

NAMI EDUCATION MEETING

SEPTEMBER 11, 2008

DR. JOSE APUD

THE PHARMACOGENOMICS OF COGNITIVE FUNCTION: THE ROLE OF DOPAMINE IN SCHIZOPHRENIA AND INFORMATION PROCESSING

Dr. Apud began with a discussion of cognitive deficiency in schizophrenia.

-not in DSM IV as criteria

-occurs in front of cortex (visible with MRI)

Studies started in 1995, understanding genetic basis for cognitive deficiency

In 2003, the studies on cognitive deficits in schizophrenia were named the #2 most important research by the Journal Science

The focus is on how genes interact to form illness

5 genes were focused on at the start of the study, now expanded to many more

genes combine to form phenotypes or traits

phenotypes combine to form positive/negative symptoms or cog. deficits and environment determine how disease is expressed

Do genotyping then study cognitive testing and cortical --> N-BACK TEST

COMT gene discovered in late 50s, Dr. Axelrod received Nobel Prize

catechol-O-methyl-transferase enzyme destroys dopamine (COMT found in chromosome 22)

Study is based on the idea that if COMT activity is responsible for reduced prefrontal cognition, then the hypothesis is that a COMT inhibitor would prevent dopamine destruction. However, this isn't the whole story. There is an optimal amount of dopamine with regards to cognitive efficiency. Increasing dopamine can increase cognitive efficiency, but there is a point where too much dopamine then starts to result in reduced cognitive efficiency.

The NIMH study looked at the use of the drug tolcapone to treat these cognitive deficiencies. Tolcapone inhibits COMT and is often used to treat people suffering from Parkinson's disease.

Phase 1 of the study involved "normal" volunteers who do NOT suffer from schizophrenia. It was a double-blind study where volunteers participated in a seven day trial. The drug seemed effective in inhibiting COMT vs. placebo with no mood impact. Dr. Apud did NOT discuss other side effects, however, of long term tolcapone use. He also made a comparison to amphetamines in aiding cognitive deficits.

Phase 2 of the study involved volunteers suffering from schizophrenia, however they are still waiting for the results.

There is a specific allele (gene pair) that this COMT inhibitor is targeted at and shown useful for called val-val as opposed to val-met and met-met.

Note, study does not look at schizo-affective...