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TREATING COGNITION IN SCHIZOPHRENIA: SEARCHING FOR THE BEST EVIDENCE-BASED PRACTICES

Abstract

Objectives: Treating cognition in schizophrenia has been one of the major challenges in psychiatry during the last decades. Developing medications and cognitive therapies to treat the cognitive deficits associated with schizophrenia is a high priority.

Methods: A critical review of the bibliography has been performed. We focused on some aspects like the choice for best evidence-based practices in clinical practice that remain as an open questions.

Results: Cognitive remediation therapies seem to have beneficial effects on cognitive global functioning and psychosocial functioning. Unfortunately, cognitive remediation is not recommended by international guidelines because there are still some open questions regarding generalisation to daily functioning and no widely accepted cognitive remediation approach. Combining cognitive remediation and pharmacotherapy is an interesting line but it still has not been well studied. Besides, there are currently no indicated cognitive-enhancing drugs.

Conclusions: All in all, at the present time cognitive remediation can be considered as possibly the best evidence-based intervention to treat cognition in schizophrenia.

Key words: Schizophrenia, Cognition, Cognitive Remediation, Pharmacotherapy, Cognitive-enhancing drugs

Introduction

Treating cognition in schizophrenia has been one of the major challenges in psychiatry during the last decades, as the cognitive impairment has been reported to be a major determinant of clinical outcomes in this population [1]. Approximately 75-85% of patients with diagnosis of schizophrenia suffer from impairment in cognition and that has been associated with negative outcomes, low rates of medication compliance and higher rates of psychotic relapses, in particular in first-episode patients with psychosis [2 3]. Thus, developing medications and cognitive therapies to treat the cognitive deficits associated with schizophrenia is a high priority. At the same time, some aspects like the choice for best evidence-based practices in clinical practice have not been so well studied.

Pharmacotherapy

Pharmacotherapy interventions, such as antipsychotic treatments, have been reported to be effective in treating positive symptoms in schizophrenia [4], although studies focusing on the efficacy of antipsychotics on cognitive deficits have shown controversial results [1 2 5]. This lack of

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effective treatment strategies has encouraged recent research to investigate the underlying neurobiological mechanisms involved in cognitive impairment in schizophrenia [3 6]. Further, this need of biological research has led to the MATRICS initiative (Measurement and Treatment Research to Improve Cognition in Schizophrenia) to identify seven cognitive domains that should be addressed as molecular targets for treating cognition in schizophrenia [3,6]. These domains included working memory, attention and vigilance, processing speed, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition.

In this line, recent research has identified different molecular targets that would be implicated in the development of new drug strategies for the treatment of cognition in schizophrenia [6 7]. These molecular targets include cholinesterase inhibitors (e.g. rivastigmine, donapezil, galantamine), nicotinic and muscarinic receptor agonists, glutamatergic targets (e.g. glycine site agonists, glycine reuptake inhibitors, metabotropic receptor agonists), antipsychotics with affinity for dopamine D4 receptors, psychostimulants (e.g. inhibitors of COMT), serotonergic targets (e.g. serotonin partial agonists) and modafinil [3 7].

A recent meta-analysis investigated the efficacy of adjunctive pharmacotherapy for cognitive deficits in schizophrenia [5]. Acetylcholinesterase inhibitors, such as rivastigmine and donepezil, were reported to have a positive effect on verbal learning and memory, but, unfortunately, with a moderate significance, and non-stable effects on spatial learning and memory [5]. The same authors reported that glutamatergic medications and serotonergic agonists had a small effect-size improvement in psychotic symptoms, but no effects for cognitive symptoms, suggesting that the combination of antipsychotics and these drugs would not be useful in treating cognitive impairment in schizophrenia [5].

With regard to the effects of antipsychotics on cognitive impairment in schizophrenia, a recent meta-analysis compared the efficacy of antipsychotics on overall cognition, as well as on specific cognitive domains [8]. The authors found that treatment with quetiapine, olanzapine and risperidone was associated with better improvement in overall cognitive scores compared to amisulpride and haloperidol. Further, quetiapine, olanzapine and risperidone were better than amisulpride in terms of executive functions, and quetiapine had better positive effects on attention and processing speed tasks than the other antipsychotics. These findings support the notion that significant differences in cognitive effects can be found between antipsychotics according to specific cognitive domains. The median duration of included trials was around 52 weeks [8].

In summary, acetylcholinesterase inhibitors have shown a marginal improvement in verbal learning and memory when cognitive remediation therapy is not provided. Other cholinergic, glutamatergic and serotonergic drugs would have no effects on the specific cognitive domains, as defined by the MATRICS initiative. When focusing on the effects of antipsychotics, quetiapine and olanzapine were found to have the most positive effects.

Cognitive Remediation Therapies

Cognitive remediation therapy for schizophrenia is a behavioural training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization, as defined at the Cognitive Remediation Experts Workshop (Florence, Italy, April 2010) [9]. Thus, cognitive remediation is a psychological therapy that aims to enhance cognition with a further goal that improved cognition will affect community functioning [9].

A range of cognitive remediation programs have been developed and evaluated over the past 40 years. After a period of time with non-conclusive studies, we have now meta-analytic studies with positive results [9-11]. Meta-analytic studies are considered to be the highest level of evidence in the evidence-based medicine. Thus, one recent meta-analysis [9] was based on 40 studies with 2104 patients and it concluded that cognitive therapies produce long-lasting improvements on cognitive global functioning in patients diagnosed with schizophrenia. Cognitive remediation is efficacious in improving global cognition (Cohen's d = 0.448). Particularly, significant benefits for the majority of cognitive domains were found as in attention (d = 0.250), speed of processing (d = 0.258), working memory (d = 0.346), verbal learning and memory (d = 0.410), problem solving (d = 0.572) and social cognition (d = 0.651). The effect was significant after the follow-up (d = 0.428). There also were significant benefits for symptoms (d = 0.177) and functioning (d = 0.418). Fortunately, at follow-up the effect was still significant for functioning but not for symptoms. Finally, results did not seem to be affected by study methodology.

Nonetheless, in despite of having an amount of studies focused on efficacy, there still are some many other data that deserve a deeper analysis in order to

help clinicians to provide best evidence-based services. Firstly, a greater effect on psychosocial functioning when patients received cognitive remediation together with an adjunctive psychiatric rehabilitation compared to cognitive rehabilitation alone. Secondly, the use of a more strategic cognitive remediation approach would be more useful to improve daily functioning. Recently, it has been suggested that drill and practice and strategy learning could be complementary and maybe they have their specific effects on outcome. Thus, drill and practice training programs seem to be more frequently used for neurocognitive deficits and strategy learning for functional disability [12]. However, studies using drill and strategy could have a particular interesting impact on other variables outside of cognition, such symptoms of quality of life [12]. Finally, cognitive remediation was more effective when patients were clinically stable.

In summary, recent reviews indicated that cognitive remediation therapy produced beneficial effects on cognitive global functioning and psychosocial functioning on the patients diagnosed with schizophrenia. Furthermore, the type of therapy plays an important role for generalization the outcomes than duration therapy or type of presentation.

Combining pro-cognitive drugs and cognitive therapies

Traditionally, clinicians focused on two different strategies: pharmacotherapy or cognitive therapies when treating cognition in schizophrenia patients. Nonetheless, in order to find new evidences able to improve our clinical practice, the therapeutic approaches maybe should diverge from the prevailing models (antipsychotics and cognitive therapies) and focus instead on a different and more practical treatment strategy. Swerdlow [13] has proposed a new framework accounting for the following elements:

- antipsychotic medications to constrain the scope and severity of psychotic exacerbations and thereby facilitate engagement in cognitive rehabilitation;
- cognitive therapies designed to engage healthy neural systems to compensate for and replace dysfunctional higher circuit elements;
- medications that specifically target cognitive mechanisms engaged by these rehabilitative psychotherapies.

In this approach, the importance to combine CRT, antipsychotics and pro-cognitive pharmacology is emphasised. Swerdlow [14] suggests that specific pro-cognitive drugs could be ineffective when administered without the demands of cognitive therapies and nonetheless they can still be effective when delivered together with CRT as a synergy facilitator. Swerdlow [14] proposed the lack of efficacy of pro-cognitive drugs could be due to the fact that those trials have being done using drugs that were designed to surmount neuropathological changes in schizophrenia (e.g., D-cycloserine) [15]. An alternative strategy is suggested: using medications that enhance spared neural functions in these patients. Unfortunately, evidence showing the existence of those 'spared' healthy circuitries is still scarce and for that reason some specific research is needed. Such new approaches would require a revision of regulatory guidelines to make such trials feasible and economically possible.

Controversies and open questions

Positive results for cognitive therapies have been shown in different randomised and controlled trials and also in meta-analytic studies. Although that is encouraging evidence, there are still some controversial and open questions. To start with, a number of studies with negative results have been published [16-18]. Thus, in order to avoid negative results something must be learned about those studies with negative results, for instance they tend to be based on computer programs with few participation of the therapist. Moreover, even when results are able to improve cognition it seems that not all treatments are able to translate this improvement into functional benefits. Further studies examining the generalisation of cognitive improvement to functioning are needed. Another important question is about the so-called practice effect. Practice effect is a consequence of the familiarity with test instructions, and it is likely for individuals to obtain higher scores on many measures upon repeated testing. Thus, the effect of practice in cognitive assessment has to be taken into account when outcomes of different studies are considered. Goldberg et al. [19] showed a gain of 0.36 effect size (Cohen's d) upon repeat testing in a composite global cognition measures in a first-episode of psychosis patients treated with second-generation antipsychotics. Similarly, a comparison sample of healthy controls showed an observed effect size gain of 0.33. Thus, the practice effect has to be taken into account because different treatments could not be exceeding the expected practice effects (Figure 1).

Furthermore, some other barriers might be preventing researchers and clinicians to get better empirical

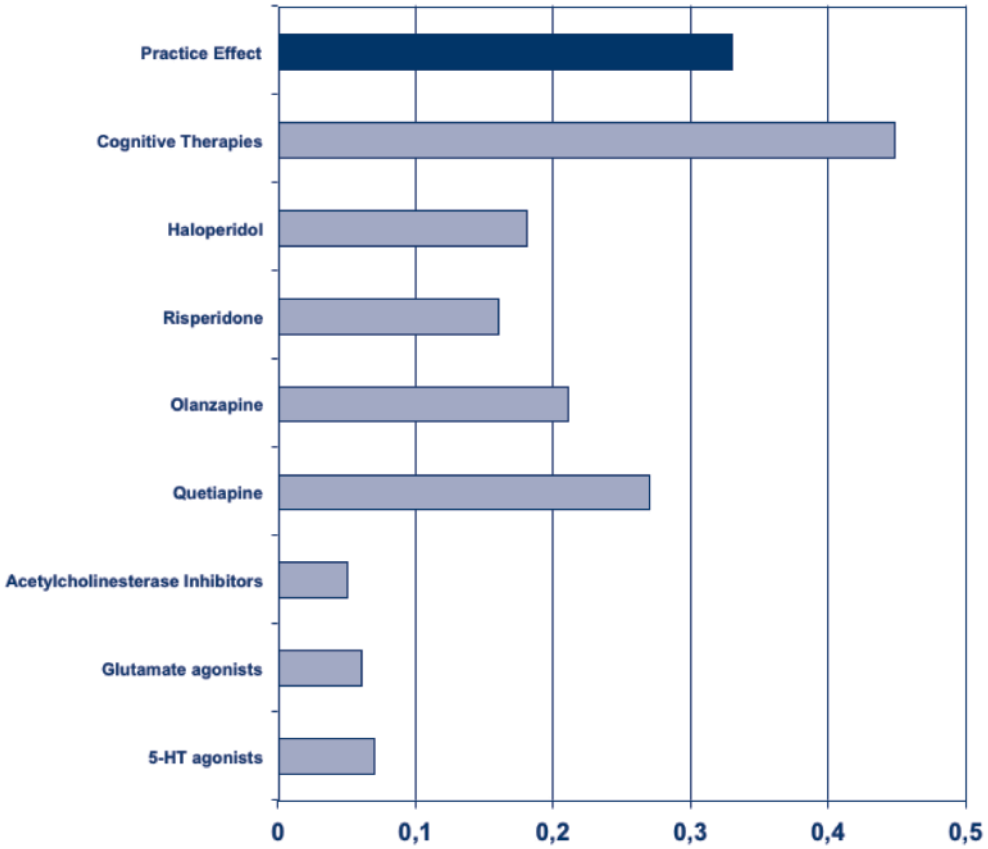

FIGURE 1.

Comparison of the effect sizes of different treatments and practice effect. Effect sizes has been calculated over whole cognition by de Cohen's d. Results have been taken from the meta-analyses by Choi et al.[5], Wykes et al.[9] and the study by Goldberg et al.[19] for the practice effects.

evidence. Bromley [20] has suggested three of the problems regarding the use of cognitive enhancers in the treatment of schizophrenia that still remain controversial. Firstly, ecological validity of cognitive constructs. It seems like constructs researchers use to describe cognition are not always totally equivalent to the cognitive skills and behaviours that clinicians see in their clinics. Secondly, perceptions of cognitive impairments show an intriguing discrepancy between patients and clinicians. That can be particularly problematic, for instance discrepancy between objective and subjective assessments can complicate some practical aspects as monitoring cognitive-enhancer medication. Thirdly, after cognitive treatment improvements in functionality are expected by patients and clinicians. However, even though that is a desirable gain, assessments of patients functional status may not be the best way to establish the cognitive-enhancers' efficacy. Functionality is a very complex variable and also a considerable amount of variables can be mediating in the relationship between cognition and functioning. In the next future, research on mediators between cognition and functioning should help us to have a better understanding about more complex assessment strategies in the frame of empirical mediation models.

Finally, one great challenge is the use of cognitive-enhancer medication in combination with cognitive therapies. However, this strategy will predictably be difficult to implement in clinical practice. For instance, it is necessary to know exactly when the cognitive-enhancing drug should be administered relative to cognitive remediation. Michalopoulou [21] has discussed this topic indicating that all drugs show changing plasma levels through the day and ideally cognitive remediation should have to coincide with the time window of maximal plasticity enhancement by the cognitive-enhancing drug. At this moment independent measures of the plasticity window and therefore drug plasma levels serve as the most relevant proxy are not available. Besides, it is important to consider potential harms of these drugs, for example interactions with antipsychotic medications, substance abuse, or other unknown effects. Information regarding actual use of the cognitive-enhancers, their security and benefit balance and potential harms are harshly lacking [22].

Conclusion

There are currently no indicated cognitive-enhancing drugs and no widely accepted or applied cognitive remediation approach. Cognitive remediation therapies have beneficial effects on cognitive global functioning and psychosocial functioning on the patients diagnosed with schizophrenia. Unfortunately, cognitive remediation is not recommended by international guidelines because there are still some open questions regarding generalisation to daily functioning. Nonetheless, at the present time cognitive remediation can be considered as probably the best evidence-based intervention to treat cognition in schizophrenia.

Take home messages for psychiatric care

- Evidence-based therapies for treating cognition in schizophrenia are highly warranted
- Cognitive remediation has beneficial effects on cognitive global functioning and psychosocial functioning, possibly, being the best evidence-based intervention when treating cognition in schizophrenia
- Effectiveness of combination of cognitive remediation and pharmacotherapy seems to be still unclear

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