

Cannabis-based medication may help to treat tics in Tourette's Syndrome

Dr Kirsten Müller-Vahl is a Professor of Psychiatry who specialises in general psychiatry and neurology at the Hannover Medical School in Germany. Her research focuses on examining the underlying neurobiological mechanisms in Tourette's Syndrome.

Tourette's syndrome (TS) is a neurological-psychiatric disorder characterised by motor and vocal tics. Motor tics are abrupt and repetitive movements and are among the most prevalent symptoms of the disease, often starting during childhood between ages six to eight. In addition, TS patients often suffer from behavioural deficits such as ADHD, obsessive-compulsive behaviour, anxiety and depression, as well as rage attacks and self-injurious behaviour.

TOURETTE'S & THERAPEUTICS

Therapeutic approaches to treat tics have largely focused on behavioural therapy, such as Habit Reversal Training, and psychotropic drugs, predominantly neuroleptics. However, these have proved challenging. On the one hand, there are not enough qualified therapists to administrate Habit Reversal Training, so only a small number of patients are offered training places. In addition, neuroleptics such as risperidon, pimozide and aripiprazole, as well as other dopamine blockers, yield unsatisfactory results and come with serious side effects such as sedation, weight gain, and sexual dysfunction.

This has led Dr Kirsten Müller-Vahl of the Hannover Medical School to examine alternative treatment approaches, including cannabis-based pharmaceuticals.

NEUROBIOLOGICAL FEATURES OF TS

Though the exact neurobiological mechanisms of TS are not fully known, studies have shown that it involves a network spanning the frontal areas and the basal ganglia areas typically involved in the planning, control and initiation of movement. Whilst some have suggested that TS may be due to increased activity of striatal neurons in the basal ganglia, others have proposed that frontal lobe dysfunction may be to blame in regulating basal ganglia function. In addition, neurotransmitters including dopamine, glutamate, and GABA may also be playing a vital role in TS.

CANNABIS TO THE RESCUE?

Given the unsatisfactory nature of current treatment options, many TS patients have sought alternative therapies. Among them, cannabis was previously found to be successful in weakening the occurrence of tics in TS. That is why researchers, including Dr Müller-Vahl, have spent years examining the effects of cannabis-based medications

Dr Müller-Vahl has spent years examining the effects of cannabis-based medications on the symptoms of Tourette's syndrome





as well as its active ingredient delta-9-tetrahydrocannabinol (THC).

In addition to THC, cannabis contains over 100 cannabinoids as well as plant extracts. However, the dominant effect of THC can be attributed to cannabinoid CB1 receptors—largely located in brain areas associated with movement control. As such, a higher density of CB1 receptors can be found in the basal ganglia. Furthermore, it has been demonstrated that the endocannabinoid system (ECS) has a modulating function on the brain's neurotransmitter network. This has led some researchers to conclude that TS could be a dysfunction of the ECS.

CLINICAL TRIALS

In 1998, Dr Müller-Vahl conducted a clinical survey among 64 TS patients of whom 17 had reportedly consumed cannabis. Approximately 82% of these patients reported a reduction in symptoms, and subsequent studies of single cases confirmed that administration of 10mg THC led to an 80% reduction in tics and a simultaneous increase in the attention of patients. A randomised, placebo-controlled six-week trial of up to 10mg THC per day confirmed the previous findings.

However, until more recently, clinical trials into medical marijuana use were largely

The TS-EUROTRAIN training network has the potential to aid in the discovery of new pharmaceutical interventions and ultimately help Tourette's patients improve their quality of life

Q&A

The TS-EUROTRAIN study sounds fascinating. What are you looking at as part of this collaborative effort?

TS-EUROTRAIN (FP7-PEOPLE-2012-ITN, Grant Agr.No.316978) is a Marie Curie Initial Training Network (<http://ts-eurotrain.eu>) that aims to elucidate the complex aetiology of the onset and clinical course of TS, investigate the neurobiological underpinnings of TS and related disorders, translate research findings into clinical applications and establish a pan-European infrastructure for the study of TS. This includes the challenges of **(i)** assembling a large genetic database for the evaluation of the genetic architecture with high statistical power; **(ii)** exploring the role of gene-environment interactions including the effects of epigenetic phenomena; **(iii)** employing endophenotype-based approaches to understand the shared aetiology between TS, OCD and ADHD; **(iv)** establishing a developmental animal model for TS; **(v)** gaining new insights into the neurobiological mechanisms of TS via cross-sectional and longitudinal neuroimaging studies; and **(vi)** partaking in outreach activities including the dissemination of scientific knowledge about TS to the public.

unavailable in Germany due to legal restrictions. In what is hopefully the beginning of more clinical research into this field, a large study of Nabiximols was approved in 2016. Run by the Hannover Medical School, Dr Müller-Vahl will be the principal investigator of a team examining the clinical effects and side effects of Nabiximols – a cannabis-based medication with the cannabinoids THC and cannabidiol (CBD) (CANNATICS). At the same time, a second study of similar design will investigate the efficacy of THC in combination with Palmitoylethanolamide (PEA) in adults presenting with TS. Dr Müller-Vahl is hopeful that this could offer comparative insights into the effectiveness and tolerance of THC plus CBD, as well as THC with PEA. A third study will investigate how an inhibitor of the hydrolysis of the endocannabinoid 2-AG, ABX-1431, affects the tic symptoms of adults with TS.

21 partners, from academia and industry, and 12 PhD candidates, pursue the project. Our ultimate aims are to elucidate the complex aetiology and neurobiological underpinnings of TS, translate research findings into clinical applications, and establish a pan-European infrastructure for the study of TS and associated disorders.

Have there been any trials of THC treatment in combination with behavioural therapy? If so, what was the outcome?

No, however, that would be very interesting.

How effective is surgical intervention in the treatment of TS?

There is indeed some evidence that deep brain stimulation is effective in the treatment of TS. However, there is a debate on how and when and in which patients to use it. Most experts think that it should be used only in severely affected, otherwise treatment-resistant patients.

How did you get involved in this field of research?

I started my medical practice as a neurologist and worked together with a very experienced neurologist and movement disorder specialist.

EFFECTS AND SIDE EFFECTS

So far, available clinical studies have not found any detrimental effects of THC as part of neuropsychological testing. While cannabis may lead to cognitive impairment in healthy individuals, it seems to have a different effect on TS patients, where it has been shown to boost concentration and visual perception. Though cannabinoids are generally well-tolerated over time, initial psychological effects such as euphoria, relaxation, heightened sensory and emotional perception, as well as disorientation, have been reported.

ON TO BETTER TREATMENT SOLUTIONS

As part of her efforts to understand the neurological basis of TS and develop viable treatment strategies, Dr Müller-Vahl heads the study group "Tourette Syndrome" in Hannover. In addition, she is second chairwoman of the "International Association for Cannabinoid Medicines"

He was interested in tics and so I learnt a lot about movement disorders in general and tics in particular. At that time, very few medical doctors were interested in TS and offered treatment and psychoeducation to patients. Thus, our outpatient clinic grew up quickly and it was quite easy to find patients who were interested in participating in clinical trials. After a substantial number of patients reported beneficial effects of cannabis, I became more and more interested in this area – in particular against the background that all other treatment options have significant drawbacks.

Which therapeutic strategies are safe to use in children?

In children we use the same treatments: Habit Reversal Training and neuroleptics such as tiapride, aripiprazole and risperidone. We only use cannabinoids in otherwise treatment-resistant, severely affected individual cases and normally not before the age of 16 to 17 years. However, with increasing evidence suggesting that cannabis-based medications are effective and safe in the treatment of tics, we will consider using these substances in younger adolescents.

as well as a board member of the "German Association for Cannabinoid Medicines". Her work has contributed in large to a draft bill by the German federal government to include cannabis as an officially recognised pharmaceutical option.

Additionally, she is part of a large-scale, interdisciplinary investigation into the genetic and pathophysiological factors underlying TS and its associated conditions. The EU-funded Marie Curie initial training network TS-EUROTRAIN is being run across 15 academic partners as well as industry and 12 PhD students. Researchers are hopeful that the project will offer a more rounded picture of the biological aspects of the disease. This has the potential to aid in the discovery of new pharmaceutical interventions and ultimately help TS patients improve their quality of life.

Detail

RESEARCH OBJECTIVES

Dr Müller-Vahl's research focuses on Tourette's syndrome, and has been particularly interested in determining the neurobiological underpinning mechanisms involved in the disorder. Her research has also determined that cannabinoids, found in cannabis, can have preventative effects on TS patients and the tics they suffer from.

FUNDING

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- Kröner-Fresenius foundation
- Pharmaceutical companies

COLLABORATORS

The CANNA-Tics study will be performed at the Clinical Research Center CRC Hannover, Director Prof C. Schindler. Five other centres will be involved in the study.

BIO

Prof Kirsten Müller-Vahl is a Professor of Psychiatry and a specialist in general psychiatry and neurology. Since 1995, she has been the head of the largest specialist Tourette's clinic in Germany and is involved in several national, European and international scientific projects related to Tourette's syndrome.

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