Prozac works better when used with other therapies

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Fluoxetine HCl 20mg Capsules (Prozac) Image: Tom Varco / Wikipedia

(Medical Xpress) -- The antidepressant fluoxetine, which is marketed under the name "Prozac," has been approved for use in the US for over two decades, and while some people find it effective, the results vary widely from one person to another, and scientists do not fully understand how it works to change a person's mood over time. Now a study in mice has found that Prozac's benefits are enhanced by the addition of other therapies.

Researchers led by Eero Castrén of the Neuroscience Center at the University of Helsinki in Finland, divided mice into two groups, one of which was given fluoxetine for three weeks. After this period they

taught the mice in both groups to be frightened of a noise by giving them an electric shock every time they heard it. They then gave some of the mice in each group a form of therapy, which the scientists refer to as "extinction training," in which the noise was played but they were no longer given a shock. They were then given a shock five times without the noise being played.

On the final day of the experiments, the researchers played the noise and noted the reactions of the mice and then examined their brains. They found that around 60 percent of the mice that had received neither fluoxetine nor extinction therapy froze when they heard the noise in the final stages of the experiment, while those that had received extinction therapy but no fluoxetine froze at a rate of 40 percent.

Among the mice that received fluoxetine, almost 40 percent of those that had not received extinction therapy froze, while only around 15 percent of those receiving both froze on hearing the noise.

The results of the experiments add weight to earlier research in humans that found that the benefits of the drug are improved if patients receive other psychological therapies. While the study was carried out on mice, the implication is that fluoxetine works by affecting the re-wiring and growth of brain neuons, which would explain why the antidepressant drug does not usually have an immediate impact.

Castrén said the study of differences found in the brains of the mice provides evidence that the drug reactivates a "plastic state in the amygdala," which is usually seen in early postnatal life. Research reported earlier this year also suggested fluoxetine reorganizes brain plasticity.

Extinction therapy given when the brain is in this plastic state may influence connectivity in this region of the brain to produce a long-term

reduction in fear. The therapy helps the drug to work better by guiding the rewiring process.

The research also suggests that many people who are taking the drug but receiving no other psychological therapies might receive no benefit. A 2008 meta-analysis suggested the same thing: that people receiving antidepressants alone often find no benefit unless they are severely depressed. Castrén said the findings of the current research strongly suggest that additional psychotherapies should always be considered for everyone who is prescribed antidepressants such as Prozac.

The study follows research carried out in rats in 2008, in which Castrén and colleagues found that administering fluoxetine could affect the treatment in adults of lazy eye (amblyopia), which is not treatable in adults. In this study fluoxetine also appeared to work by restoring the brain to an earlier, plastic state, and the study also found additional therapies were important.

The paper is published in the December 23rd issue of the journal *Science*. Professor Castrén was a co-founder of the Finnish biopharmaceutical company, Hermo Pharma Ltd., and is currently a member of Hermo's Scientific Advisory Board.

More information: Fear Erasure in Mice Requires Synergy Between Antidepressant Drugs and Extinction Training, *Science* 23 December 2011:
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ABSTRACT
Antidepressant drugs and psychotherapy combined are more effective in treating mood disorders than either treatment alone, but the neurobiological basis of this interaction is unknown. To investigate how antidepressants influence the response of mood-related systems to

behavioral experience, we used a fear-conditioning and extinction paradigm in mice. Combining extinction training with chronic fluoxetine, but neither treatment alone, induced an enduring loss of conditioned fear memory in adult animals. Fluoxetine treatment increased synaptic plasticity, converted the fear memory circuitry to a more immature state, and acted through local brain-derived neurotrophic factor. Fluoxetine-induced plasticity may allow fear erasure by extinction-guided remodeling of the memory circuitry. Thus, the pharmacological effects of antidepressants need to be combined with psychological rehabilitation to reorganize networks rendered more plastic by the drug treatment.