Evaluate Vantage

April 18, 2012

Therapeutic Focus – research into autism gains momentum

Joanne Fagg

Launched with what was described as the largest single grant for autism research to date, $37.8m, a huge academic-industry coalition last month embarked on a five-year search for novel treatments for the complicated and still little understood developmental brain disorder. Led by Roche, Kings College London and advocacy group Autism Speaks, the consortium hopes to find new methods to develop drugs for a disorder that in many cases the medical profession struggles to treat.

Interest in developing therapeutics for autism has grown as researchers have become increasingly convinced that combining a drug with behavioural interventions and support has the best chance of improving the lives of patients. With no known single cause and a huge variety of symptoms this is no small task and, as a result, little work has historically been done by commercial pharmaceutical companies, although interest is growing. There are a couple of agents in the pipeline now that are attracting interest and with results due in the next few years as well as substantial efforts from the new consortium and other groups, it is hoped that new treatment options in autism will soon start to emerge (see table).

The lifelong condition

Autistic individuals share three main core areas of difficulty: social deficits, repetitive behaviours and language impairment. It affects patients differently and to varying degrees and is often known as autism spectrum disorders, which includes autistic disorder, Asperger syndrome and Pervasive Developmental Disorder Not Otherwise Specified.

The US Centers for Disease Control and Prevention estimates that 1 in 88 American children have been diagnosed with an autism spectrum disorder; symptoms of autism typically appear during the first three years of life. Prevalence of the disorder has grown substantially in last 40 years and this can only partly be explained by improved diagnosis and awareness.

Autism is associated with abnormal brain development and signal disruption and does occur more frequently in individuals with some genetic disorders including Angelman syndrome, tuberous sclerosis, Rett syndrome and Fragile X syndrome. It is hoped that recent advances in potential treatments for these conditions will translate into treatments for autism more broadly (*Therapeutic Focus - Turning point ahead for Fragile X syndrome, February 28, 2012*).

Outside of these disorders, elucidating the cause has proven complicated since there is no known single factor, with genetic and environmental factors thought to play a part. There is a strong genetic component with early twin studies estimating the heritability of autism to be 90%. However, because multiple genes are implicated with potential interaction with the environment, it is not a straightforward genetic relationship - a study in 2010 identified 226 gene mutations in people with autism."

It is increasingly recognised that considerable heterogeneity underlies autism, and this is likely to hamper efforts to identify causes of, or treatments for, autism," says Dr Michael Spencer of the Autism Research Centre, Cambridge University.

"In order to develop targeted treatments of the future, an important first step is to tease apart what we currently classify as autism into component aetiological 'building blocks'".

Current treatment approaches

Current treatments are tailored to the individual to a certain extent. The condition is managed through behavioural and communication therapy such as social skills training and specialist education, to help improve functioning, with medication used to control associated issues.

A range of drugs such as anti-psychotics, anti-depressants and anti-epileptics are prescribed to autistic patients. For example approved to treat irritability in autistic children are the atypical anti-pyschotics aripiprazole and risperidone, while serotonin reuptake inhibitors such as the anti-depressant fluoxetine, or Prozac, are used to ameliorate repetitive, aggressive and compulsive behaviours.

While these drugs improve behavioural symptoms such as irritability and aggression, they do not specifically treat the core social or communication impairments. The side effects of these agents also mean they are not without their issues. Despite this and the limits to their utility, many believe they still have a role to play.

“Treating associated symptoms can have positive effects on the core symptoms as it can render a child, for example, more amenable to interventions orientated to the social deficits if they are more attentive and less irritable,” says Dr Joseph Horrigan, assistant vice president of medical research, Autism Speaks. “It is not uncommon to see that when we use medicine as part of the treatment package, we see more substantial gains or benefits when also using these other approaches.”

Synaptic targets

Experts recognise, however, that there is a lot more that could be done for autistic patients, and many see drugs as a viable route for treatment improvements. However, with vast heterogeneity and opaque causality, autism research has yet to reveal anything close to a disease modifying target to drug.

This has contributed to limiting the pharmaceutical industry’s interest, despite the commercial potential of any effective treatment. Advancements in the last decade in understanding of genomics and proteomics and how these factors are playing a role in the condition has prompted many companies to look again, with work now ongoing in a number of areas.

“In neuro-developmental disorders the goal or endeavour is to improve the strength of appropriate synaptic connectivity, with the ultimate goal to improve functioning in core areas,” says Dr Horrigan.

“Many of the proteins that have been identified in autism appear to play a regulatory role in appropriate synaptic connectivity. This then plays a material role in the quality of the neuronal network performance between key areas of the brain such as the cerebral cortex, cerebellum and other related areas, which have an important role in social relatedness, language and communication.”

Given neurotransmitters’ role in synaptic connectivity, this is a relatively fertile area of research.

Two drugs that target neurotransmitter pathways are in phase II autism studies - Forest Laboratories Namenda, an NMDA receptor antagonist, and Seaside Therapeutics’ GABA-B receptor agonist arbaclofen (see table).

Marketed in Alzheimer’s disease, senile dementia and post operative pain, Namenda works by blocking the neurotransmitter glutamate’s access to cells. Glutamate toxicity and a poorly functioning GABAergic system are suspected to have a causal role in autism.

A trial in 110 children with autism aged 6-12 years old is investigating a once daily oral administration of the drug for 12 weeks. Results are due later this year and the primary endpoint is change in social responsiveness.

Arbaclofen or STX209, which is also in phase III for Fragile X syndrome, acts on GABA-B receptors which play a part in modulating the release of glutamate.

In 2010 a phase IIa open-label study with the drug reported a statistically significant improvement in irritability and social withdrawal of participants. Further results from that trial are anticipated, while a larger phase II trial currently looking to enrol 200 patients will measure the drug’s impact on social withdrawal.

“The arbaclofen program is getting a lot of attention right now, mainly because it had some affirmative findings in autism in the early trial. I think people are following it closely because there could be some intriguing and potentially exciting findings that could come within the next year,” says Dr Horrigan.

Autism spectrum disorders pipeline						
Status	**Product**	**Generic Name**	**Pharmacological Class**	**Company**	**Proprietary Level 2**	**Tria**
Phase III	Kuvan	sapropterin dihydrochloride	Tetrahydrobiopterin	BioMarin Pharmaceutical/Merck KGaA	NME	NCT
	CM-AT	-	Pancreatic enzyme product	Curemark	NME	NCT NCT
	AT001	fluoxetine hydrochloride	SSRI	Autism Therapeutics	NDA	-
Phase II	Namenda/Axura	memantine hydrochloride	NMDA antagonist	Forest Laboratories/Merz	NME	NCT
	STX209	arbaclofen	GABA B agonist	Seaside Therapeutics	NDA	NCT NCT NCT
Phase I	RG7314	-	V1a receptor antagonist	Roche	NME	-
	RO5028442	-	CNS agent	Roche	NME	NCT
	Carbetocin Nasal Spray	carbetocin	CNS agent	Marina Biotech/Royalty Pharma	NDA + Proprietary Drug Delivery	-
	NNZ-2566 Oral	-	IGF-1 analogue	Neuren Pharmaceuticals	NME	-
Pre-clinical	KM 391	-	CNS agent	Cellceutix	NME	-
	Oxytocin	oxytocin	Oxytocic agent	Shin Nippon Biomedical Laboratories	NDA + Proprietary Drug Delivery	-
	STX110	-	mGluR5 antagonist	Seaside Therapeutics	NME	-

Peptide hormones

Oxytocin, its analogue carbetocin, and the closely related peptide vasopressin are in very early stage testing. Oxytocin and vasopressin are thought to play an important role in the development of social behaviour and cognition, so abnormalities in the neural pathways for oxytocin or vasopressin could account for aspects of autism, including difficulties in social anxiety and relatedness.

“Oxytocin has a decent amount of preliminary evidence to firm the idea that it could be helpful with regards to social relatedness in individuals with and without autism, but it is early on,” says Dr Horrigan.

Roche meanwhile has RG7314, a small molecule antagonist of the V1A vasopressin receptor, in early phase I testing. The company says it has demonstrated that the drug modulates brain emotional networks and is active in the rodent model of autism. It believes the compound has the potential to be the first that treats all three core symptoms of autism - impaired social interaction, impaired communication and repetitive behaviour.

“Evidence from both human and animal studies strongly implicate the V1a receptor in mediating emotional processing and modulating key social deficits that are at the centre of autism spectrum disorders. A V1a antagonist may provide a novel approach to treat these deficits,” they told *EP Vantage* in an emailed response to queries.

Enzyme replacement uncertainties

Fairly advanced in clinical trials are two therapies looking to exploit enzyme deficiency in autism, and the role that this might play in brain functioning. A fair amount of scepticism surrounds this approach, as it is unknown whether there is an explicit role between replacing enzymes and autism.

Kuvan, a treatment for phenylketonuria, which was approved in 2007, is being investigated by The Children's Health Council, supported by the drug's manufacturer, Biomarin. The product is a synthetic version of the enzyme cofactor tetrahydrobiopterin; there is some evidence that people with autism have depleted tetrahydrobiopterin.

A phase II study which completed last year, involving 46 children, failed to meet the primary endpoint although it did show improvements on secondary measures including social interaction and language. Results from a phase II/III open-label extension study are due in mid 2013.

Another enzyme replacement therapy, Curemark's CM-AT, reported improvements in core and non-core symptoms of autism in a phase III trial last year. Research by the New York company has shown that children with autism can have enzyme deficiencies that prevent them from being able to digest proteins; CM-AT increases protein digestion and the availability of essential amino acids. Further data is awaited.

Future directions

Of course even if all of these experimental agents proved successful, the incredibly complex and varied condition that is autism means they would be very unlikely to work in all patients. Fitting the patient to the therapy is one of the major challenges that face researchers, hence the need to be able to describe individual patients more specifically.

One of the main tasks of the consortium that launched last month is to address exactly this challenge. Called European Autism Interventions – A Multicentre Study for Developing New Medications, or EU-AIMS, by the end of the project the group expects to provide novel validated cellular assays, animal models, new analysis techniques and new PET radioligands, as well as new genetic and proteomic biomarkers for patient-segmentation or individual response prediction. It also aims to establish a research network that can then move on to testing investigational treatments in humans.

One company that has already recognised the importance of patient stratification is Autism Therapeutics, which hopes to move into phase III soon with a formulation of fluoxetine, the anti-depressant Prozac.

"There is literature of individuals with autism who were treated with fluoxetine for many years from the ages of 2 to 10, and about 20% of individuals no longer met the diagnostic criteria for autism," says Dr Mike Snape, chief scientific officer of the UK company. "It clearly does have the potential for long term developmental benefit. In the short term, fluoxetine produces a significant reduction of the core symptom of repetitive behaviour of autism."

However Dr Snape says that it is clear from previous studies that not all patients respond. The company is attempting to find a way to identify specific subpopulations of high responders that a phase III trial can be designed to target.

"There will be a way of identifying patients, whether you screen with a scale or a biological measure or whether you just change the way you run the trial. We are at the last stages of an analysis in that direction," he says.

Sub groups

Researchers believe that as autism is broken down into genomic subtypes, sub populations of patients can be identified who have the same mutation or mutations that lie along the same path. This should help focus future pharmaceutical research in autism.

"I know groups that are adopting exactly that approach at the minute, so over the next two to three years that is what is going to have to be tried and presumably if it pays some dividend that's how people will focus their work," says Dr Snape.

"It is truly an interesting and exciting time. The minute anyone gets a major success other companies will follow suit," he says, adding that many big pharma companies are looking for ways into autism.

Much progress has been made in the last decade in autism research. With substantial efforts underway to gain a much deeper understanding of the disease itself, hopes are high for even broader breakthroughs.

"These days we have a much clearer elucidation of the biological underpinning of autism and understanding of which of these proteins have a role in synaptic connectivity and neuronal network performance, and a much better idea about how to effect functioning. The promise there is that we will move beyond just symptom management to disease modification," says Dr Horrigan.

More from Evaluate Vantage

Evaluate HQ
44-(0)20-7377-0800

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754