New study suggests drug affects negative memories

Promising research findings could help patients to 'forget' painful memories.

Researchers from the University of Montreal, QC, Canada, have recently discovered that administration of the drug metyrapone can weaken the strength with which emotional memories are formed in an enduring response. These results could have significant implications for the therapeutic treatment of post-traumatic stress disorder.

The results, published online in the *The Journal of Clinical Endocrinology & Metabolism*, demonstrated that reducing levels of glucocorticoid, using a drug that causes a drop in cortisol levels (a stress hormone involved in memory recall), close to the time of new memory formation can significantly decrease the negative emotions that may be associated with them.

The experiment, conducted at the Centre for Studies on Human Stress of Louis-H Lafontaine Hospital, QC, Canada, required 33 male participants to commit to memory a slide show, which comprised both neutral and negative events. After 3 days the men were then divided into three treatment groups, each receiving either a single (750 mg) or double (1500 mg) dose of metyrapone, or placebo. Memory performance was examined following treatment and again 4 days later, once the drug had been eliminated from their systems.

> "*...reducing levels of glucocorticoid ... close to the time of new memory formation can significantly decrease the negative emotions that may be associated with them.*"

The findings demonstrated that the memories of the men who received the double-dose of metyrapone were significantly impaired when recalling the negative events of the story but showed no such impairment when retrieving the neutral events. Furthermore, this effect persisted once cortisol levels had returned to baseline, demonstrating that this outcome was long lasting and persisted for a considerable length of time after the physiological effects of the drug had subsided.

It has been suggested that during the memory reconsolidation process the reactivated memories are destabilized, during which time they are vulnerable to pharmacological interference. By reducing cortisol levels at approximately the time of memory formation or retrieval, the brain's ability to restabilize the negative memories is impaired. These findings challenge the theory that memories cannot be modified once stored in the brain, supporting previous research, which suggests that memory formation is a dynamic process that can be altered during memory recall.

> "*...the memories of the men who received the double-dose of metyrapone were significantly impaired when recalling the negative events of the story...*"

The implications of these results are promising in terms of the future for clinical treatments for sufferers of post-traumatic stress disorder. Lead Researcher, Marie-France Marin, stated that "our findings may help people deal with traumatic events by offering them the opportunity to 'write-over' the emotional part of their memories during therapy". However, there are still many obstacles that remain to be overcome before such treatment strategies are able to become a reality, "One major hurdle… is the fact that metyrapone is no longer commercially produced," she continued. Further studies on other drugs that decrease cortisol levels will enable us to gain better understanding of the brain mechanisms involved in the modulation of negative memories.

Sources: Marin MF, Hupbach A, Maheu FS, Nader K, Lupien SJ. Metyrapone administration reduces the strength of an emotional memory trace in a long-lasting manner. J. Clin. Endocrinol. Metab. *DOI: 10.1210/jc.2011-0226 (2011) (Epub ahead of print); http://psychcentral.com/news/2011/05/27/drug-metyrapone-to-erase-bad-memories/26532.html; http://jcem.endojournals.org/content/early/2011/05/18/jc.2011–0226.abstract*

in the news...

future medicine part of fsg

US FDA approves fidaxomicin for the treatment of *Clostridium difficile*-associated diarrhea

the US FDA approval of fidaxomicin (DIFICID™) for the treatment of *Clostridium difficile* associated-diarrhea (CDAD) in adults aged 18 years or older, making it the first antibacterial indicated for the disease to be approved by the FDA in nearly 30 years. Fidaxomicin is the first in a new class of antibiotics termed macrocycles that function by rapidly killing *C. difficile* by inhibiting the bacterial enzyme RNA polymerase.

It is estimated that CDAD may affect more than 700,000 people in the USA each year; however, as many cases are believed to be undiagnosed, untreated and underreported, the incidence may in fact be higher. "CDAD is a serious illness that can be incredibly disruptive to patients' lives," Kathleen Mullane, Associate Professor of Medicine, Section of Infectious Diseases and Global Health, University of Chicago (IL, USA) explained to *Future Microbiology*.

The safety and efficacy of fidaxomicin was demonstrated in two randomized, multicenter, double-blinded Phase III trials that included 564 patients with CDAD. In both trials, fidaxomicin was compared with vancomycin, a common antibiotic used to treat CDAD. The results demonstrated that fidaxomicin exhibited noninferior clinical response rates compared with oral vancomycin at the end of treatment, and was superior to vancomycin in sustaining clinical response for 25 days after treatment. A greater number of patients treated with fidaxomicin had a sustained cure 3 weeks after treatment ended versus those patients treated with vancomycin. The most common side effects reported with DIFICID included nausea, vomiting, headache, abdominal pain and diarrhea.

"With previously used treatments up to 30% of patients experienced a clinical recurrence following the completion of initial antibiotic therapy. Now that we have an option like DIFICID that has been proven to produce sustained clinical responses in patients with CDAD, physicians should identify patients who are most at-risk of disease recurrence and consider a treatment approach that may help reduce the risk," pointed out Mullane.

Optimer Pharmaceuticals are currently conducting a microbiological surveillance program in order to identify the potential for decreased susceptibility of *C. difficile* to fidaxomicin, as well as two postmarketing studies in pediatric patients. The company also plans to conduct a randomized clinical trial to evaluate the efficacy of DIFICID in the treatment of patients with multiple CDAD recurrences.

Sources: www.optimerpharma.com; Louie TJ, Miller MA, Mullane KM et al. *Fidaxomicin versus vancomycin for* Clostridium difficile *infection.* N. Engl. J. Med. *364(5), 422–431 (2011).*

Bavarian Nordic announces data from trial of vaccine for patients with locally recurrent prostate cancer

Bavarian Nordic recently announced data from their prostate cancer vaccine trial of PROSTVAC® at the 2011 ASCO Annual Meeting. Researchers from the National Cancer Institute presented data from their trial into the vaccine PSA-TRICOM (PROSTVAC™, BN Immunotherapeutics, CA, USA) for treating patients with locally recurrent prostate cancer.

In the USA in 2008, there were an estimated 186,320 people diagnosed with prostate cancer, of which there were 28,660 deaths. Over the past few years, a new generation of hormonal therapies for the treatment of prostate cancer has emerged and Phase III trials into these therapies have demonstrated a survival advantage in patients refractory to the docetaxel chemotherapy.

A previous Phase II trial of PROSTVAC demonstrated an increased median overall survival in vaccine compared with placebo-treated patients suffering from metastatic castration-resistant prostate cancer, thus prompting the recent study into its use in earlier-stage disease.

The aim of the study presented at the 2011 ASCO meeting was to demonstrate that intraprostatic administration of the PSA-TRICOM vaccine was safe. The study recruited 21 patients with locally recurrent prostate cancer after radiation who received an initial vaccination with subcutaneous recombinant PSA-TRICOM and booster with intraprostatic recombinant fowlpox PSA-TRICOM.

A total of 18 out of the 21 participants showed a stable or improved PSA and 16 of the participants showed a stable or improved PSA doubling time. The results showed that the vaccine was well tolerated with only one participant presenting with fever (a grade 3 adverse event). Based on these results, the authors concluded that administration of PSA-TRICOM is safe, feasible and can generate a substantial immune response.

Anders Hedegaard, President and CEO of Bavarian Nordic is "delighted to again present convincing data that support the use of PROSTVAC in earlier disease settings, suggesting a potential for broader usage of the vaccine in prostate cancer". Phase III trials with PROSTVAC are scheduled to begin later this year.

Sources: Bavarian Nordic Announces Presentation of PROSTVAC® Data at the 2011 ASCO Annual Meeting: www.bavarian-nordic.com/investor/pressreleases/2011–06–01.aspx; Heery CR, Pinto PA, Schlom J et al. *Intraprostatic PSA-TRICOM vaccine administration in patients with locally recurrent prostate cancer.* J. Clin. Oncol. *29(Suppl.) (2011) (Abstract 2530); Shah S, Small E. Emerging biological observations in prostate cancer. Expert Rev.* Anticancer Ther. *10, 89–101 (2010); Madan RA, Aragon-Ching JB, Gulley JL, Dahut WL. From clinical trials to clinical practice: therapeutic cancer vaccines for the treatment of prostate cancer.* Expert Rev. Vaccines *10, 743–753 (2011).*

Adalimumab and methotrexate combination could improve disease control for early-stage rheumatoid arthritis patients

Treatment of early-stage (less than 1 year) rheumatoid arthritis (RA) patients with adalimumab (ADA) plus methotrexate (MTX) has been discovered to allow high levels of disease control in many of the patients in a recent trial. The data from the large trial, which included 1032 patients, was presented at The European League Against Rheumatism 2011 Annual European Congress of Rheumatology (London, UK, 25–28 May 2011).

While treatment with ADA plus MTX had previously been shown to be effective in inducing low disease activity in early, active, MTX-naive RA, it was not known if subsequent removal of ADA would allow maintenance of this response.

Initially, the response to treatment was assessed after 26 weeks with 40 mg of ADA every other week plus MTX versus MTX alone. A total of 44% of patients treated with the combination therapy achieved sustained low disease activity at week 26, versus 24% of those treated with MTX alone. Combination therapy responders were then further randomized to continue or withdraw from treatment with 40 mg ADA every other week. These patients maintained good clinical, radiographic and functional responses through to week 78, including a high proportion achieving higher measures of disease control.

Paul Emery, who was involved in the study commented; "Data from the … study has confirmed previous studies in showing that initial and continued ADA treatment in early RA can ensure that higher levels of disease control can be achieved and maintained. Importantly, results of this first global study assessing biologic-free disease control demonstrate that it may be possible to successfully withdraw anti-TNF therapy in certain patients and maintain long-term positive outcomes, although further studies in this area are needed."

The safety profile of this new drug combination was similar to the profile seen with anti-TNF treatments in the treatment of active RA. Adverse events were evaluated for 850 patients who received ADA: serious adverse events included nine deaths, 39 serious infections, 11 malignancies including five nonmelanoma skin cancers; eight opportunistic infections (excluding TB); with four confirmed as TB.

Sources: www.eurekalert.org/pub_releases/2011–05/elar-tat052411.php; Emery P, Smolen JS , Kavanaugh A et al. *Maintenance of biologic-free disease control in early rheumatoid arthritis patients after induction of low disease activity with adalimumab plus methotrexate. Presented at:* The European League Against Rheumatism 2011 Annual European Congress of Rheumatology. *London, UK, 25–28 May 2011.*

Early study demonstrates promising results for novel injectable back pain solution

A recent study has demonstrated promising early results for the use of microgel particles in the treatment of back pain. Chronic back pain can be caused by degeneration of the intervertebral discs and the research team from the University of Manchester, UK, hope that the work they have conducted can form the basis of a method of permanently replacing the workings of the intervertebral disc. Tony Freemont from the University of Manchester School of Biomedicine described some of the problems caused by degenerating: "Degeneration of the intervertebral disc results in chronic back pain, which costs the country billions of pounds per annum and causes untold misery for sufferers and their families… We have been working for 25 years to identify methods for treating degeneration of the intervertebral disc."

It has been demonstrated previously that an injectable fluid of singly crosslinked, pH-responsive microgel particles can form a gel that is capable of restoring the mechanical properties of models of damaged discs. The Manchester team have now advanced this research; they have covalently linked the microgel particles to form pH-responsive doubly crosslinked microgels.

> *"The Manchester team … have covalently linked the microgel particles to form pH-responsive doubly crosslinked microgels."*

The new microgels were found to have improved mechanical properties compared with the earlier microgels and could undergo significant changes in form for long periods without breaking; these are improvements that were necessary in order for the microgel technology to have the durability that is essential in a medical device.

Commenting on the results of the study, Brian Saunders, the lead researcher of the team, from the University of Manchester School of Materials, said, "Our team has made a breakthrough through innovative materials design that brings the prospect of an injectable gel for treating degeneration of the intervertebral disc a step closer."

Sources: The University of Manchester: www.manchester.ac.uk/aboutus/news; Liu R, Milani AH, Freemont TJ, Saunders BR. Doubly crosslinked pH-responsive microgels prepared by particle interpenetration: swelling and mechanical properties. Soft Matter. *7, 4696–4704 (2011).*

Drug Approvals April 2011 to June 2011.

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Cardiology					
Revatio®	Sildenafil citrate	For the treatment of pediatric patients aged 1 to 17 years old with pulmonary arterial hypertension	EU	Pfizer	May 2011
Oncology					
Afinitor®	Everolimus	For the treatment of progressive neuroendocrine tumors of pancreatic origin in patients with unresectable, locally advanced or metastatic disease	USA	Novartis	May 2011
Potiga™	Ezogabine	As adjunctive treatment for adult patients with partial-onset seizures with or without secondary generalization	USA	Valeant Pharmaceuticals	June 2011
Sutent®	Sunitinib	For the treatment of progressive well-differentiated pancreatic neuroendocrine tumors in patients with unresectable, locally advanced or metastatic disease	USA	Pfizer	May 2011
Zytiga™	Abiraterone acetate	In combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel	USA	Centocor Ortho Biotech	April 2011
Pain management					
Lazanda®	Fentanyl	For the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain	USA	Archimedes Pharma	June 2011
Oxecta™	Oxycodone HCl	For the management of acute and chronic moderate-to-severe pain where the use of an opioid analgesic is appropriate	USA	Pfizer and Acura Pharmaceuticals	June 2011
Rectiv™	Nitroglycerin ointment 0.4%	For the treatment of moderate-to-severe pain associated with chronic anal fissures	USA	ProStrakan Group	June 2011
Infection and immunity					
Dificid™	Fidaxomicin	For the treatment of *Clostridium difficile*-associated diarrhea in adults 18 years of age and older	USA	Optimer Pharmaceuticals	May 2011
Edurant™	Rilpivirine	In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naive adult patients	USA	Tibotec Therapeutics	May 2011
Fluzone®	Influenza virus vaccine	To be used for patients aged 18–64 years of age to protect against influenza subtypes A and B	USA	Sanofi-Pasteur	May 2011
Incivek™	Telaprevir	For use in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment-naive or who have been previously treated, including prior null responders, partial responders and relapsers	USA	Vertex Pharmaceuticals	May 2011
Nulojix®	Belatacept	For the prophylaxis of graft rejection in adult patients receiving a kidney transplant	EU	Bristol-Myers Squibb	June 2011
Victrelis™	Boceprevir	For the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients, 18 years of age and older, with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy	USA	Schering Corporation	May 2011
Other					
Cinryze®	C1 inhibitor (human)	For use in adults and adolescents with hereditary angioedema for routine prevention, preprocedure prevention and acute treatment of angioedema attacks	EU	ViroPharma	June 2011
Eliquis®	Apixaban	For the prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery	EU	Pfizer and Bristol-Myers Squibb	May 2011
Tradjenta™	Linagliptin	An adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus	USA	Boehringer Ingelheim Pharmaceuticals	May 2011