

PTSD Treatment Research Begins to Target Memory Reconsolidation

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MONTREAL – The field of psychiatry is facing a paradigm shift with new research suggesting that medications and psychotherapy may be able to permanently erase the "trauma" from traumatic memories, according to several experts.

The experimental treatment, known as reconsolidation blockade, has been shown to interrupt the neurobiologic process of memory formation.

"We do not erase people's memories," Alain Brunet, Ph.D., said at the annual meeting of the International Society for Traumatic Stress Studies. Dr. Brunet of the department of psychiatry at McGill University, Montreal, is one of the first researchers to report results of the treatment in patients with posttraumatic stress disorder (PTSD).

Rather than erasing an entire memory, reconsolidation blockade appears to erase the emotional reaction to the memory, explained Dr. Roger K. Pitman, director of the posttraumatic stress disorder and psychophysiology laboratory at Massachusetts General Hospital and professor of psychiatry at Harvard Medical School, both in Boston.

The treatment, which normally involves two doses of the beta-blocker propranolol administered between 75 minutes and 2 hours apart, is "pioneering" in that it upends traditional theories about the permanence of memory, said Dr. Charles Marmar, professor and chair of the department of psychiatry and director of the Trauma Research Group at New York University.

Traditional cognitive-behavioral treatment for PTSD is based on the premise that traumatic memory is permanent, and therefore therapy should focus on learning a less emotional response to it, explained Gregory Quirk, Ph.D., professor of psychiatry and director of the laboratory of fear learning at the University of Puerto Rico, San Juan.

This learned response, known as "extinction," changes the body's physiologic, amygdala-based memory, and teaches a cognitive, hippocampal response to the memory instead, he said. "With extinction, you reroute the stimulus so it does not go to the amygdala. You're teaching the brain – it's a learned thing – but the original memory is still in the amygdala somewhere. Extinction does not alter the original memory – we know that from Pavlov." Extinction works well in certain psychiatric conditions, such as phobia, but people with PTSD have hippocampal and prefrontal deficits that frequently cause extinction failure, he said.

In contrast, reconsolidation blockade does not recruit the hippocampus but instead targets the amygdala-dependent reaction. "As a prominent extinction researcher, I am very excited about reconsolidation blockade," Dr. Quirk said. "What's new and exciting about this paradigm shift is that you don't have to struggle your whole life with these terrible memories. You can alter them instead."

The theory behind reconsolidation blockade is that after a traumatic memory is consolidated in the brain, it can be reactivated and exist in a labile, modifiable state. During the labile window, which is believed to last up to 6 hours, propranolol can block protein synthesis involved in amygdala-dependent reconsolidation. "There's no loss of the hippocampal-dependent declarative memory – what's lost is the amygdala-dependent reaction that makes patients sick," Dr. Quirk said. "And that's exactly the thing we want to erase – the part of the memory that makes them ill."

In one study conducted by Dr. Pitman and Dr. Brunet, PTSD patients treated with propranolol after memory reactivation showed a significantly decreased physiologic response when they engaged in script-driven mental imagery of their traumatic event 1 week later, compared with placebo-treated patients ([J. Psychiatr. Res. 2008;42:503-6](#)). But a more recent study by Dr. Pitman's group found improvements in two separate propranolol-treated PTSD groups – one treated after memory reactivation, and one treated without reactivation. This suggests "there may be nonspecific effects of propranolol – which does not support the theory of reconsolidation blockade," Dr. Pitman commented.

Not everyone agrees on the mechanism through which propranolol impacts memory.

Earlier this year, at a meeting of the Canadian Psychiatric Association, Dr. Robert Menzies, a psychiatrist in private practice in Saskatoon, Sask., reported that his PTSD patients experience fragmented memories, emotional distance, and even amnesia after treatment with propranolol. In 31 patients (21 men) treated over a 2-year period, there was a 90% response rate, with the duration of effect continuing up to 2 years. The patients' duration of traumatic memories ranged from 3 months to 38 years.

Dr. Menzies said he did not measure physiologic response after the treatment; he simply asked patients how their traumatic memories have changed. "My patients come back and say they can't remember certain memories at all," he said in an interview.

A drug-free approach to reconsolidation blockade that uses psychotherapy during the labile window to "rewrite" fearful memories also has been reported by researchers at the center for neural science at New York University ([Nature 2010;463:49-53](#)). This approach is basically a variation of traditional extinction training, but because it is done during the window of biochemical lability, it permanently alters the amygdala-dependent memory.

The researchers wrote that they "provide evidence that old fear memories can be updated with nonfearful information provided during the reconsolidation window. As a consequence, fear responses are no longer expressed, an effect that lasted at least a year and was selective only to reactivated memories without affecting others."

Although targeting the traumatic memory is an important part of PTSD therapy, it is not the only part, noted several experts. "We might have to go beyond simply

looking at the traumatic memory piece of things," said Rachel Yehuda, Ph.D., director of the traumatic stress studies division at Mount Sinai School of Medicine and director of mental health at the James J. Peters VA Medical Center, both in New York. "There are other components to PTSD – there's loss, there's grief, there's sadness, there's inability to experience pleasure, there's anger and rage, there's feelings of shame. Those are things that also have to be addressed," she said in an interview.

"This is important work – I am excited about it – but cognitive work also has to happen," added Dr. Thomas C. Neylan, professor of psychiatry (in residence) at the University of California, San Francisco, and director of the posttraumatic stress disorder program at the San Francisco VA Medical Center. "People who have been traumatized often have a whole new set of assumptions about their world and their place in the world that are sometimes erroneous – that the world is overly dangerous, or you can't trust anybody," he said in an interview. "That's cognitive work that has to be done, separate from reconsolidation or extinction work."

Dr. Menzies reported receiving honoraria and other fees from Wyeth. Dr. Brunet, Dr. Neylan, Dr. Pitman, Dr. Quirk, and Dr. Yehuda reported having no relevant financial disclosures. Disclosure information was not available for Dr. Marmar.

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