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Cognitive Enhancement in Schizophrenia: Pharmacological and Cognitive Remediation Approaches

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Overview

Cognitive impairments in schizophrenia are a major contributor to the inability to function adequately in everyday life that is commonly seen in people with schizophrenia. There has been substantial attention paid to cognitive impairments as determinant of these functional deficits and our understanding of the subtleties of the relationships between cognitive impairments and disability has been refined considerably as a result. In this chapter we discuss the measurement of cognition in schizophrenia, its role as a determinant of disability, and treatment efforts to date. This will include both pharmacological and behavioral interventions and critical components of effective treatments that lead to improvements in everyday outcomes. We also comment in detail on how functioning can and should be measured in the office when patients with schizophrenia receiving treatment.

There is no need for another detailed review of the nature of deficits in people with schizophrenia. Such reviews have been done multiple times (1,2) and there have not been substantial new findings for cognitive functioning assessed with clinical neuropsychological tests. The new developments have been in the area of the creation and adoption of a consensus method for the assessment of cognitive functioning in treatment studies and in the increased appreciation for the needs for assessment of functional skills in the prediction of everyday outcomes, as well as new developments in the basic neuroscience of cognition. As these developments are not yet ready for use in treatment studies, we will defer detailed reviews of their findings.

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Cognitive Enhancement as a Therapeutic Target

Almost ten years ago, the senior leadership at the US National Institute of Mental Health, Hyman and Fenton (3) set the stage for the development of consensus cognitive assessments for clinical treatment studies aimed at cognitive enhancement in schizophrenia. This initiative led to the award of a contract for a project entitled Measurement and Treatment Research for Improving cognition in schizophrenia (MATRICS;4). This MATRICS initiative led to consensus meetings, literature reviewers, and the eventual selection of a consensus cognitive assessment battery (i.e., the MATRICS consensus cognitive battery: MCCB;5–7) endorsed by academia and regulatory agencies as the standard performance-based cognitive assessment measure for treatment outcomes studies. This battery is presented in Table 1 and the premises on which this battery is based are presented below.

In the development process of the MCCB, the initial consensus was that cognitive functioning in general was composed on separable cognitive domains and that schizophrenia was marked by the presence of impairments in most of these domains. Thus, the development process was based on the initial selection of important domains of functioning (e.g., verbal memory, processing speed, etc.) and then selection of representative and psychometrically useful exemplars of those domains. It was further designated that unless otherwise specified by the entity conducting the study, the outcome measure would be the composite, which is an un-weighted average of the cognitive domains. Thus, despite the focus on selection of tests from domains, global cognitive functioning is the default treatment target.

Functional Capacity

A concurrent development to the MCCB was the increased interest in the identification of the specific functional skills that underlie everyday functioning. Performance-based assessments have been developed that are targeted at the skills required to engage in community activities, social, and vocational activities (8). While there has been a long-term interest in social competence dating back to behavior therapists in the 1970s, interest in everyday living and vocational skills developed in the 1980s and flowered in the early 2000s. Both comprehensive and abbreviated assessments have been developed that examine performance in areas such as shopping, cooking, traveling, and financial management (9–10). These assessments have been found to be quite strongly related to cognitive performance and may actually be an intermediate step between neurocognition and everyday functioning.

As reviewed by Leifker et al. (11) the correlation between measures of functional capacity aimed at everyday living skills and performance on a variety of neurocognitive measures is quite high ($r>0.60$) and extraordinarily consistent. Several studies published since that review have found the same correlations. Further, three separate large-scale ($n>200$) studies identifying the predictors of real-world functioning as rated by highly knowledgeable informants have found that functional capacity measures are more strongly related to everyday outcomes than performance on neuropsychological tests (Bowie et al., 2008; 2010 Sabbag et al., 2011). These data suggest a model where neurocognitive abilities influence the ability to perform the functional skills which are required to succeed in everyday activities. The real world outcomes have been shown to be influenced by symptoms and opportunities as well as by cognitive and functional abilities. The amount of variance accounted for in activities such as vocational and residential outcomes has been in the vicinity of 40 to 50%, which means that there are substantial influences yet to be identified.

Social Cognition

This concept refers to the cognitively demanding skills that are required for socially relevant activities (12). These include the perception, processing, and interpretation of emotional displays, the ability to infer intentions, and judge facial and nonfacial gestures. While there are some methodological limitations to date in the study of social cognition, these are important abilities. Meta-analyses have shown that social cognition and neurocognition are minimally related to each other (13) and that social cognition is more consistently associated with social outcomes than neurocognition (14). This is consistent with some of our most recent work, where we have found that neurocognition was minimally associated with social outcomes when other factors, such as negative symptoms, were considered (15).

Social cognition is represented in the MCCB, but with only a single test that is aimed at understanding complex social transactions. Research has suggested that this test, the Meyer-Solovey-Caruso Emotional IntelligenceTest (MSCEIT;16), does not correlate particularly highly with other measures on the MCCB, as would be expected on the basis of the Ventura et al. meta-analysis (17). Thus, treatment of social cognition would likely not be assured by successful treatment of cognitive impairments and we will examine the information available on treatment of social cognition separately.

Cognitive Enhancement Research Design

As described below, there are potential interventions for cognition and functional capacity that are delivered through both pharmacological and behavioral methods. As result of the MATRICS process, a consensus research design has been endorsed by the US Food and Drug Administration (FDA). This design would apply to studies of pharmacological cognitive enhancement as well as for software or other computer programs aimed at computerized cognitive remediation. The FDA issues approvals for medications and medical devices for specific uses. Their primary criteria for approval of an “indication” for a drug or device are evidence that the drug or device is “safe” and “effective.” While psychiatric conditions are primarily defined by their symptoms in the DSM, other aspects of these illnesses often do not benefit from treatments approved for primary indications. Clear examples of this disconnect are psychosis and agitation in dementia and cognitive impairments in schizophrenia. The FDA has previously allowed attempts to develop a treatment indication for these features, as long as it could be provided that these other features were not improved by standard, previously approved treatments. Referred to as a concern about “pseudospecificity”, this means that a treatment cannot be approved for the specific treatment of an illness feature already approved for treatment. An example would be an attempt to seek an approval a treatment for “hallucinations in schizophrenia”, when the same treatment is already approved for the treatment of schizophrenia (which includes hallucinations).

Beyond these issues, the FDA has in the past required that treatments aimed at cognitive enhancement to be supported by evidence of clinical benefit beyond improvements in performance-based assessments. These so-called “co-primary” measures in studies of dementia typically have included care-giver assessments of the detectable benefits of cognitive enhancing treatments, collected in double-blind trials (18). While it might be asked whether our society might benefit if similar expectations were imposed for approval of treatments such as collagen, botox, and breast implants, similar standards to AD have been imposed for the approval of cognitive enhancement agents in schizophrenia and the functional capacity measures described above are expected to be commonly employed. Similarly, the FDA has imposed a 6-month duration requirement for the active phase of “acute” treatment trials for cognitive enhancement in schizophrenia, despite the fact that antipsychotics have been approved in 6-week clinical trials and that an atypical

antipsychotic medication (aripiprazole) received approval for treatment resistant depression on the basis of two 3-week double blind trials (19).

As described above the MATRICS initiative had several critical outcomes from this project realized. A consensus research designed was proposed (20) and then revised after 5 years experience (21). So, at this time, there is a path toward approval for cognitive enhancing medications and devices in schizophrenia. Table 2 presents the critical features of this regulatory pathway. Included are patient populations, trial design and duration, and primary and co-primary outcomes measures. There are several critical corollary features of this design. Functional improvements in the real world are not required for approval of a treatment, acknowledging that this seems unlikely in a short term study. No a priori magnitude of improvement is specified, other than significantly greater improvement than placebo in an add-on design. The typical research design aimed at indications for the treatment of cognitive impairments will be an add-on “polypharmacy” approach. This design would result in interpretable results from a clinical trial, in that active treatment added to standing treatment compared to placebo treatment on two separate outcomes measures that would only have to achieve an a prior level of statistical significance of $p<0.05$ each.

Cognitive Remediation

Behavioral treatments for cognitive impairments in schizophrenia have a long history, originating with behavioral modification techniques and borrowing largely from the drill and practice restorative philosophy behind neuropsychological rehabilitation for traumatic brain injury. In recent years the number of published studies has accelerated and reflects not only a refinement in treatment techniques, but an expansion of the outcomes measured. These strategies, variously referred to as cognitive remediation therapy, cognitive enhancement, or cognitive training (among others) have many similarities but have branched out to differ quite substantially with regard to the emphasis on the specific techniques.

Although contemporary approaches differ, a commonality includes the recognition that in order to be viewed as a successful intervention, the treatment related changes in cognition should manifest in improved everyday functioning and/or quality of life. Earlier efforts faced criticism that the treatments were simply `teaching the test' and the burden of proof for real cognitive change would evidence for an underlying change to neurobiological functioning or generalization to everyday behavior change. In the past ten years new treatments provide substantial evidence for neurobiological mechanisms of action as well as improvements in functioning.

The variety of treatment procedures for cognitive remediation underscores the excitement in the field but also reveals its developmental stage as refined but still evolving. Some approaches rely heavily on a therapist involvement to modify strategies and facilitate the bridging of cognitive gains to everyday behaviors exercises (22). Drill and practice exercises have been used with (23) and without (24) computer software to present and modify the complexity of stimuli. Treatment programs that can be quite labor intensive include several non-cognitive and social cognitive aspects (25–26). Improvements in functioning have also been found with compensatory strategies. These techniques place the point of treatment not on modification of the individual's abilities but on the alteration of the environment and/or adaptive technologies with which an individuals cognitive strengths and weaknesses interact (27–28). Most recently, “neuroplasticity based treatment” has recently emerged (this term should not confuse the fact that all the aforementioned treatments presuppose the treatments operate on the malleability of the organism's brain) for schizophrenia (29). The philosophy behind this treatment is that manipulation of early sensory processing is critical to improve

the signal-to-noise ratio in schizophrenia. Until very recently, there were no direct comparison studies on the type, duration, or style of therapy, which has perhaps slowed replication and widespread clinical dissemination of cognitive remediation. The only direct comparison published to date found more robust improvements in neurobiological (M50, a measure of sensory gating) and neurocognitive abilities with early sensory training compared to an older and graphically underwhelming computer software package that was not specifically developed for schizophrenia (30). As the field continues to advance, more studies that examine which strategies work for whom will be a priority.

Evidence for Neurobiological Change with Cognitive Remediation

Although cognitive remediation studies appeared in the literature in the 1960s, it has been only 10 years since Wykes and colleagues (31) first demonstrated changes in brain function for schizophrenia patients who received cognitive remediation. Following forty hours of paper and pencil drill and practice techniques coupled with strategic monitoring, patients had increased activation in the frontal cortex during a verbal working memory task. This important study provided evidence to deflect the early criticisms that cognitive impairments in schizophrenia, which were believed to represent a stable or progressive encephalopathy, were not truly modifiable but simply the artifact of teaching a person how to take a test better.

In a series of recent studies by Vinogradov and colleagues, the neuroplasticity based cognitive remediation strategies that target early auditory processing produced normalization in serum levels of brain-derived neurotrophic factor, which provides an indirect measurement of neuroplasticity (32), and a normalization in electrophysiological markers of auditory stimuli (33). Further evidence for the validity of cognitive remediation to produce neurobiological changes comes from the limited gains that are found as a function of genes associated with degradation of dopamine (34) and anticholinergic medication usage, which inhibits new learning (35). One of the most encouraging findings for long-term prognosis comes from a study by Eack and colleagues (36). This study used a two year social and neurocognitive training program and found that, compared to a placebo group, the treatment effectively staved off structural gray matter loss in brain regions thought to be critical to the neuropathophysiology of schizophrenia. Longer term outcomes for those treated early in the illness will be a critical further step toward evaluating the cost-effectiveness of the intervention.

The biological mechanisms underpinning cognitive remediation have been an important finding and have occurred alongside another fundamentally important series of studies: the transfer of cognitive gains with cognitive remediation to changes in functioning. Early studies were criticized for failing to demonstrate effectiveness that would be indexed by this generalization of gains to everyday functional behavior changes. As mentioned above, concomitant changes in functioning following cognitive improvements might be an unrealistic criterion for many individuals with schizophrenia. This neurodevelopmental disease is associated with cognitive impairments well before the onset of psychosis, often disrupting opportunities for engaging in and learning the complex behavior sets that are required for successful academic achievement, occupational success, social skills, and independent living. Unlike traumatic brain injury, where we hope that neuropsychological rehabilitation will restore the cognitive functions necessary for the patient to *return* to his or her level of functioning, people with schizophrenia often have impaired functioning before and throughout the illness Thus, it is difficult to imagine how treatments that focus on cognitive impairments but do not take a skills training approach would manifest in real world behavior change. A recent meta-analysis supports this notion. McGurk and colleagues (37) found larger effect size changes in distal measures such as social functioning when cognitive remediation was used within a larger psychosocial treatment framework. The very

small and non-significant effects on functioning when cognitive remediation is used in isolation speak to the idea that cognitive improvements occur, and indeed might be quite robust, but the likelihood of these changes transferring to real world functional behavior is greatly diminished and perhaps not likely if the patient is not engaged in other activities that create and environment where s/he has the opportunity to learn and use new skills.

What are the societal and health care implications of treating cognition?

Schizophrenia is an exceptionally costly disease to the individual and to society. Loss of productivity and disability results in the billions of dollars in indirect costs each year (38). Treatments that enhance cognition could reduce this burden if they result in more independence in living and vocational productivity. Several recent studies suggest that this might be the case. When cognitive remediation is used within the context of vocational rehabilitation services, patients have improved outcomes that include reduced time to employment and greater maintenance of jobs, earning higher wages, and working more hours (39–40). Future work might further examine the role that cognitive remediation plays with other costs such as independent living and use of intensive clinical services. With clinically meaningful effects that generalize to improvements in everyday functions, cognitive remediation therapy is poised for widespread use in clinical environments.

Pharmacological Cognitive Enhancement

Target selection for pharmacological cognitive enhancement is complicated and has been reviewed elsewhere (41–42). Neurotransmission is a complex phenomenon and, despite remarkable advances in neuroscience, is still only partially understood. Developing targets for cognitive enhancement requires the decision as to whether to attempt to increase activity by stimulation of receptors (agonist), reducing activity by blocking receptors (antagonist), modifying the endogenous processes of down regulation of activity, either through stimulating autoreceptors, blocking re-uptake (transport), or reducing degradation of transmitters. While many of these actions would seem to lead to the same result, the complexities of neurotransmission suggest that the situation is not that simple. For instance, stimulating serotonin receptors directly has no impact on depression, but increasing serotonin activity through blocking transport is a very effective antidepressant strategy (serotonin reuptake inhibition; SRI).

Pharmacological Cognitive Enhancement

There have been multiple recent studies on pharmacological cognitive enhancement, with somewhat disappointing results. Table 3 presents a list of the studies that have had negative results so far. These studies are clearly negative, with an occasional minimal signal for cognitive change that would not meet the FDA standard for being meaningful. We review some recently promising results and discuss possible reasons for the lack of effects. See Harvey (42) for a detailed review of those previous treatment failures.

One strategy with some promise for efficacy has been implemented to examine medications that otherwise regulate glutamatergic activity. For instance, lamotrigine, an approved anticonvulsant medication, reduces glutamatergic release and may adjust glutamatergic tone. Lamotrigine pretreatment has been shown (56) to reduce the adverse effects of ketamine administration in healthy individuals. Several studies have reported beneficial effects of lamotrigine on symptoms in people with schizophrenia (e.g.,57), so an assessment of its cognitive effects seems reasonable.

In two highly similar clinical trials reported in a single paper, Goff et al. (58) found that double-blind placebo controlled treatment with lamotrigine was possibly associated with

cognitive improvements. In the two studies the cognitive composite score was improved by z = 0.58 and z=0.47 in the lamotrigine group, with corresponding improvements in the placebo group of z=.21 and z=.20. The effect of treatment compared to placebo was statistically significant in one study and it was not in the other. These data suggest improvements beyond placebo that are consistent with a small effect size. Improvements of this magnitude may not be clinically significant, but the relative importance of different degrees of cognitive improvements is not well understood at this time.

Modafinil

Modafinil is an alertness-promoting medication that has a mechanism of action that may be distinct from amphetamine, but likely still involves monoaminergic mechanisms. Multiple studies have provided information regarding modafinil that is partially supportive of cognitive enhancing properties. As reviewed by Morein-Zamir et al. (59), there are more strong findings in areas of executive functioning and attentional processes than in enhancement of memory functions. Further, evidence of heterogeneity of response is clearly evident, with less severe cognitive impairment and several different genetic polymorphisms predicting better response. Cognitive enhancement in healthy individuals is also reported with modafinil, but these improvements are much more substantial in individuals who are sleep deprived at baseline (60). A further issue with modafinil is the sporadic case reports of exacerbation of psychosis in patients with schizophrenia taking the compound. It is not clear if these are direct medication effects or of if they are associated with misuse of the medication, which could then lead to sleep deprivation and associated adverse events.

GABA Based interventions

GABA modulating compounds have been used for years as anxiolytics and these compounds, such as lorazepam, are agonists at the $GABA_A$ benzodiazine site. In a study (61) that employed both cognitive assessments and fMRI evaluations, a small sample of schizophrenia patients were compared to a similar sized sample of healthy controls (n's=11) were while receiving lorazepam, placebo, or flumazenil, an antagonist at this same GABA site. The primary cognitive outcomes measure was the n-back working memory test, a commonly used tested of working memory with maintenance, manipulation, and updating requirements.

In this study, flumazenil was associated with improved N-back performance under conditions of increased processing load in people with schizophrenia and simultaneously led to a normalized pattern of cortical activity associated with load response. By contrast, lorazepam led to worsened n-back performance compared with placebo. Healthy individuals performed more poorly than placebo in both active pharmacological conditions. These data, albeit in a small sample and with a single cognitive test, suggest cognitive performance improvements and changes in brain activation compared to placebo and treatments that enhance GABA activity. Further, the effect is not a generalized one, because healthy individuals were adversely affected by both pharmacological manipulations. Convergence of cortical activation changes and cognitive task performance stand in contrast to previous studies of noradrenergic and cholinergic medications where brain activation was changed but behavioral performance was unaffected. That study seems quite promising and requires replication with a larger sample size and a more comprehensive cognitive assessment battery. Note that other GABA-ergic compounds have not met with much success in large-scale trials.

Non-Transmitter Interventions

Neuroscience discoveries have identified pharmacological compounds that have effects other than transmitter manipulation/modulation. These include compounds that have other

CNS effects. These have been the result of long-term interest in development of compounds that promote neurogenesis or other brain growth processes, For example, davunetide is a neuroactive peptide that appears to promote neurite outgrowth in animal models. Since post mortem findings of neurite abnormalities are quite consistent, this appears to be a potentially promising intervention. In a single study examining davunetide in people with schizophrenia, Javitt et al. (62) found that intranasal administration of one of two doses of davunitide lead to statistically significant improvements in the UPSA compared to placebo treatment. The other, higher, dose was not associated with improvements in the UPSA and neither dose improved the MCCB compared to placebo. However, this study had a very small sample size and several of the MCCB domains improved to an extent that would have been significant with even a modestly larger sample (n=50). The effect size for UPSA change was d=.74, which is a large and potentially quite clinically meaningful effect and the effect size for changes on the MCCB was d=0.4, which is moderate, close to statistically significant, and potentially clinically meaningful. As interventions such as davunitide bypass some of the shortcomings of transmitter-based interventions (as described below), this may be a promising compound and even more promising cognitive enhancement strategy.

Why the negative results?—As can be seen in this review, with some minor exceptions, the pharmacological cognitive enhancement studies to date have been negative. These results span multiple targets and have used compounds that are known to be effective to treat cognitive impairments in other conditions such as attention deficit disorders, people with schizotypal personality disorder, and in healthy individuals. We review several possibilities for these results: [comp, link this list, below, to the headers in the manuscript where each is discussed.]

- Cognitive Impairment is not modifiable by pharmacological means.
- The use of concurrent medications may interfere with the effects of cognitive enhancers.
- Dosing of add-on compounds may be critically important for their efficacy.
- Delivery and Pharmacokinetics may lead to problems in administration.
- Neurotransmitters may not be the viable target for cognitive enhancement.

Cognitive Impairment is not modifiable by pharmacological means—There is evidence of progressive cortical volume loss in people with schizophrenia (63) which include progressive loss of gray matter and reduced growth of white matter particularly in cases with multiple exacerbations (64). It could be argued that the progressive volumetric changes constrain the ability of pharmacological treatments to induce a benefit. However, the strongest argument against the notion that progressive brain changes preclude cognitive enhancement is that cognitive remediation has been shown to produce cognitive changes and lead to relevant real-world functional improvements, as reviewed above.

The use of concurrent medications may interfere with the effects of cognitive enhancers—Patients with schizophrenia are typically treated with antipsychotic medications. The entire spectrum of effects of these medications is not wholly understood and it is possible that in some way antipsychotic medications alter the effects of add-on pharmacological cognitive enhancers. This is a substantial problem, because symptomatic relapse associated with antipsychotic medication discontinuation poses a considerable clinical problem, so simply suggesting that potential cognitive enhancing medications be tested or employed in patients who are not receiving medications is not practical. There are several ways in which antipsychotic medications could interfere with the effects of add-on pharmacotherapy. The first is through their common mechanism of antipsychotic action:

dopamine D_2 receptor blockade. The high levels of reduction of activity required to lead to clinical response following exacerbations (65) might lead to reductions in plasticity of other receptor systems that interact with this receptor subtype, including cholinergic, glutamatergic, and serotonergic systems. A second possibility is through the joint activity of atypical medications at the 5-$HT2_A$ receptor system. All of these medications blockade this receptor subtype to a greater or lesser extent and the serotonergic system is intimately involved in the regulation of multiple other neurotransmitters. A third and even more challenging possibility is the additional pharmacological effects of antipsychotic medications in some way contribute to these negative results. While all atypical antipsychotics share serotonin-dopamine antagonism (SDA), they vary markedly in their activity at other receptors, including muscarinic cholinergic, serotonergic (including 2_a, 1_a, 7, and 6_a), adrenergic, and histaminergic receptors with a mix of agonist and antagonist effects.

Dosing of add-on compounds may be critically important for their efficacy— Although medication doses for treatments that are in current clinical use for other conditions (guanfacine, cholinesterase inhibitors, atomoxetine) are established for the original illnesses, it is not clear if the same doses would be required to enhance cognition in people with schizophrenia. Many of these treatments have dose-dependent side effects (e.g., nausea, hypotension) that limit the potential for dose increases in the original target populations, and concurrent antipsychotic medications may either suppress or exacerbate some of these side effects. As most neurotransmitter activity is regulated by multiple other systems, it is hard to estimate a priori what the potential dose of medications that are introduced into an already altered biological system because of antipsychotic effects.

Delivery and Pharmacokinetics may lead to problems in administration—Some drugs, such as the dopamine D1 agonist SKF 38393 that has been shown to be very effective in studies of animals using direct administration into the CNS (e.g., 66), may not cross the-blood brain barrier when administered peripherally. The consequence is that it is not currently possibly to deliver a definitive, specific D1 agonist directly into the brain, Other potentially effective cognitive enhancers either have short half-lives (alpha-7 nicotinic agonists) or lead to receptor sensitization. As a result, some treatments that have solid basic science support (D1 and Alpha-7 agonists) have proven difficult to develop into medications that would be useful for treatments. New developments, such as identification and development of additional compounds, including specific precursors or pro-drugs for D1 agonists that cross the blood-brain barrier or compounds which provide allosteric modulation of cholinergic receptors may be required

Neurotransmitters may not be the viable target for cognitive enhancement— Neurotransmitter manipulations have the potential to influence cognition, as shown in multiple previous studies. This intervention strategy is, however, predicated on the idea that neuronal targets are intact and available. This has already proven problematic in Alzheimer's Disease, where cholinergic interventions may be handicapped by the widespread loss of cholinergic neurons by the time that the intervention is delivered. Similar problems may exist in schizophrenia, where abnormalities in cortical structure, circuit connectivity, and axonal/neuronal integrity could possibly reduce the beneficial effects of receptor stimulation. Behavioral interventions may actually have their effect through altering CNS circuitry or connectivity across multiple linked transmitter systems (67–68). If this was found to be the case, interventions aimed at neurites, circuits, and white matter may provide a more effective intervention strategy and these interventions may not be sensitive to the effects of a single transmitter system. The case of davunetide (see above) is a perfect example of where an intervention that has potentially direct effects on brain structure and

function provides a signal of a magnitude not seen in studies of medications with known beneficial effects.

Cognitive remediation as a platform for pharmacologic studies

It is possible that many of the experimental pharmacologic interventions will be of only minimal benefit when patients are evaluated in the context of their habitual low level of cognitive stimulation. Part of the explanation for why clinical trials testing the efficacy of cognitive-enhancing medications have so far been largely unsuccessful may be that patients in these trials are not provided with substantive opportunity to utilize the cognitive benefit that they may have acquired during the drug treatment study. Thus, analogous to the need for physical exercise in an individual who takes steroids to increase muscle mass, schizophrenia patients in pharmacological intervention trials may require systematic cognitive training to “exercise” any newfound cognitive potential that they may have acquired from drug treatment (69).

Cognitive remediation may provide an excellent platform for enriching the cognitive environment of patients engaged in pharmacologic trials to improve cognition. As noted above, cognitive remediation produces medium to large effect size improvements in cognitive performance and, when combined with psychiatric rehabilitation, also improves functional outcomes (see 70 for a review). Patients find these programs to be enjoyable and engaging, and they have been linked with increases in participant self-esteem. Ongoing treatment with cognitive remediation may thus provide schizophrenia patients with the necessary cognitive enrichment and motivation to demonstrate the true potential of effective cognitive enhancement with pharmacologic intervention. Recent work suggests that these methods are feasible in clinical trials even at sites without cognitive remediation experience (71). These results suggest that clinical delivery of cognitive enhancement treatments may be feasible in many different clinical service systems.

Conclusions

Cognitive remediation combined with psychosocial interventions improves everyday functioning in people with schizophrenia. Similar consistent positive results have not been shown with pharmacological interventions. However, studies of combined pharmacological/psychosocial interventions have not been completed. While pharmacological cognitive enhancement to date has been largely negative, new compounds and research designs are on the horizon. Combined pharmacological and cognitive enhancement interventions, with concurrent psychosocial interventions appears to be the intervention of the future.

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Synopsis

The authors discuss the measurement of cognition in schizophrenia, its role as a determinant of disability, and treatment efforts to date, including both pharmacological and behavioral interventions and critical components of effective treatments that lead to improvements in everyday outcomes. They detail how functioning can and should be measured in the office when patients with schizophrenia receive treatment.

The focus of this review is on new developments in the area of the creation and adoption of a consensus method for the assessment of cognitive functioning in treatment studies and in the increased appreciation for the needs for assessment of functional skills in the prediction of everyday outcomes, as well as new developments in the basic neuroscience of cognition.

Key Points

Practice Recommendations.

1. Patients with schizophrenia benefit from cognitive remediation and their everyday functioning has been shown to improve with concurrent psychosocial interventions. Neither treatment alone seems to have similar efficacy.
2. Cognitive remediation causes neurobiological changes and has evidence of biological validity. The changes that occur do suggest evidence of activation of brain repair mechanisms.
3. Anticholinergic medications negate the benefit of cognitive remediation and other learning-based interventions. Their use should be kept to a minimum.
4. Pharmacological compounds commonly used as off-label add on therapies for cognitive enhancement (cholinesterase inhibitors; mood stabilizers) have no demonstrated efficacy.
5. Modafinil appears to have benefits in reversing the effects of sleep deprivation on cognition and amphetamine improves cognition. Both have safety concerns, with amphetamine more risky.

TABLE 1

MATRICS Consensus Cognitive Battery

Speed of Processing:
Category Fluency
Brief Assessment of Cognition in Schizophrenia (BACS) - Symbol-Coding
Trail Making A
Attention/Vigilance
Continuous Performance Test - Identical Pairs (CPT-IP)
Working Memory
Verbal: University of Maryland - Letter-Number Span
Nonverbal: Wechsler Memory Scale (WMS) - III Spatial Span
Verbal Learning
Hopkins Verbal Learning Test (HVLT) – Revised
Visual Learning
Brief Visuospatial Memory Test (BVMT) – Revised
Reasoning and Problem Solving
Neuropsychological Assessment Battery (NAB) – Mazes
Social Cognition
Meyer-Solovay-Caruso Emotional Intelligence Test

Table 2

NIMH, FDA, Academia, and Pharmaceutical Industry Consensus Entry Criteria for Cognitive Enhancement Interventions

Criteria for Enrollment into cognitive enhancement trials
Diagnosis of Schizophrenia
No major change in antipsychotic medications for at least 6 weeks prior to screening;
No medications that can influence cognitive functioning:
Anticholinergics
Amphetamines
L-dopa
No hospitalization for psychiatric illness for at least 8 weeks prior to screening
Moderately severe or less (<5) severity rating on selected PANSS positive scale items at both screening and baseline.
No evidence of current major depression

Table 3

Negative Results by Mechanism of Action[1]

Mechanism	Specific Drug	Reference	Notes
Cholinergic			
Muscarinic	Donepezil	43	Worse than placebo
	Rivastigmine	44	Small sample
	Galantamine	45	Some domains improved
Nicotinic	DMX-B	46	Cross over design
	AZD3480	47	
Glutamatergic			
NMDA	Glycine, D-cycloserine	48	large-scale study
AMPA	AMPA-Kine	49	
Noradrenergic	Guanfacine	50	Some domains improved
	Atomoxatine	51	Brain activity changed
GABA	MK0877	52	
Serotonergic	Tandospirone	53	
	Buspirone	54	
Cannabinoid	Rimonabant	55	

[1]When multiple studies produced similar results, the largest sample size study is presented.