Most antidepressants miss key target of clinical depression

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A key brain protein called monoamine oxidase A (MAO-A) - is highly elevated during clinical depression yet is unaffected by treatment with commonly used antidepressants, according to an important study published today in the *Archives of General Psychiatry*. The study has important implications for our understanding of why antidepressants don't always work.

Researchers at the Centre for Addiction and Mental Health (CAMH) used an advanced brain imaging method to measure levels of the brain protein MAO-A. MAO-A digests multiple brain chemicals, including serotonin, that help maintain healthy mood. High MAO-A levels excessively remove these brain chemicals.

Antidepressant medications are the most commonly prescribed treatments in North America, yet 50 per cent of people do not respond adequately to antidepressant treatment. Dr. Jeffrey Meyer the lead investigator explains, "Mismatches between treatment and disease are important for understanding why treatments don't always work. Rather than reversing the problem of MAO-A breaking down several chemicals, most antidepressants only raise serotonin."

Understanding the Problem of a Persistent Illness

Depression ranks as the fourth leading cause of disability and premature death worldwide, according to the World Health Organization. Recurrent illness is a major problem. Even under the most optimal treatment circumstances, recurrence rates for clinical depression are at least 20 per cent over two years.

The new study also focused upon people who had fully recovered from past episodes of clinical depression. Some people who appeared to be in recovery actually had high levels of MAO-A. Those with high levels of MAO-A then had subsequent recurrence of their depressive episodes.

This new idea of high levels of MAO-A lowering brain chemicals (called monoamines), then falling into a clinical depression is consistent with the historical finding that medications which artificially lower monoamines can lead to clinical depression as a side effect. In the 1950's some medications to treat high blood pressure also lowered monoamines and people began to experience depressive episodes. When the medications were removed, people recovered.

From Technology to Treatment

VP of Research Dr. Bruce Pollock highlights the study's use of advanced brain imaging technology. "CAMH has the only positron emission tomography (PET) centre in the world that is dedicated solely to mental health and addiction treatment and research. As a consequence, we were able to develop this new technology to measure MAO-A levels."

Virginia Wilson knows first-hand the struggle it can be to find effective medication. After being diagnosed with depression, eight years passed before a medication was developed that worked well for her. "During this time I was on every type of antidepressant available. This process was enormously frustrating, painful - and took a great toll on my personal life." The current research into depression gives Virginia hope for others who struggle as she did. "Understanding of the biochemical mechanisms behind depression is so important and can really improve the treatments that are available - it can save lives."

Some early antidepressant medications did target MAO-A, but these MAO-A inhibitors fell out of favour in the 1970s due to adverse interactions with certain foods. There have been advances that overcome these problems, but the vast majority of antidepressant development and use has

overlooked the MAO-A target.

According to Dr. Meyer, "Since most antidepressants miss MAO-A, we are counting on the brain to heal this process of making too much MAO-A, and that doesn't always happen. The future is to make treatments that tell the brain to make less MAO-A, even after the antidepressant treatment is over, to create better opportunities for sustained recovery."

Source: Centre for Addiction and Mental Health