

Genetic link to rapid weight gain from antipsychotics discovered

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Scientists have discovered two genetic variants associated with the substantial, rapid weight gain occurring in nearly half the patients treated with antipsychotic medications, according to two studies involving the Centre for Addiction and Mental Health (CAMH).

These results could eventually be used to identify which <u>patients</u> have the variations, enabling clinicians to choose strategies to prevent this serious side-effect and offer more personalized treatment.

"Weight gain occurs in up to 40 per cent of patients taking medications called second-generation or atypical antipsychotics, which are used because they're effective in controlling the major symptoms of schizophrenia," says CAMH Scientist Dr. James Kennedy, senior author on the most recent study published online in the *Archives of General Psychiatry*.

This weight gain can lead to obesity, type 2 diabetes, heart problems and a shortened <u>life span</u>.

"Identifying genetic risks leading to these side-effects will help us prescribe more effectively," says Dr. Kennedy, head of the new Tanenbaum Centre for Pharmacogenetics, which is part of CAMH's Campbell Family Mental Health Research Institute. Currently, CAMH screens for two other genetic variations that affect patients' responses to <u>psychiatric medications</u>.



Each study identified a different variation near the melanocortin-4 receptor (MC4R) gene, which is known to be linked to obesity.

In the <u>Archives of General Psychiatry</u> study, people carrying two copies of a variant gained about three times as much weight as those with one or no copies, after six to 12 weeks of treatment with atypical antipsychotics. (The difference was approximately 6 kg versus 2 kg.) The study had four patient groups: two from the U.S., one in Germany and one from a larger European study.

"The weight gain was associated with this <u>genetic variation</u> in all these groups, which included pediatric patients with severe behaviour or mood problems, and patients with schizophrenia experiencing a first episode or who did not respond to other antipsychotic treatments," says CAMH Scientist Dr. Daniel Müller. "The results from our genetic analysis combined with this diverse set of patients provide compelling evidence for the role of this MC4R variant. Our research group has discovered other gene variants associated with antipsychotic-induced weight gain in the past, but this one appears to be the most compelling finding thus far."

Three of the four groups had never previously taken atypical antipsychotics. Different groups were treated with drugs such as olanzapine, risperidone, aripiprazole or quetiapine, and compliance was monitored to ensure the treatment regime was followed. Weight and other metabolic-related measures were taken at the start and during treatment.

A genome-wide association study was conducted on pediatric patients by the study's lead researcher, Dr. Anil Malhotra, at the Zucker Hillside Hospital in Glen Oaks, NY. In this type of study, variations are sought across a person's entire set of genes to identify those associated with a particular trait. The result pointed to the MC4R gene.



This gene's role in antipsychotic-induced weight gain had been identified in a CAMH study published earlier this year in The Pharmacogenomics Journal, involving Drs. Müller and Kennedy, and conducted by PhD student Nabilah Chowdhury. They found a different variation on MC4R that was linked to the side-effect.

For both studies, CAMH researchers did genotyping experiments to identify the single changes to the sequence of the MC4R gene – known as single nucleotide polymorphisms (SNPs) – related to the drug-induced weight gain side-effect.

The MC4R gene encodes a receptor involved in the brain pathways regulating weight, appetite and satiety. "We don't know exactly how the <u>atypical antipsychotics</u> disrupt this pathway, or how this variation affects the receptor," says Dr. Müller. "We need further studies to validate this result and eventually turn this into a clinical application."

Provided by Centre for Addiction and Mental Health

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