

The ‘Entourage Effect’: How THC can team up with PEA to treat symptoms of Tourette syndrome

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Dronabinol, a synthetic delta-9-tetrahydrocannabinol (THC), is currently approved by the U.S. Food and Drug Administration (FDA) to treat the management of loss of appetite associated with weight loss in AIDS, as well as for the management of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional treatment to relieve these symptoms.

Palmitoylethanolamide (PEA) is a cannabinoid found in our bodies and as a natural food ingredient found in egg yolk, soybeans, and milk. It is marketed as an anti-inflammatory supplement in parts of Europe under the brand names Normast and Pelvilen. In April 2015, Health Canada added PEA to its list of Natural Health Products, a class of health products that includes vitamins, mineral supplements, herbal preparations, traditional and homeopathic medicines, probiotics, and enzymes.

Through an agreement between Therapix Biosciences and Catalent Pharma Solutions, the two cannabinoids, THC and PEA, will be combined to develop the investigational drug THX-TS01 to address the symptoms of Tourette syndrome.

Drug Discovery & Development interviewed Adi Zulloff-Shani, Ph.D, chief technology officer of Therapix Biosciences, via email to find out more about the drug combination, how it works, and where it is in the pipeline.

Drug Discovery & Development: Can you explain the “Entourage Effect” of combining THC and PEA?

Adi Zulloff-Shani: The “Entourage Effect” was first described by Professor Raphael Mechoulam in 1998. Professor Mechoulam is a world-renowned expert on pharmaceutical cannabinoids and chairman of the Therapix Medical Advisory Board. Based on Therapix research and preclinical studies, dronabinol (synthetic THC) and PEA have been shown to work better together than use of THC or PEA alone. PEA is in the endocannabinoid family and is believed to be a pain reliever and anti-inflammatory agent. Combining PEA with dronabinol may stimulate cannabinoid receptors, inhibit metabolic degradation, and thus increase uptake of THC. The overall benefits of the THC/PEA combination are considered to be an increase in efficiency of oral administration, enabling a decrease in dosage and lowering of side effects and adverse events.

The major limitations of both cannabis and dronabinol, when administered individually, involve the adverse psychoactive side effects they induce in higher doses. The psychoactive effects of delta-9-THC (dronabinol) are primarily mediated by its activation of CB1 G-protein coupled receptors. In order to harness the therapeutic potential of THC for patients with Tourette syndrome, there is a need to reduce the accompanied adverse effects. The basic idea of the “Entourage Effect” is that cannabinoids possess synergy and affect the body in a mechanism similar to the body’s own endocannabinoid system.

PEA is a lipid messenger known to mimic several endocannabinoid-driven activities, although it does not bind the classical CB receptors; PEA may enhance the physiological activity of THC by potentiating its affinity for a receptor and by inhibiting THC metabolic degradation. PEA may also indirectly stimulate the effects of both cannabinoids—or endocannabinoids—by its role as an agonist of the transient receptor potential vanilloid type 1 (TRPV1), peroxisome proliferator-activated receptor- α (PPAR- α), and the cannabinoid receptors.

Drug Discovery & Development: Where is THX-TS01 in the clinical pipeline?

Adi Zuloff-Shani: Therapix has nearly completed a Phase IIa clinical study at Yale University to assess the potential for its investigatory compound THX-TS01 for Tourette syndrome. Top-line results from the Phase IIa study are expected in early 2018; Therapix will proceed accordingly from there.

The Yale study is a single-arm, open-label study in which subjects receive once-daily oral treatment of the investigational drug for 12 weeks. The objective of the clinical study is to prove the safety, tolerability and efficacy of the combination of dronabinol and PEA in adult patients with Tourette syndrome. The primary efficacy endpoint is the change from baseline to end of 12 weeks treatment in the Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS), which is a clinical rating instrument designed to provide an evaluation of tic severity. Secondary efficacy endpoints include demonstrating the safety and tolerability of the dronabinol and PEA combination and to evaluate its benefit on premonitory urges, quality of life, disease severity and comorbidities including ADHD, OCD, depression, and anxiety.

Drug Discovery & Development: What are the benefits of this combination?

Adi Zuloff-Shani: Therapix is studying the combination of dronabinol (synthetic THC) and PEA in THX-TS01 in hopes of addressing the symptoms of Tourette syndrome, which include motor and vocal tics that can be disabling and associated with hyperactivity, anger control problems, sleep disorders, and obsessive-compulsive behavior.

Biological evidence suggests that the endocannabinoid system may contribute to the pathophysiology of Tourette syndrome, as it plays an important role in motor inhibition. The highest density of central cannabinoid (CB1) receptors is located in the frontal cortex, basal ganglia, cerebellum, hypothalamus, hippocampus and nucleus accumbens, all areas that have been implicated in Tourette syndrome pathology.

Endocannabinoids bind to CB1 receptors and affect the activity of monoamines (*e.g.*, dopamine), excitatory (glutamate) and inhibitory (GABA, glycine) transmitters. There are several lines of evidence suggesting a complex interaction between the CB1 receptor and the dopaminergic systems.

It has been demonstrated that treatment with dronabinol increases intracortical inhibition. Researchers have suggested that dronabinol might counteract deficits of intracortical inhibition by modulating the release of several neurotransmitters including dopamine.

Many TS patients have reported to their physicians that smoking marijuana helps reduce tic severity. Also, anecdotal evidence suggests that cannabis addresses many comorbidities associated with Tourette syndrome, such as anxiety, OCD and depression. For example, in the 1990s, Tourette syndrome patients reported a reduction or complete remission of tics and an amelioration of premonitory urges, OCD, and ADHD after use of marijuana—without significant adverse events (SAE).

In 2002, in a randomized, double-blind, placebo-controlled, crossover single-dose trial, 12 adult patients were treated with up to 10 mg of dronabinol and demonstrated the following: 10 of the 12 patients experienced a global improvement after treatment (mean of +35%), whereas only

three of the 12 experienced a muted improvement after placebo (mean of +7%). Higher doses (7.5 or 10.0 mgs) appeared to have a more dramatic effect (n=8). No SAEs occurred.

In 2003, another randomized, double-blind, parallel group, placebo-controlled study was conducted with dronabinol target dosage 10 mg/day over six weeks, including 24 adult patients with Tourette syndrome. A significant difference was found between the dronabinol and placebo groups. No SAEs occurred, including no decline in cognition and neuropsychological performance.

Drug Discovery & Development: How will the treatment be delivered?

Adi Zuloff-Shani: Therapix has entered into an exclusive agreement with Catalent Pharma Solutions, the leading global provider of advanced delivery technologies and development solutions for drugs, biologics and consumer health products, for the formulation, development and clinical manufacturing of THX-TS01. Catalent will develop THX-140 in softgel form in support of Therapix’s clinical development program and in accordance with current good manufacturing practice (cGMP). The formulation, development, analytical and cGMP manufacturing activities will be conducted at Catalent’s primary softgel development and manufacturing facility in St. Petersburg, Florida.

Drug Discovery & Development: Can you discuss other delivery technologies that Therapix is developing?

Adi Zuloff-Shani: Therapix has also created a unique and proprietary drug development platform—the “Ultra Low-Dose”—for its development of THX-ULD01 for the treatment of mild cognitive impairment (MCI). Therapix has compelling preclinical animal data demonstrating that ultra-low dose dronabinol improves cognitive abilities. Recent studies have found that an ultra-low dose of THC protects the brain from long-term cognitive impairment that may be caused by lack of oxygen supply, seizures or use of drugs. Studies also suggest that ultra-low doses of THC cause animals to improve performance in behavioral tests that measure learning and memory.

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