenberg et al., 2009), and a range of neurotransmitter systems known to be important for intact cognitive function. These cognitive impairments are typically present prior to the onset of the illness (Cornblatt et al., 1999; Niendam et al., 2003), and there is even some data to suggest that the degree of impairment in certain aspects of cognition predicts the subsequent onset of schizophrenia (Cornblatt et al., 1999; Sorensen et al., 2006). Importantly, individuals who share unexpressed genetic components of vulnerability to schizophrenia also experience impairments in cognitive function, including first degree relatives (Delawalla et al., 2006; Snitz et al., 2006) and individuals with schizotypal personality disorder (Barch et al., 2004; Dickey et al., 2005; Voglmaier et al., 2000). 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). These cognitive deficits persist throughout the course of the illness in individuals with schizophrenia (Heaton et al., 2001; Irani et al., 2010), and may be important in constraining functional outcome and quality of life (Gold et al., 2002; Green et al., 2004). Thus, it is a high priority to identify the biological underpinnings of cognitive deficits in schizophrenia and to develop effective treatments.

1.2 Trial Design for Agents to Treat Cognitive Deficits in Schizophrenia

In 2003, experts from academia, industry, and the FDA were brought together by the NIMH-funded “Measurement and Treatment Research to Improve Cognition in Schizophrenia” (MATRICS) project to develop guidelines for clinical trials of cognitive enhancing drugs for schizophrenia (Buchanan et al., 2005). One of several accomplishments by this group was

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the creation of the MATRICS consensus cognitive battery (MCCB), which tests seven domains of cognition intended to represent functionally-significant areas of impairment in schizophrenia that may be amenable to pharmacologic treatment (Nuechterlein and Green, 2006); the MCCB has become the standard assessment tool for clinical trials. Although cognitive tests were selected to minimize practice effects, experience with the MCCB indicates that small practice effects may complicate the interpretation of results and so a placebo control is necessary in clinical trials (Buchanan et al., 2010b). However, this issue of practice effects is not unique to the MCCB and will be an issue with almost any cognitive battery. In addition, because no agent has established efficacy for cognition in schizophrenia, an active control condition is not available to provide a measure of assay sensitivity (i.e., the ability of the trial to differentiate active drug from placebo). As a result, negative trials of cognitive enhancing agents can't be differentiated reliably from failed trials, in which an effective agent would also fail to separate from placebo.

Several other issues were raised during the MATRICS discussion of clinical trial design, including a concern on the part of the Food and Drug Administration (FDA) about “pseudospecificity”, or the possibility that cognitive function might be improved indirectly by a drug that primarily improves psychosis, agitation, apathy, Parkinsonism or mood. Precautions to avoid secondary causes of cognitive impairment in participants were recommended, such as restricting study samples to patients who are stable, without significant psychosis, depression, Parkinsonism, negative symptoms or use of drugs that impair cognition, such as anticholinergics and benzodiazepines. It remains unclear whether common neurobiologic mechanisms may underlie both cognitive deficits and negative symptoms of schizophrenia, and so the wisdom of excluding patients with negative symptoms is debated (Buchanan et al., 2010b). The consensus view of experts at the MATRICS meeting was that most patients with schizophrenia have experienced some decrement in cognitive functioning associated with the illness; hence the only restrictions regarding cognitive functioning in subject selection are that participants are not at the “ceiling” level for a test nor too impaired to provide valid results. Because the second generation antipsychotics bind to a wide range of receptors, potential pharmacodynamic interactions may complicate add-on trials of cognitive enhancing agents. Drugs known to possess the potential for pharmacodynamic or pharmacokinetic interactions with the experimental agent may be best excluded at early stages of clinical development prior to embarking on an “all-comers” approach to enrollment.

A common problem with trials of cognitive enhancing agents has been the analysis in small subject samples of more than one cognitive test score without correction for multiple comparisons, thus increasing the likelihood of false positive results. As such, it is recommended that investigators use a single composite cognitive score or, if *a priori* evidence supports it, a single domain score, as the primary outcome measure. If the composite cognitive score significantly improves with treatment compared to placebo, additional sub-analyses of cognitive domains can be performed as exploratory analyses. The FDA also requested a co-primary outcome measure of function, such as the UCSD Performance Based Skills Assessment (UPSA) (Patterson et al., 2001). According to the FDA position expressed at the MATRICS meetings, both co-primary outcome measures (cognitive score and functional outcome) must be significantly improved compared to placebo in order for the trial to be considered a positive demonstration of drug efficacy.

2. Pharmacologic Targets for Cognitive Enhancement in Schizophrenia

Many different drug targets and strategies for drug development have been employed for enhancement of cognition in schizophrenia; the relative lack of success to-date indicates the difficulty that this therapeutic area poses. Receptor targets have been identified on the basis

of pharmacologic challenges that mimic schizophrenia (e.g., dopamine agonists and NMDA receptor antagonists), receptor abnormalities found on postmortem analysis of schizophrenia brain, and genetic linkage studies. Other approaches have emphasized the use of drugs that enhance learning or memory in animal models, or that are effective in other disorders of cognitive dysfunction, without a specific link to schizophrenia. More recently, investigators have focused on putative neuroprotective agents and drugs that may enhance neuroplasticity or neurogenesis.

It is possible that heterogeneity of mechanisms responsible for cognitive deficits in schizophrenia may in part be responsible for the lack of success of any single approach and that matching of treatments to appropriate subgroups of patients may be necessary to establish efficacy. Subgroups could be broadly based on theoretical etiologies of cognitive deficit (neurodevelopmental, biochemical or neurodegenerative), or on genetic markers, and treatment could entail strategies of prevention for neurodevelopmental processes, genetically-defined pharmacological augmentation or supplementation for biochemical deficits, and neuroprotective approaches for neurodegenerative processes (Goff, 2005). Recent promising results with cognitive remediation have raised the possibility that promotion of neuroplasticity could be an effective approach for a wider range of etiologies.

2.1 Dopamine

Dopamine neurotransmission has long been central to models of schizophrenia and its treatment (Davis et al., 1991). Dopamine agonists produce psychosis indistinguishable from schizophrenia in healthy individuals, although cognitive impairment is not prominent. The revised model of dopamine dysregulation posits excessive activity in mesolimbic pathways producing psychosis and diminished activity in prefrontal cortex producing cognitive deficits and negative symptoms (Davis et al., 1991). Dopamine release in the striatum in response to amphetamine is increased in medication-naive schizophrenia subjects compared to healthy controls and correlates with psychotic symptoms in chronic patients (Laruelle and Abi-Dargham, 1999). Cognitive deficits of schizophrenia, including attention and memory, are predicted by COMT genotype, believed to reflect dopamine metabolism in forebrain (Egan et al., 2001). All currently-approved antipsychotic agents block D_2 receptors and may improve cognitive function, although whether this represents a direct effect rather than a secondary effect resulting from improvement of psychotic disorganization, is difficult to establish. Of note, chronic antipsychotic treatment may also adversely affect cognition. Castner and colleagues (Castner et al., 2000) demonstrated progressive cognitive impairment in monkeys exposed to haloperidol over a six month period; in addition, histopathological evidence of neuropathology characteristic of schizophrenia was found after healthy monkeys were exposed to haloperidol or olanzapine for approximately two years (Dorph-Petersen et al., 2005; Konopaske et al., 2007). However, it is also possible that antipsychotics have a different effect in populations with an underlying impairment, and thus findings of haloperidol induced cognitive impairment in healthy animals may not generalize to schizophrenia. Based on early uncontrolled trials, an expectation was widely held that cognition would improve with second generation antipsychotics compared to first generation. However, the CATIE trial failed to find any advantage of second generation agents compared to the representative first generation agent, perphenazine (Keefe et al., 2007). Nonetheless, uncertainty regarding chronic antipsychotic effects upon cognition complicates interpretation of add-on strategies for cognitive enhancement.

2.1.1 Psychostimulants—Psychostimulants act by increasing release of dopamine and norepinephrine and are a well-established treatment for attentional disorders. Mattay and colleagues (Mattay et al., 2000) found that D-amphetamine improved working memory in healthy subjects who performed poorly at baseline, whereas working memory worsened in

subjects with superior working memory performance. In a subsequent study, COMT genotype predicted enhanced prefrontal activation in response to D-amphetamine as assessed by fMRI during a working memory task in healthy subjects (Mattay et al., 2003). Similarly, COMT genotype predicted improvement of executive functioning and verbal episodic memory in healthy subjects in response to the COMT inhibitor, tolcapone (Apud et al., 2007).

Due to concerns about exacerbating psychosis, psychostimulants have not been widely used in schizophrenia, although controlled studies have provided some evidence of cognitive improvement without symptomatic worsening when D-amphetamine is added to antipsychotics in single-dose trials. In schizophrenia patients treated with haloperidol, D-amphetamine was found to enhance prefrontal cortical activation during performance of the Wisconsin Word Sort Test and to improve processing speed, whereas performance on memory and attentional tasks did not improve significantly (Daniel et al., 1991; Goldberg et al., 1991). Barch and Carter (Barch and Carter, 2005) found that, compared to placebo, D-amphetamine improved reaction times on spatial memory and Stroop tests, working memory accuracy, and language production when added to first generation antipsychotics; healthy subjects displayed a similar pattern of cognitive improvement except working memory accuracy did not change. Pietrzak and colleagues (Pietrzak et al., 2010) reported improvement in executive function, attention, and speed of processing with D-amphetamine compared to placebo in chronic schizophrenia patients.

2.1.2 D_1 Agonists—D_1 activation in prefrontal cortex has been linked to working memory in an inverted U-shaped relationship, such that both low and excessively high levels of D_1 activation are associated with impaired memory (Goldberg et al., 1991). D_1 sensitivity has been shown in monkeys to decrease with age and with chronic antipsychotic administration in concert with diminished working memory (Goldman-Rakic et al., 2004). Intermittent treatment with a D_1 agonist was shown to “sensitize” D_1 receptors and improve memory in both aged (Castner and Goldman-Rakic, 2004) and antipsychotic-treated (Castner et al., 2000) monkeys. Clinical trials of D_1 agonists in schizophrenia have been delayed due to poor tolerability related to orthostatic hypotension and nausea. However, a single low dose of the short-acting, selective D_1 agonist, dihydrexidine, recently was adequately tolerated in schizophrenia subjects and acutely increased both prefrontal and non-prefrontal cortical perfusion (Mu et al., 2007). Cognitive testing performed five hours after subcutaneous injection of dihydrexidine showed no effect, but due to its 30 minute half-life, blood levels of dihydrexidine were essentially undetectable at the time of cognitive testing (George et al., 2007).

2.1.3 Conclusion—Consistent with effects in healthy subjects and individuals with attention deficit disorder, amphetamine may produce some improvement of concentration, memory and processing speed and co-administration with antipsychotics appears to protect against psychotic exacerbation by the psychostimulant, although long-term effects with repeated dosing remain uncertain. Agents that inhibit COMT are promising, particularly when subjects are selected by COMT genotype, although concerns about hepatotoxicity make tolcapone, the only currently-approved COMT inhibitor, problematic. If tolerability issues can be surmounted, D_1 selective agonists appear quite promising, perhaps following an intermittent schedule of dosing as developed by Castner and colleagues (Castner and Goldman-Rakic, 2004) to optimally “sensitize” prefrontal D_1 receptors.

2.2 Glutamate

Over the past decade, models of glutamatergic dysregulation have gained prominence for drug development in schizophrenia (Goff and Coyle, 2001; Javitt, 2004). This approach

followed from observations that the NMDA channel blockers, ketamine and phencyclidine, produce psychotic and negative symptoms and cognitive deficits suggestive of schizophrenia in healthy subjects, and symptom exacerbation in stable schizophrenia patients. Chronic phencyclidine abuse is associated with a persistent psychotic syndrome and cognitive deficits often indistinguishable from schizophrenia (Javitt and Zukin, 1991; Jentsch and Roth, 1999). This model compliments the dopamine model, since ketamine replicates in healthy subjects the excess striatal dopamine release in response to amphetamine observed in schizophrenia (Kegeles et al., 2000). The glutamate dysregulation model increasingly has focused on NMDA receptors located on GABAergic inhibitory interneurons (Lisman et al., 2008); disruption of inhibitory input is expected to produce excessive glutamate release, aberrant spread of excitatory transmission, and loss of neuronal network synchronization necessary for working memory and other cognitive functions (e.g. gamma oscillations). The administration of ketamine in rodents is now widely used to screen for cognitive enhancing agents; while this approach has identified some agents with possible benefit for negative symptoms, translation into clinically-effective agents for cognition has largely been unsuccessful, raising questions about the predictive validity of this model.

2.2.1 Glycine site agonists—Because excessive activation of the NMDA receptor can produce neurotoxicity, early treatment studies focused on the glycine modulatory site of the NMDA receptor. The glycine-site agonists, glycine, D-serine, and D-alanine, produced improvement in negative symptoms in small trials and some improvement in measures of cognition, although formal cognitive testing was not performed (Tuominen et al., 2005). D-cycloserine, which, depending on the subunit composition of NMDA receptors, is either a partial or full-agonist (Dravid et al., 2010), demonstrated inconsistent improvement of negative symptoms and no improvement in two studies that utilized formal cognitive testing (Goff et al., 1999; Goff et al., 2005). In the large CONSIST study, neither glycine nor D-cycloserine improved negative symptoms or cognition (Buchanan et al., 2007).

Recently, Kantrowitz and colleagues (Kantrowitz et al., 2010) conducted 4-week open-label add-on trials of D-serine 30 mg/d, 60 mg/d and 120 mg/d to establish safety and tolerability with escalating doses. Significant cognitive improvements of large effect size were noted at high doses (60 mg/d and 120 mg/d) but not at the low dose (30 mg/d); cognitive improvement correlated with plasma D-serine levels and was associated with reductions in psychosis and negative symptoms.

It has been well-established that single dose administration of D-cycloserine improves consolidation of memory in animal models, and that once-weekly dosing improves response to cognitive behavioral therapy in patients with anxiety disorders (Davis et al., 2006). However, repeated daily dosing results in rapid tolerance for cognitive effects (best studied with fear extinction) (Parnas et al., 2005), believed to reflect trafficking of NMDA receptors from the cell membrane to the intracellular compartment (Nong et al., 2003). In a recent study, a single dose of D-cycloserine improved memory consolidation (7-day delayed recall) on the Logical Memory Test of the revised Wechsler Memory Scale and once-weekly dosing produced persistent improvement of negative symptoms in patients with schizophrenia (Goff et al., 2008a). Another strategy to avoid tachyphylaxis with NMDA receptor activation is to target intracellular pathways downstream of NMDA receptors. In one unsuccessful example, the PDE 5 inhibitor, sildenafil, did not improve cognition in a placebo-controlled single-dose crossover trial (Goff et al., 2009). Several other agents targeting intracellular second messengers, including inhibitors of PDE 2, 4, 9 and 10, are in development as potential cognitive enhancers (Reneerkens et al., 2009).

2.2.2 Glycine reuptake inhibitors and AMPA modulators—Other approaches to enhance NMDA channel opening via the glycine recognition site include glycine reuptake

blockers (Javitt, 2009) and the reduction in levels of the endogenous glycine site antagonist, kynurenic acid, by enzymatic inhibitors (Potter et al., 2010). Several studies with the weak endogenous glycine reuptake inhibitor, sarcosine, demonstrated efficacy for negative symptoms, but formal cognitive testing results have not been reported (Lane et al., 2009; Tsai et al., 2004). Selective glycine reuptake inhibitors (GlyT1) are currently under development with preliminary results suggestive of benefit for negative symptoms but not cognition. Positive modulators of the glutamatergic AMPA receptor enhance NMDA channel opening and long term potentiation (LTP) by initiating rapid cellular depolarization (Black, 2005). In animal models, single and intermittent dosing with AMPA positive modulators, produced improvement in learning and memory (Hampson et al., 1998; Staubli et al., 1994), as did a pilot trial of daily dosing with the short-acting, relatively low-potency ampakine, CX516, in clozapine-treated schizophrenia patients (Goff et al., 2001). However, a large four-week add-on trial with daily dosing of CX516 failed to demonstrate cognitive or symptomatic benefit (Goff et al., 2008b).

2.2.3 Lamotrigine and metabotropic glutamate receptor agonists—Therapeutic strategies have also focused on the reduction of excessive postsynaptic glutamate release hypothesized to result from dysfunction of NMDA receptors on inhibitory interneurons. Lamotrigine, which reduces glutamate release, attenuated ketamine effects on cognition in healthy subjects (Anand et al., 2000) and one of two large trials found significant improvement on the composite cognitive score with lamotrigine up to 400 mg daily compared to placebo (Goff et al., 2007). Similarly, the metabotropic mGlu2/3 agonist, LY354754, which also reduces glutamate release (Moghaddam and Adams, 1998), attenuated working memory deficits produced by ketamine in healthy subjects (Krystal et al., 2005). However, studies of mGluR2/3 agonists have not produced consistent evidence of cognitive benefit in animal models (Schlumberger et al., 2009). The mGluR2/3 agonist prodrug, LY2140023, administered as monotherapy, significantly improved positive and negative symptoms in schizophrenia patients in one of two trials, but cognitive effects were not reported (Patil et al., 2007). A more recent class of glutamatergic agents, mGluR5 allosteric modulators, have demonstrated dose-dependent improvement of recognition memory in rats (Uslaner et al., 2009) but results of human trials are not yet available.

2.2.4 Conclusion—Glutamatergic dysregulation is a compelling model for schizophrenia, with converging evidence from genetics, postmortem histopathology and pharmacologic provocation of symptoms. However, clinical trials of agents representing a wide range of glutamate-related strategies have provided very little evidence of cognitive enhancement. The recent findings with open-label high-dose D-serine are quite promising and require replication in controlled trials. The best evidence to-date comes from a multicenter trial of lamotrigine, although a second trial failed to replicate this finding. Single-dose administration of D-cycloserine has strong support from the animal literature and has shown promise in one small study, whereas strategies that produce persistent elevation of glycine site occupancy have improved negative symptoms response without strong evidence of cognitive enhancement. Several additional approaches await clinical trials, including mGlurR5 agonists and inhibitors of kynurenic acid biosynthesis.

2.3 GABA

Postmortem findings in schizophrenia brain of reduced GABA synthesis by inhibitory interneurons, as evidenced by decreased glutamtamic acid decarboxylase (GAD_{67}), and by a compensatory increase in postsynaptic density of $GABA_A$ receptors containing the α_2 subunit, have led to the development of selective $GABA_A$ receptor agonists as a strategy to improve working memory (Lewis et al., 2004). The rationale is complicated, however, by the recent finding that the nonselective $GABA_A$ antagonist (inverse agonist), flumazenil,

improved working memory in healthy subjects and schizophrenia patients, whereas lorazepam, which is a nonselective $GABA_A$ agonist, markedly impaired working memory (Menzies et al., 2007). The adverse cognitive effects of benzodiazepines may reflect sedation mediated by $GABA_A$ receptors containing α_1 and α_5 subunits.

2.3.1 $GABA_A$ Agonists—In a four-week placebo-controlled add-on pilot trial in 15 schizophrenia patients, Lewis and colleagues (Lewis et al., 2008) administered MK-0777, which is a selective partial agonist at $GABA_A$ receptors containing α_2 and α_3 subunits. Results are difficult to interpret, since the two groups were not well-matched at baseline due to the small sample size, and the pre-specified primary outcome measure (total score on the Repeated Battery for the Assessment of Neuropsychological Status) was negative. However, large effect sizes suggestive of benefit for attention and working memory on the AX Continuous Performance Task (CPT) and N-Back Task were noted. In addition, EEG results were suggestive of increased gamma band power in the frontal area. However, a recent placebo-controlled add-on trial of MK-0777 in 60 schizophrenia patients failed to find any cognitive benefit, including negative findings on the CPT and N-Back tasks (Buchanan et al., 2010a).

2.3.2 Conclusion—The evidence linking $GABA_A$ receptor activation and working memory impairment in schizophrenia remain intriguing and worthy of future therapeutic development of higher potency $GABA_A$ α2 agonists. Because MK-0777 is a partial agonist with only 10%–20% of full agonist activity, it may not represent an adequate test of this hypothesis. However, results with benzodiazepine receptor agonists and antagonists suggest that an exclusive focus on $GABA_A$ agonists, rather than antagonists, may be premature.

2.4. Serotonin

2.4.1 Agents acting at $5HT1_A$, $5HT_{2A}$ & $5HT_6$ receptors—There are multiple classes of serotonin (5HT) receptors in the brain and several have been targeted by cognitive enhancing drugs (Terry et al., 2008). $5HT_6$ receptors have received the most attention, based in part on their exclusive location in hippocampus and cortex and because $5HT_6$ antagonists release acetylcholine and glutamate, which could enhance memory and attention (Johnson et al., 2008). Studies of the $5HT_6$ antagonist, SB 743457, in animals have been promising, as were early studies in Alzheimer's disease (Upton et al., 2008). Other investigators have studied $5HT1_A$ partial agonists in schizophrenia: in a pilot trial, tandospirone produced improvements in memory, verbal learning, and executive functioning (Sumiyoshi et al., 2001), whereas a placebo-controlled trial of buspirone in 73 schizophrenia patients that employed a cognitive battery of eight tests assessed at three time points found improvement in only one test of attention at three months only (Sumiyoshi et al., 2007). $5HT1_A$ antagonists have also demonstrated cognitive enhancement in animal models and are in development for schizophrenia (Schechter et al., 2002). In a placebo-controlled trial in 30 schizophrenia patients, the $5HT_{2A}$ (and alpha2 adrenergic) antagonist, mianserine, added to first generation antipsychotics significantly improved memory (Poyurovsky et al., 2003). However, since second generation antipsychotics are $5HT_{2A}$ antagonists with high occupancy at therapeutic doses, this mechanism would not be expected to enhance cognitive effects of these drugs.

2.4.2 Conclusions—Serotonergic receptors have been identified as promising targets for cognition (Roth et al., 2004) but to-date, none has demonstrated compelling evidence for efficacy in schizophrenia. Trials with 5HT6 antagonists are awaited, given early promise in animal models and in Alzheimer's disease.

2.5 Acetylcholine

Studies in animals and humans have demonstrated an essential role for acetylcholine, acting at muscarinic and nicotinic receptors, in the regulation of attention, memory, and sensory processing (Furey et al., 2000; Gold, 2004; Hasselmo and Bower, 1993; Vitiello et al., 1997). Unlike Alzheimer's disease, in which cholinergic dysregulation is associated with degeneration of cholinergic neurons, cholinergic dysregulation in schizophrenia is thought to result from alterations in muscarinic and nicotinic receptor expression and function (Breese et al., 2000; Crook et al., 2001; Dean et al., 2002; el-Mallakh et al., 1991; Freedman et al., 1995). Whereas activity of choline acetyl transferase (ChAT), a marker for cholinergic activity, is normal in schizophrenia brain, levels of ChAT correlate with cognitive performance, suggesting that, in the compromised schizophrenia brain, increasing cholinergic transmission may improve cognition (Powchik et al., 1998). The study of cholinergic transmission and of drugs acting via cholinergic mechanisms is complicated by high rates of cigarettes smoking and by treatment with anticholinergic agents in schizophrenia patients (Goff et al., 1992; Minzenberg et al., 2004). In addition, several second generation antipsychotic drugs enhance release of acetylcholine in prefrontal cortex (Ichikawa et al., 2002).

2.5.1 Nicotinic acetylcholine receptors—Expression of low-affinity α_7 and high-affinity α_4 β_2 nicotinic acetylcholine receptors is prominent in areas of the brain associated with cognitive deficits in schizophrenia, including hippocampus, cortex, striatum and thalamus, and is reduced in hippocampi of patients with schizophrenia compared to controls (Breese et al., 2000; Freedman et al., 1995). The reduced binding density of high-affinity α_4 β_2 nicotinic receptors in hippocampi of schizophrenia patients is impressive given that exposure to nicotine and haloperidol increased α_4 β_2 nicotinic receptor density in rats (Breese et al., 2000). The α_7 neuronal nicotinic acetylcholine subunit gene (CHRNA7) has been implicated as a candidate risk gene in schizophrenia based on linkage at 15q14; moreover, the prevalence of CHRNA7 functional promoter variants is increased in schizophrenia subjects and a functional promoter polymorphism in CHRNA7 was associated with an auditory sensory processing deficit in healthy subjects (Leonard et al., 2002).

2.5.1.1 Nicotine: Nicotine enhances many aspects of cognition in both healthy subjects and people with schizophrenia, although tachyphylaxis may develop with repeated administration. In a placebo-controlled single-dose crossover trial of transdermal nicotine in 60 nonsmoking schizophrenia patients and controls, nicotine significantly improved attentional performance in both groups and inhibited impulsive responses to a greater degree in schizophrenia subjects than in controls (Barr et al., 2008). Transdermal nicotine administration also improved novelty detection in schizophrenia nonsmokers (Jubelt et al., 2008) and improved delayed recognition memory in schizophrenia smokers (Myers et al., 2004). In a test that maximally taxed working memory, nicotine improved performance in schizophrenia smokers and worsened performance in healthy controls; greater activation of a regional network and greater modulation of thalamocortical functional connectivity by nicotine were also observed in schizophrenia patients compared to controls (Jacobsen et al., 2004).

2.5.1.2 DMXB-A: Considerable industry investment has been directed at the development of agents acting at α_7 or α_4 β_2 nicotine receptors, generally either as partial agonists or positive allosteric modulators in order to minimize the likelihood of tachyphylaxis. A placebo-controlled cross-over add-on pilot study in 12 schizophrenia nonsmokers of two doses of the α_7 partial agonist, DMXB-A, each administered as a loading dose and a second maintenance dose during a single day of cognitive assessments, found significant improvement in the composite cognitive score with the lower DMXB-A dose (Olincy et al.,

2006). Inhibition of the P50 auditory evoked potential was also significantly improved. In a follow-up placebo-controlled crossover add-on trial of the same two doses of DMXB-A, the duration of exposure to DMXB-A was increased to 4 weeks in a sample of 31 schizophrenia patients (Freedman et al., 2008). Neither dose improved cognition compared to placebo, whereas the higher dose improved negative symptoms. Another α_7 agonist, trepisetron, has also produced promising results in single dose trials, including normalization of the P50 auditory evoked potential (Koike et al., 2005), but cognitive effects of trepisetron in an 8-week placebo-controlled trial in 40 schizophrenia patients did not significantly differ from placebo (Shiina et al., 2010).

2.5.2 Muscarinic Agonists—Several lines of evidence have implicated muscarinic receptors in cognitive dysfunction in schizophrenia (Friedman, 2004). Muscarinic receptor density is reduced in many brain regions of medication-free schizophrenia patients compared to healthy controls (Raedler et al., 2003); of the five subtypes of muscarinic receptor, evidence is strongest for a reduction in M_1 receptors which are known to play a role in memory (Friedman, 2004). Drug development has focused on selective M_1 agonists, thereby avoiding unwanted side effects resulting from the activation of M_2 and M_3 receptors in the gut, heart, genitourinary tract and exocrine glands which may complicate therapy with cholinesterase inhibitors. In a placebo-controlled four-week add-on pilot study in 20 schizophrenia patients, the M_1/M_4 agonist, xanomeline, significantly improved measures of working memory and delayed memory compared to placebo, although this finding must be considered preliminary since it was not corrected for multiple comparisons (Shekhar et al., 2008). Other M_1 agonists are currently in development, including N-desmethylclozapine, although recent evidence suggests it may be an antagonist rather than a partial agonist at human cortical M_1 receptors (Thomas et al., 2010).

2.5.3 Cholinesterase Inhibitors

2.5.3.1 Rivastigmine & donapezil: Activation of muscarinic and nicotinic acetylcholine receptors is enhanced by cholinesterase inhibitors. Whereas cholinesterase inhibitors have demonstrated modest benefit in Alzheimer's disease, the evidence for cognitive benefit in schizophrenia has been less compelling. Several open-label add-on trials of rivastigmine and donapezil reported improvements in cognitive performance, whereas a series of small placebo-controlled trials failed to demonstrate benefit (Fagerlund et al., 2007; Freudenreich et al., 2005; Friedman et al., 2002; Tugal et al., 2004). In a large add-on trial reported by Keefe and colleagues (Keefe et al., 2008), 245 schizophrenia patients were randomly assigned to donepezil titrated up to 10 mg/d or placebo for twelve weeks. Donepezil did not improve performance on any cognitive test compared to placebo and was associated with worsening of negative symptoms. In the observed case analysis, placebo was associated with a greater improvement on the cognitive composite score compared to donepezil (effect size 0.45 vs. 0.26, p=0.04).

2.5.3.2 Galantamine: Galantamine is a nonselective cholinesterase inhibitor at higher doses and a relatively selective positive allosteric modulator at nicotinic α_4 β_2 and α_7 receptors at lower doses. Evidence of cognitive benefit with galantamine has been mixed. One of two small controlled add-on trials reported evidence suggestive of benefit for memory and attention in schizophrenia (Lee et al., 2007; Schubert et al., 2006) . Buchanan and colleagues (Buchanan et al., 2008) randomly assigned 86 schizophrenia patients to a 12 week placebo-controlled trial of galantamine titrated up to a dose of 24 mg/d. Galantamine did not improve the cognitive composite score compared to placebo, but did improve digit symbol score (a test of attention and processing speed) and the California Verbal Learning Test (verbal memory) while worsening performance on the GDS Distractibility Test. In contrast, the manufacturer, Johnson and Johnson, conducted an 8 week placebo-controlled add-on trial in

100 schizophrenia patients randomized to an extended release formulation of galantamine at doses of 16 mg/d and 24 mg/d and did not find benefit on the Brief Assessment of Cognition in Schizophrenia (BACS) battery or on additional measures of attention and processing speed (Clinicaltrials.gov NCT00077727). In addition, a small placebo-controlled trial in which galantamine was administered at a higher dose of 32 mg/d reported cognitive worsening (Dyer et al., 2008).

2.5.4 Conclusion—The evidence is strong that both muscarinic and nicotinic acetylcholine receptors may play a role in cognitive impairment in schizophrenia and remain promising targets, particularly for attention and memory. To-date, the M_1/M_4 agonist, xanomeline, has demonstrated the most impressive cognitive benefit with repeated dosing. Tachyphylaxis with nicotine receptor agonists and the high prevalence of cigarette smoking in schizophrenia patients complicate therapies targeting nicotine receptors, although positive allosteric modulators may circumvent these problems.

2.6 Miscellaneous

2.6.1 Modafinil—Modafinil is a wakefulness-promoting agent with an uncertain mechanism of action. It has been reported to increase activity of catecholamines, glutamate, serotonin, GABA, orexin and histamine, and to enhance cognitive functioning in several models (Minzenberg and Carter, 2008). Turner and colleagues (Turner et al., 2004) found improvements in short-term verbal memory and attentional set-shifting in a placebo-controlled single-dose cross-over trial of modafinil 100 mg in 20 schizophrenia patients. Three groups have found changes in brain activation patterns following a single dose of modafinil in placebo-controlled studies in the absence of improvement in cognitive performance (Hunter et al., 2006; Minzenberg et al., 2008; Spence et al., 2005). However, despite encouraging results from single-dose studies, several small clinical trials have failed to find cognitive benefit with modafinil. Placebo-controlled, eight-week add-on trials of modafinil up to 200 mg/d in samples of 20 and 24 schizophrenia patients failed to find benefit for cognition despite a reduction in fatigue or sedation (Pierre et al., 2007; Sevy et al., 2005), as did a placebo-controlled eight-week trial of modafinil up to 300 mg/d in 35 clozapine treated patients (Freudenreich et al., 2009). In addition, a four-week trial in which 60 schizophrenia patients were randomly assigned to placebo or to three doses of armodafinil (the active metabolite of modafinil) also did not find cognitive enhancement but negative symptoms were improved(Kane et al., 2010).

2.6.2 Pregnenolone—Pregnenolone, an endogenous neurosteroid, is reported to modulate $GABA_A$ and NMDA receptors, as well as hippocampal dopamine. It is also involved in neurodevelopment and may have neuroprotective properties. In an eight-week placebo controlled add-on trial comparing two doses of pregnenlone and DHEA in 58 schizophrenia patients, low dose (30 mg/d) pregnenolone improved measures of attention (Matching to Sample Visual Search) and memory (Delayed Match to Sample) as well as psychotic symptoms, compared to placebo, whereas pregnenolone 200 mg/d had no effect (Ritsner et al., 2010). Because effects of three treatment groups on five cognitive outcomes were analyzed without correction for multiple comparisons, these positive findings need be interpreted with caution. In addition, an 8-week placebo controlled add-on pilot trial of pregnenolone 500 mg/d in 18 patients with schizophrenia (9 in each treatment group) improved negative symptoms (Marx et al., 2009). Pregnenolone and placebo did not differ in effects on the MCCB composite score (mean T score change of 7.0 for both) whereas the investigators noted both an inverse correlation between cognitive function and baseline pregnenolone blood concentrations and a positive correlation between change in pregnenolone concentrations and improvement in cognition.

2.7 Neuroprotection, Neuroplasticity and Cognitive Remediation

The relative lack of success with a wide range of candidate therapeutic agents has led to the view that cognitive deficits may not result from dysregulation of a single neurotransmitter or class of receptors, but rather may reflect a more fundamental abnormality of "wiring" resulting from abnormal neurodevelopment or from a neurodegenerative process. In keeping with this model, potential therapeutic agents include neuroprotective agents, including neurosteroids (e.g., pregnenolone (Ritsner et al., 2010; Wojtal et al., 2006)), anti-oxidants (e.g., N-acetyl cysteine (Berk et al., 2008)), omega 3 fatty acids (Palacios-Pelaez et al., 2010), anti-inflammatory agents (e.g., aspirin & celecoxib (Laan et al., 2010; Muller et al., 2010)), agents such as memantidine (Lieberman et al., 2009) and lamotrigine (Goff et al., 2007) that protect against excitotoxicity, and neurotrophic factors and agents involved in neurogenesis (e.g. erythropoietin (Wustenberg et al., 2010) and davuletide (Javitt, 2010)). Neuroprotective agents would be expected to require an extended duration of treatment to prevent, halt, or reverse neurotoxicity. None has convincingly demonstrated cognitive benefits, although in a recent pilot study, omega 3 fatty acids appeared to prevent high-risk individuals from progressing to schizophrenia when administered for only 12 weeks (Amminger et al., 2010).

2.7.1 Cognitive remediation—Perhaps the best-supported therapeutic approach based on a neurodevelopmental model for cognitive deficits in schizophrenia is cognitive remediation. Although the mechanism remains speculative, cognitive remediation has demonstrated cognitive benefits in most studies as demonstrated by a meta-analysis(McGurk et al., 2007), although at least one well-designed study found that cognitive improvement failed to generalize beyond practice effects on tests administered as part of the cognitive exercises (Dickinson et al., 2010). One approach to cognitive remediation, based on principles of neuroplasticity, targets auditory discrimination; in a randomized study in 55 schizophrenia subjects 50 hours of this method of cognitive remediation produced broad improvement on most domains of the MCCB and significantly elevated peripheral blood levels of the neurotrophin, BDNF, compared to an active control condition (Adcock et al., 2009; Fisher et al., 2009; Vinogradov et al., 2009). Similarly, a two-year intervention combining cognitive remediation and social skills training early in the course of schizophrenia improved cognitive performance as measured by a composite cognitive score (Eack et al., 2009); cognitive enhancement was associated with gray matter preservation in several brain regions as well as an increase in gray matter volume in the left amygdala (Eack et al., 2010). However, it remains unclear what form of repetitive challenge is required to stimulate neuroplasticity; for example, daily aerobic exercise for a period of three months was also associated with increased hippocampal volume and improved short-term memory in both schizophrenia patients and healthy subjects compared to a sedentary control group (Pajonk et al., 2010).

2.7.2 Conclusion—Although the evidence supporting cognitive remediation has not yet achieved the level necessary to merit inclusion in evidence-based treatment guidelines (Dixon et al., 2010), this approach, combined with other psychosocial interventions, is promising. Several pharmacologic approaches are currently under study to facilitate neuroplasticity; these pharmacologic approaches might also be combined with cognitive remediation to explore a possible synergist effect on cognition.

2.8 Summary

Despite advances in genetics, imaging, and the post-mortem characterization of neurochemistry, progress in the development of cognitive enhancing agents in schizophrenia has been relatively disappointing. A wide range of pharmacological targets that are well-supported by basic neuroscience have tended to produce promising findings in small pilot

trials only to fail larger replication trials. This pattern could reflect many possible factors, including early publication bias towards positive studies lacking methodological and statistical rigor, whereas failure to replicate could in part result from biological heterogeneity and the many obstacles associated with clinical trials in psychiatry, including high placebo response rates, high attrition, poor adherence, and surreptitious substance abuse. It is also possible that current animal models used in drug discovery do not adequately represent the complex neurodevelopmental abnormalities underlying cognitive impairment. While several approaches discussed in this review merit further study, the generally disappointing results suggest that novel paradigms for target selection and clinical trial design also deserve consideration, possibly as exemplified by recent work with cognitive remediation and agents that facilitate neuroprotection and neuroplasticity. Pharmacogenetic approaches in turn may improve our ability to detect treatment effects by reducing biological heterogeneity. Because cognitive impairment is a major cause of disability in schizophrenia, the search for effective treatments must remain a high priority despite the difficulty of this problem.

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