DO ATYPICAL ANTIPSYCHOTICS IMPROVE COGNITION?

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SUMMARY

One of the major symptoms of schizophrenia is cognitive deficits. Despite this, these impairments still lack an effective treatment. It was hoped that atypical antipsychotics would treat these symptoms better than their first generation counterparts, but unfortunately the likes of quetiapine and clozapine did not do so. Asenapine and lurasidone, two newer atypicals, have shown promise, as have agents that interact with the glutamate system. Another approach has been to add agents such as modafinil. More research is needed to consolidate the findings of these studies.

Key words: schizophrenia – atypical – antipsychotic – cognition – asenapine – lurasidone – CATIE – glutamate - modafinil

INTRODUCTION

Schizophrenia affects 5 in 1000 in the UK population, with around 7000 new cases a year (NCCMH 2010). Significant numbers of patients diagnosed with schizophrenia continue to struggle with long-term impairments, including cognitive deficits. Problems include information processing speed, visual memory and attention (Rajji 2014). These impairments are one of the core symptoms seen in schizophrenia, along with positive and negative symptoms. Whilst the latter two have been the focus of large amounts of research, it is only more recently that cognition has become the focus of research and the target of treatment.

Studies have shown that cognitive deficits can be seen in the prodromal phase that typically precedes schizophrenia. Cognitive impairment is thought to precede clinical presentation of symptoms (Reichenberg 2010). Reviews of longitudinal studies have found patients deemed to be of a clinically high risk of schizophrenia have higher rates of general and specific problems with cognition when compared to healthy people (Addington 2012).

Consideration of cognitive impairments is clinically very important. With further investigation, it could possibly be used as a predictive tool for the outcome of functional ability in schizophrenia (Addington 2012). Functional ability, in collaboration with self-motivation and insight, is an important factor determining chance of recovery. Cognition is also a common factor considered when measuring quality of life. It is therefore crucial that we find pharmacological treatments that address not only the positive symptoms, but the cognitive problems too.

ANTIPSYCHOTICS AND THE TREATMENT OF SCHIZOPHRENIA

First generation (typical) antipsychotics such as chlorpromazine and haloperidol were first introduced to treat the positive symptoms of schizophrenia, like agitation, hallucinations and mania. At the time of their introduction in the 1950s little consideration was given to the cognitive impairments that came before, during and after psychotic episodes. Typical antipsychotics work by antagonising the dopaminergic pathways, causing significant adverse effects such as extrapyramidal motor symptoms and higher cognitive function disruption. Multiples studies using rat models and healthy human volunteers have demonstrated that typical antipsychotics have detrimental effects on working memory, motor skills and other higher order cognitive functions (Hill 2010). Furthermore, it has been shown that cognitive deficits present before onset of illness increase sensitivity to medication side effects (Kane 2010).

The introduction of clozapine, quetiapine and the other atypical antipsychotics heralded a new treatment option for schizophrenic patients, without the life altering extrapyramidal side effects seen in older drugs. It was also believed that this group of drugs would address the cognitive impairments suffered by patients, with early studies seeming to show they were better than first generation antipsychotics (He 2009, Keefe 1999).

The landmark nationwide CATIE (Clinical Anti-psychotic Trials of Intervention Effectiveness) trial changed this view. Funded by the NIMH it compared the effectiveness of older typical antipsychotics against the newer atypical medications that became available in
the 1990s. When comparing a variety of first and second generation antipsychotics, there were small but statistically insignificant improvements in cognitive test results, and no significant difference between typical and atypical antipsychotics was seen (Hill 2010). This matches a growing consensus in more recent papers stating that any difference in cognitive improvements between atypical antipsychotics and their older counterparts are negligible (Hill 2010). The small improvements with atypical antipsychotics have been clinically insignificant, although there is some argument for how much of functional disability is reduced with their use.

ASENAPINE - AN ATYPICAL THAT IMPROVES COGNITION?

Asenapine is one of the atypical antipsychotics currently licensed for the treatment of schizophrenia. However it differs in some ways from other drugs in its class. A 2009 study of asenapine’s mechanism of action found that it had significantly different binding affinities for serotonergic, dopaminergic, histaminergic and muscarinic receptors than any of the other atypical antipsychotics (Shahid 2009). The suggestion that it therefore has a unique human receptor pattern from other drugs in its class gave rise to ideas that it may be able to correct problems previously untouched by past medications, i.e. cognitive impairment.

Subsequent animal models have supported the theory that asenapine may be an atypical antipsychotic that breaks the mould and improves cognition as well as resolving positive symptoms. In one such trial were monkeys trained to perform tasks that demonstrated cognitive ability, before being administered PCP to mimic the cognitive decline seen in patients with schizophrenia. Monkeys treated with asenapine made substantial improvements in their executive function and maintained them with continued administration (Elsworth 2012). Similar results were found in a number of other studies (Snigdha 2011). Significant increases in serotonin and dopamine support the theory that asenapine may be able to act through these pathways to improve cognition.

Different studies have suggested the drug has an especially high affinity to the 5HT1a and D1 subtypes (Meltzer 2011, Snigdha 2011, Tarazi 2010). The 5HT1a receptor has garnered particular interest as a potential target for cognitive enhancement (Sumiyoshi 2013). There is also evidence that the drug may act on glutamate receptors, a pathway we shall consider later.

LURASIDONE - THE NEW “NEW” ATYPICAL

The relatively new atypical antipsychotic lurasidone has also received interest with regard to its procognitive effects. It is thought to act through a variety of receptors including 5HT1a, one of the subtypes targeted in the quest for cognitive improvement (Meltzer 2011), and 5HT7. The 5HT7 receptor subtype is another target thought to improve both negative symptoms and cognition (Nolan 2012).

The drug appears to differentiate itself from other atypical antipsychotics in a number of ways. Lurasidone has been shown to possibly prevent the detrimental cognitive deficits from developing past the prodromal stage (Yasui-Furukori 2012). The drug is also thought to increase BDNF mRNA levels in the hippocampus and prefrontal cortex (Yasui-Furukori 2012). BDNF is a mediator involved in cell plasticity and resilience under stress, and could lead to an increase in function ability and cognition.

Lurasidone is not without its limitations however. Studies have reported that the antipsychotic comes with a risk of akathisia and extrapyramidal symptoms, such as rigidity, tremors and abnormal gait (Samalin 2011). Although the drug has a lower risk of these symptoms than first generation antipsychotics, the risk is not negligible.

THE GLUTAMATE PATHWAY IN SCHIZOPHRENIA

We are seeing the rise of a new hypothesis of the pathophysiology of schizophrenia, based around the NMDA receptor hypofunction rather than dopamine (Moghaddam 2012). The glutamate pathway can be implicated in positive, negative and cognitive symptoms, so naturally has been a target for therapies of treatment resistant cases. Particular attention is being paid to drugs that can regulate the NMDA receptor (Hashimoto 2013, Spangaro 2012), through which an abundance of presynaptic, post synaptic and regulatory proteins may be targeted.

Researchers investigating glutamate based treatments have a number of possible options to follow. Increasing the available endogenous glycine may increase NMDA receptor activity, as might administering an exogenous version of the amino acid or analogue (Citrome 2014). Sarcosine, a glycine transporter inhibitor that works to increase endogenous glycine, has been shown to have efficacy in treatment both as an adjunct and a monotherapy (Lane 2008). Although this field is being actively investigated, there are not as yet any clinically available treatments.

ATYPICAL ANTIPSYCHOTICS AND MODAFINIL

There has already been great interest in the use of modafinil, the anti-narcoleptic drug, in the increase in cognition. Studies have considered its use in healthy people and a number of conditions including treatment resistant depression and alcohol dependence. A trial of the drug with schizophrenic patients found that it enhanced cognition in a similar way to what was seen
with healthy volunteers and ADHD sufferers (Turner 2004). Improvements were seen in short-term verbal memory, visual memory and spatial planning.

With data from a decade ago supporting the use of modafinil as an adjunct to antipsychotics, one must ask why this has not become a regular treatment option. Reviews in the last two years have suggested that results related to cognition seen were non-conclusive, and therefore modafinil was not a recommended therapeutic option (Lohr 2013, Wittkampf 2012). However, as with the atypical antipsychotics, although improvements seen have been statistically not significant, one cannot forget that individual cases might greatly benefit.

**CONCLUSION**

Whilst the treatment of the positive symptoms of schizophrenia seems to have many drug options available, the same cannot be said for negative and cognitive symptoms. In this paper we have considered just a few of the possibilities, some of which are in their fledgling stages of development. It was hoped that atypical antipsychotics would fill the void left by first generation drugs, but unfortunately it became clear that they too did not touch the cognitive deficits seen in the disorder. A few new atypical antipsychotics have been released with similar promises, but again their efficacy may too be inflated by hope. We can look to pharmaceutical development, where many believe that mastering the NMDA receptor holds the key to treating these symptoms. Finally, we have the option to try different adjuncts known to improve cognition in other scenarios. Again here we see that optimism may have distorted adjuncs known to improve cognition in other scenarios. We can look to pharmaceutical development, where many believe that mastering the NMDA receptor holds the key to treating these symptoms. Finally, we have the option to try different adjuncts known to improve cognition in other scenarios.

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**References**

12. NCCMH: Schizophrenia - The NICE Guideline on Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care, 2010.

20. Sumiyoshi T, Higuchi Y, Uehara T: Neural basis for the ability of atypical antipsychotic drugs to improve cognition in schizophrenia. Front Behav Neurosci 2013; 7:140. doi:10.3389/fnbeh.2013.00140


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