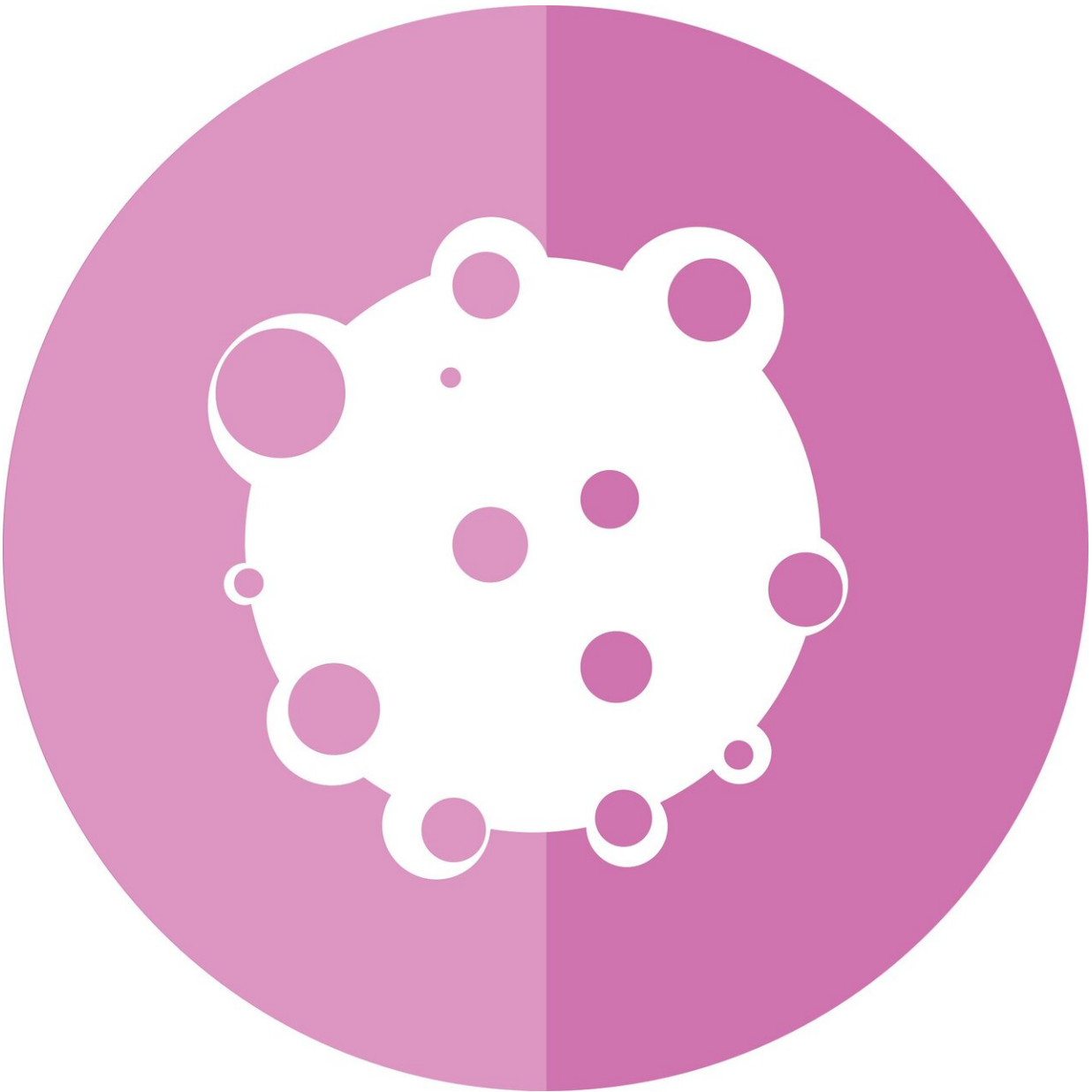


Metformin trial dramatically reduces seizures in tuberous sclerosis

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A team of researchers led by UCL Great Ormond Street Institute of Child Health (ICH) and Great Ormond Street Hospital (GOSH) has found that metformin—a drug commonly used to treat Type 2 diabetes—can successfully reduce symptoms associated with tuberous sclerosis complex (TSC), including reduction in the frequency of seizures and the size of brain tumors.

The study, which also included teams from Royal United Hospitals Bath NHS Foundation Trust (RUH) and University Hospitals Bristol and Weston NHS Foundation Trust, recruited 51 patients with TSC who were randomly assigned a placebo or [metformin](#) for one year on a dose similar to that given for Type 2 diabetes.

TSC is a [genetic disorder](#) characterized by the development of benign tumors due to loss of inhibitory regulation of the mTOR (mechanistic Target of Rapamycin) intracellular growth pathway. As a result, people with the condition may develop tumors (hamartomas) throughout the body that can affect the heart, kidneys, brain, skin and nails. Although some with the condition may experience few issues, for others it can be disfiguring or even have life threatening complications. As tumors can form in the brain, 75% of people with TSC will have epilepsy, which can lead to daily seizures.

Throughout the study, the research team wanted to see if metformin, which inhibits the mTOR (cellular growth) pathway, could limit the tumor growth and epilepsy associated with TSC. All patients involved in the study had tumors in the kidney known as renal angiomyolipomas (AML). Of the 51 who took part, 27 patients had tumors in the brain called subependymal giant cell astrocytomas (SEGA) and 21 of them

were under assessment for seizure frequency.

Over the course of the year, the team found a 21% reduction in the size of brain tumors of those who were given metformin, compared to a 3% increase in tumor volume for those taking the placebo. Patients with epilepsy and taking metformin saw a 44% drop in the frequency of their seizures, compared to a drop of only 3% for those on the placebo.

Metformin has been gaining attention in [cancer research](#), with large population studies starting to show reduced rates of cancers in those regularly taking it. Metformin is also used to treat polycystic ovary syndrome.

Finbar O'Callaghan, professor of pediatric neuroscience at ICH and consultant pediatric neurologist at Great Ormond Street Hospital for Children NHS Foundation Trust and lead investigator of the study said: "This is the first time a cheap, readily available, safe drug has been found to improve the symptoms of TSC. And we found metformin to be even more effective in treating young people. Some patients, who were having multiple seizures a day or week became seizure free after 12 months of treatment, while others are having far fewer seizures than before. We're excited by what this could mean for the day-to day management of tuberous sclerosis patients."

After 12 months of studying patients involved in the trial, the only area where researchers saw no significant difference between the metformin and placebo group was in the reduction of kidney tumors. Previous animal studies have also indicated limited effects of metformin in the kidney.

"Unfortunately, the dose of metformin we used wasn't able to treat the kidney tumors our patients have, but we are looking into whether changing the dose could make a difference. We remain optimistic about

the impact we've seen on the treatment of brain tumors and epileptic seizures, and believe this is a very promising step forward in improving quality of life for the children and adults living with TSC," said Prof. O'Callaghan.

It is estimated that between 3,700—11,000 people in the UK live with TSC. There is currently no cure, and only its symptoms can be treated with regular monitoring by a specialist doctor. Although the tumors in TSC patients are benign, the symptoms are not, and current treatments are not only expensive but have toxic side effects as they are immunosuppressants. That's why studies like this are significant.

GOSH treats 150 children with this condition and works closely with the two other hospitals with specialist TSC services that enrolled patients. The study team run specialist TS clinics at Great Ormond Street Hospital, the Royal United Hospital in Bath, and Bristol Royal Hospital for Children. These clinics follow up the largest number of TSC patients in the UK.

Speaking about future research in the area this Prof. O'Callaghan said: "Next steps for this work will be to conduct further large-scale trials in Tuberous sclerosis patients to determine the best doses to use and to demonstrate that the effect we have seen is repeatable in a larger population of patients."

More information: Sam Amin et al, The metformin in tuberous sclerosis (MiTS) study: A randomised double-blind placebo-controlled trial, *EClinicalMedicine* (2021). [DOI: 10.1016/j.eclinm.2020.100715](https://doi.org/10.1016/j.eclinm.2020.100715)

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