Fumarate prodrugs to treat or prevent schizophrenia and other psychotic disorders

*Technology #19-0155*

**Background**

The incidence of psychotic disorders is increasing worldwide. Schizophrenia is a psychotic disorder that can become chronic, severe, and is often socially and occupationally disabling. Antipsychotic drugs are currently used to treat schizophrenia and other brain disorders like depression, dementia, and bipolar disorder. These drugs don't work for approximately one third of schizophrenia patients, while the remaining two thirds of patients often have reduced schizophrenic hallucinations. However, many other symptoms like lack of motivation continue. This has created an urgent need to develop new treatment options for schizophrenia and other psychotic disorders.

**Technical Overview**
Researchers in the Department of Psychiatry and the Renaissance Computing Institute at the University of North Carolina – Chapel Hill have developed a novel therapeutic method for psychotic disorder patients using a fumarate prodrug. Prodrugs of fumarates are currently approved by the Food and Drug Administration (FDA) to treat a variety of diseases associated with inflammation. These drugs reduce oxidative stress and are beneficial in diseases involving immunological, autoimmune, and/or inflammatory processes, which would include psychotic disorders, due to the association with increased inflammation. The leading pathogenic model of schizophrenia involves hypofunction of the N-methyl-D-aspartate receptor (NMDAR). The underlying mechanism of NMDAR hypofunction is not well known. However, dysregulated redox homeostasis and inflammation are present in several animal models of NMDAR hypofunction. Intracellular glutathione (GSH) levels and NMDAR demands are matched to control intracellular redox status. NMDAR hypofunction results when oxidative stress exceeds GSH redox capacity, suggesting that dysregulation of the glutathione-mediated redox signaling contributes to the development of psychosis. GSH levels are elevated by binding of the nuclear factor erythroid 2-related factor 2 (NRF2) transcription factor to an antioxidant response element (ARE). Interestingly, the NRF2-ARE pathway is activated in the presence of fumaric acid esters and other prodrugs of fumarates. Collectively, this demonstrates fumarate prodrugs are a novel therapeutic method for treating or preventing
psychotic disorders, including schizophrenia.

**Benefits**

- Fumarate derivatives are approved by the FDA, providing accelerated path to use.
- Provides a solution for the global need of new psychotic disorder treatments, such as schizophrenia.
- Novel method of treatment for psychiatric disorders, such as PTSD or drug addiction.

**Applications**

Treatment or prevention of psychotic or psychiatric disorders with prodrugs of fumarates.

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