Use of Cotinine as a Treatment for PTSD

Cotinine enhances the extinction of contextual fear memory and reduces PTSD-related anxiety

Key Features
- Helps with fear extinction thereby reducing ongoing reactions to trauma events resulting in PTSD anxiety and depression
- Good safety profile in humans including children and infants.
- Good bioavailability and half-life (19-24 h in plasma)
- Available in oral, intravenous, and intranasal formulations
- Faster acting than current SSRIs
- No treatment-associated memory problems, like SSRIs

Technology
Post-traumatic stress disorder (PTSD) is an anxiety disorder that occurs after trauma and is characterized by anxiety, depression, aggressive behavior, fear, and sleep disruption. Researchers at the VA have discovered the use of cotinine as an effective treatment for PTSD through fear memory extinction. In a fear conditioning mouse model for inducing PTSD symptoms, mice treated with cotinine demonstrated enhanced extinction of contextualized fear, a decrease in their symptoms of anxiety, and enhanced the stability of contextual fear memories. It is believed that the mechanism of action is through decreases in neuroinflammation as well as stimulation of extracellular signal-regulated kinase activity in the hippocampus during fear extinction, which is regarded as a key molecular event during fear extinction process. The inventors’ data suggest that cotinine is a positive allosteric modulator of α7nAChRs, which play an important role in cognitive processes. The inability to extinguish traumatic memories is a key feature of PTSD and causes patients to continue to re-experience previous trauma and the triggered side effects such as anxiety, depression, and aggression. Because cotinine has been found to help with fear extinction, it could be used as a safe, once-daily therapy to help reduce ongoing reactions to trauma experienced by patients with PTSD.

Competitive Advantage
PTSD is currently managed using general anti-depressants and cognition therapy. Cotinine offers the following advantages:
- Help ease trauma memories though fear extinction and enhanced stability of contextual fear memory. Anti-depressants and therapy do not treat fear extinction.
- Decreased anxiety, depression, and aggression.
- Good safety profile in humans: several studies have investigated the pharmacokinetic profiles and physiologic effects of cotinine intravenously or orally administered.
- Good bioavailability, long half-life in plasma (19-24 hours). Likely a once a day dosing regimen.
- Can be delivered intranasally which can be used for faster delivery to the brain.
- Faster acting than currently available PTSD drugs. Unlikely to have “worse before it gets better” treatment symptoms.
- Does not induce memory problems like serotonin reuptake inhibitors.

Partnership
The VA is looking for a partner to further the development of this drug through a license or a collaborative agreement.

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Stage of Development
- PK/safety profiles of IV/oral cotinine administered in humans are known
- Initiated FDA approval of IND submission; Phase 2 ready

Patent Status
US 9,801,865
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PCT/IB2018/00306

Related publications:
Zeitlin, 2012
Perez-Urrutia N, 2017
Echeverria, V 2014

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