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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2020_riemer.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2020_schmidt_0.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00210782 - CAPSS-272 - A Double-blind Trial Comparing the Efficacy, Tolerability and Safety of Monotherapy Topiramate Versus Phenytoin in Subjects With Seizures Indicative of New Onset Epilepsy
2. NCT00210535 - TOPMATMIG3006 - A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Topiramate for the Prophylaxis of Migraine in Pediatric Subjects 12 to 17 Years of Age
3. NCT00237289 - CR002653 (CAPSS-168) - Topiramate Versus Placebo as add-on Treatment in Patients With Bipolar Disorder in the Outpatient Setting
4. NCT00240721 - CR002248 (TOPMAT-PDMD-005) - A Randomized, Double-Blind, Multicenter, Placebo-Controlled 12-Week Study Of The Safety And Efficacy Of Two Doses Of Topiramate For The Treatment Of Acute Manic Or Mixed Episodes In Subjects With Bipolar I Disorder With An Optional Open-Label Extension

5. NCT00236509 - TOPMAT-MIGR-001 - A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of Topiramate in the Prophylaxis of Migraine
6. NCT00231595 - TOPMAT-MIGR-002 - A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of Topiramate in the Prophylaxis of Migraine
7. NCT00236561 - TOPMAT-MIGR-003 - A Randomized, Double-Blind, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of Two Doses of Topiramate Compared to Placebo and Propranolol in the Prophylaxis of Migraine
8. NCT00216606 - TOPMAT-MIG-201 - A Randomized Double-Blind Placebo Controlled Trial to Investigate the Efficacy and Tolerability of Topiramate in the Prophylaxis of Chronic Migraine
9. NCT00212810 - CAPSS-381 (INTREPID) - TOPAMAX (Topiramate) Intervention to Prevent Transformation of Episodic Migraine: The Topiramate INTREPID Study
10. NCT00210912 - CAPSS-276 - A Comparison of the Efficacy and Safety of Topiramate Versus Placebo for the Prophylaxis of Chronic Migraine
11. NCT00037674 - TOPMAT-PDMD-004 - A Randomized, Double-Blind, Multicenter, Placebo-Controlled 12-Week Study of the Safety and Efficacy of Two Doses of Topiramate for the Treatment of Acute Manic or Mixed Episodes in Patients With Bipolar I Disorder With an Optional Open-Label Extension
12. NCT00035230 - TOPMAT-PDMD-008 - A Randomized, Double-Blind, Multicenter, Placebo-Controlled 12-Week Study of the Safety and Efficacy of Topiramate in Patients With Acute Manic or Mixed Episodes of Bipolar I Disorder With an Optional Open-Label Extension
13. TOPMAT-PDMD-006 - A Randomized, Double-Blind, Multicenter, Placebo-Controlled, 21-Day Study of the Safety and Efficacy of Topiramate for the Treatment of Acute Manic or Mixed Episodes in Subjects With Bipolar I Disorder With an Optional Open-Label Extension
14. YP - A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children
15. NCT00113815 - TOPMATPEP3001 - A Randomized, Double-Blind, Placebo-Controlled, Fixed Dose-Ranging Study to Assess the Safety, Tolerability, and Efficacy of Topiramate Oral Liquid and Sprinkle Formulations as an Adjunct to Concurrent Anticonvulsant Therapy for Infants (1-24 Months of Age) With Refractory Partial-Onset Seizures
16. NCT00236639 - TOPMAT-OBES-002 - A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group, Dose-Response Study to Assess the Efficacy and Safety of Topiramate in the Treatment of Patients With Obesity
17. NCT00236600 - TOPMAT-OBES-004 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Efficacy and Safety of Topiramate in Weight Loss Maintenance in Obese Patients Following Participation in an Intensive, Non-Pharmacologic Weight Loss Program
18. NCT00231530 - TOPMAT-OBDM-003 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety and Efficacy of Topiramate in the Treatment of Obese, Type 2 Diabetic Patients on a Controlled Diet
19. NCT00236665 - TOPMAT-OBHT-001 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of the Efficacy and Safety of Topiramate in the Treatment of Obese Patients With Mild to Moderate Essential Hypertension
20. NCT00210808 - CAPSS-220 - A Multicenter, Randomized, Double-blind, Placebo-controlled, Flexible-dose Study to Assess the Safety and Efficacy of Topiramate in the Treatment of Moderate to Severe Binge-eating Disorder Associated With Obesity
21. NCT00237302 - CAPSS-122 - A Comparison of the Efficacy and Safety of Topiramate Versus Placebo for the Prophylaxis of Migraine in Pediatric Subjects
22. NCT00210821 - CAPSS-277 - A Comparison of Topiramate Versus Amitriptyline in Migraine Prophylaxis
23. NCT00210496 - CAPSS-334 - Efficacy of AXERT (Almotriptan Malate) in the Acute Treatment of Migraine: A Pilot Study of the Potential Impact of Preventive Therapy With TOPAMAX (Topiramate)
24. NCT00231556 - TOPMAT-EPMN-106 - A Randomized, Double-Blind, Parallel-Group, Monotherapy Study to Compare the Safety and Efficacy of Two Doses of Topiramate in the Treatment of Newly Diagnosed or Recurrent Epilepsy
25. NCT00231647 - TOPMAT-OBD-202 - A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study to Assess the Efficacy and Safety of Topiramate OROS Controlled-Release in the Treatment of Obese, Type 2 Diabetic Subjects Managed With Diet or Metformin
26. NCT00231621 - TOPMAT-OBDL-001 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, One-year Study of the Efficacy and Safety of Topiramate in the Treatment of Obese Subjects With Dyslipidemia
27. NCT00236626 - TOPMAT-OBDM-001 - A 9 Month, Double-Blind, Placebo-Controlled Study With a Blinded Crossover Transition to Open-Label Extension, Evaluating the Safety and Effectiveness of Topiramate on

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Insulin Sensitivity in Overweight or Obese Type 2 Diabetes Patients
28. NCT00231660 - TOPMAT-OBDM-002 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of Topiramate in the Treatment of Obese, Type 2 Diabetic Patients Treated With Metformin
29. NCT00231634 - TOPMAT-OBDM-004 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of the Efficacy and Safety of Topiramate in the Treatment of Obese, Type 2 Diabetic Patients Inadequately Controlled on Sulfonylurea Therapy
30. NCT00231608 - TOPMAT-OBMA-001 - The Safety and Efficacy of Topiramate in Male Patients With Abdominal Obesity: A 6-Month Double-Blind, Randomized, Placebo-Controlled Study With a 6-Month Open-Label Extension
31. NCT00035802 - TOPMAT-PDMD-009 - A Randomized, Double-Blind, Multicenter, Placebo-Controlled 4-Week Study of the Safety and Efficacy of Topiramate in Adolescents With Acute Manic or Mixed Episodes of Bipolar I Disorder, With an Optional 6-Month Open-Label Extension
32. NCT00236418 - YTCE - Topiramate Clinical Trial in Primary Generalized Tonic-Clonic Seizures
33. NCT00230698 - TOPMAT-EPMN-104 - Topiramate (RWJ-17021-000) Monotherapy Clinical Trial in Patients With Recently Diagnosed Partial-Onset Seizures
34. NCT00253175 - CAPSS-155 - A Comparison Of The Efficacy And Safety Of Topamax® (Topiramate) Tablets Versus Placebo For The Prophylaxis Of Migraine
35. NCT00236704 - YTC - Topiramate Clinical Trial in Primary Generalized Tonic-Clonic Seizures
36. NCT00236756 - YL - A Double-Blind Trial of Topiramate in Subjects With Lennox-Gastaut Syndrome.
37. NCT00236860 - Y3 (CC2604-C-103) - Double-Blind Parallel Comparison of Topiramate 400 mg Twice Daily to Placebo in Patients With Refractory Partial Epilepsy
38. NCT00210925 - CAPSS-278 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Flexible Dose Study to Assess the Safety and Efficacy of Topiramate in the Treatment of Alcohol Dependence

What type of data are you looking for?: Full CSR

Research Proposal

Project Title

Psychiatric Symptoms as Adverse Events of Topiramate Therapy: Systematic Review and Meta-Analysis

Narrative Summary:

Topiramate which is mainly used to treat epilepsy and to prevent migraine, has frequently been associated with psychiatric adverse events such as somnolence, anorexia and concentration problems. Yet, it is frequently prescribed for a broad range of issues, including weight loss and neuropathia that are not at all linked with its main uses. The aim of this study is to systematically review studies employing Topiramate to analyse whether or not there there are certain risk factors such as age or disorder being treated that predict a higher suspectability for psychiatric adverse events. Adverse events of interest include but are not limited to somnolence, anorexia and concentration problems.

Scientific Abstract:

Background: Topiramate (TPM) is used in many contexts & has many off-label uses. This is despite the fact that its product information lists many possible psychiatric adverse events (PAE). However, up to now no one has worked on systematically categorising those PAE & linking them to certain risk groups of individuals.
Objective: The aim of our study is to systematically review all available studies employing TPM in patients with a broad range of issues such as somnolence, anorexia & concentration problems & to analyse both qualitatively & quantitatively whether there are groups associated with greater risk for these events.
Study Design: Our study is a systematic review & meta-analysis of both published & unpublished data on patients using TPM. Studies are collected after a literature search in three scientific databases (PubMed, WebOfScience, Embase) & two Clinical Trial Registries (ClinicalTrials, eudract). Data from unpublished studies are sought by contacting study authors/manufacturers. Total numbers of exposed patients & frequencies of PAE of them are extracted, categorized & reviewed.

Participants: As project is review, participant data will be extracted from resulting lit. search
Main Outcome: Frequencies of psychiatric or psychosomatic PAE for Statistical Analysis (Odds Ratios). For placebo-controlled studies, meta-analyses are calculated for PAE during TPM vs. Placebo, as well as comparing TPM to other agents.
Statistical Analysis: Comparison of Odds Ratios between different populations of patients, differing in demographics & associated disorders.

Brief Project Background and Statement of Project Significance:

Topiramate is a well-established drug in the treatment of epilepsy and migraine prevention, but which is also often used off label to treat a broad array of issues, including, but not limited to weight loss, neuropathy and aiding smoking secession. For those off-label usages, there are no reports of adverse events available in the product information.
Our project is to evaluate the risk of psychiatric or psychosomatic adverse events by the means of a systematic review and meta-analysis. If the results of our independent study show that there are groups of individuals with a greater susceptibility to mental health issues as a result of Topiramate usage, it may help raise awareness of the suitability of Topiramate in such instances and to develop alternative treatment options with a lower risk of impeding adverse mental health outcomes.
We are aware of the fact, that the general psychothrophic adverse event profile is already established, however, it has not yet been established, whether different groups of patients for which TPM has been used experimentally or in clinical use are affected to the same degree: on the one hand patients with differential diagnosis, and on the other hand patients of different age groups. As this is a question not yet discussed in the scientific literature we believe to be contributing in a substantial way.

Specific Aims of the Project:

Aim of our project is to systematically investigate and review how a therapy with Topiramate is associated with psychiatric adverse events. Product information mentions psychiatric adverse events during treatment with Topiramate in case of epilepsy. We want to support with evidence which risk factors may underlie patients using Topiramate in order to improve treatment for such risk groups. Our hypothesis is that based on the occurrence of psychiatric symptoms in Topiramate treatment of epilepsy, treatment of other disorder should also cause psychiatric symptoms, depending on several factors such as disorder being treated. To evaluate or hypothesis we will extract data on psychiatric (including psychosomatic) adverse events from interventional studies using Topiramate, determine their frequencies across studies, and meta-analytically compare the frequencies of psychiatric adverse events during Topiramate to those during placebo, controlling for factors such as age, gender and disorder treated.

In order to accomplish this we need the CSR data only with the AE case numbers for the different study arms.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment safety
Confirm or validate previously conducted research on treatment safety
Summary-level data meta-analysis
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources
Other

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

For literature search, we used 3 databases (PubMed/MEDLINE, WebOfScience & Embase) and 2 clinical trials registries (ClinicalTrials & eudract). Keywords were: “topiramate AND double AND (blind OR dummy OR masked)” Literature selection was performed manually using pre-defined criteria. We included interventional, double blind, placebo or other active agent controlled trials on humans w/ at least 1 treatment arm of TPM that reported at least 1 psychiatric adverse event (PAE). Trials include NCT00802412, NCT01859013, NCT01581281, NCT0184369
The following terms represent PAE we are interested in: “Anorexia/Reduced Appetite/Appetite Loss”, “Cognitive Impairment”, “Increased Appetite”, “Insomnia/Decreased Sleep/Sleeping Difficulties”, “Nervousness”, “Reduced Libido”, “Somnolence”, “Drowsiness”, “Suicidal Ideation/suicide attempt”, “Depression”, “Mood problems”,

“Memory impairment”, “Increased sleep”, “Concentration issues”, “Anxiety”, “Confusion”, “Irritability”, “Restlessness”, “psychomotor retardation”, “Attention disturbance”, “Language problems”, “Cognitive Problems”, “Amnesia”, “psychosis”, “Thinking abnormalities”, “Behavioural problems”, “personality disorder”, “Hallucinations”.

Main Outcome Measure and how it will be categorized/defined for your study:

Our study investigates frequencies of psychiatric adverse events during treatment with Topiramate in all included studies and analysis of risk groups. All randomized, placebo-controlled studies will be part of meta-analysis.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

For the review, the predictor for the outcome of interest is treatment with Topiramate vs. Placebo / other active agents. For the meta-analysis, the predictor for the outcome of interest is treatment (with Topiramate vs. Placebo / other active agents).
Terms which represent psychiatric adverse events and we are interested in to conduct the frequencies of, are the following: “Anorexia/Reduced Appetite/Appetite Loss”, “Cognitive Impairment”, “Increased Appetite”, “Insomnia/Decreased Sleep/Sleeping Difficulties”, “Nervousness”, “Reduced Libido”, “Somnolence”, “Drowsiness”, “Suicidal Ideation/suicide attempt”, “Depression”, “Mood problems”, “Memory impairment”, “Increased sleep”, “Concentration issues”, “Anxiety”, “Confusion”, “Irritability”, “Restlessness”, “psychomotor retardation”, “Attention disturbance”, “Language problems”, “Cognitive Problems”, “Amnesia”, “psychosis”, “Thinking abnormalities”, “Behavioural problems”, “personality disorder”, “Hallucinations”.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Frequencies of the following specified psychiatric advers events symptoms: “Anorexia/Reduced Appetite/Appetite Loss”, “Cognitive Impairment”, “Increased Appetite”, “Insomnia/Decreased Sleep/Sleeping Difficulties”, “Nervousness”, “Reduced Libido”, “Somnolence”, “Drowsiness”, “Suicidal Ideation/suicide attempt”, “Depression”, “Mood problems”, “Memory impairment”, “Increased sleep”, “Concentration issues”, “Anxiety”, “Confusion”, “Irritability”, “Restlessness”, “psychomotor retardation”, “Attention disturbance”, “Language problems”, “Cognitive Problems”, “Amnesia”, “psychosis”, “Thinking abnormalities”, “Behavioural problems”, “personality disorder”, “Hallucinations”.

Statistical Analysis Plan:

In the systematic review, data will be analyzed qualitatively. In the meta-analysis, odds-ratios will be calculated for the different adverse effects occurring under Topiramate vs. Placebo using RevMan 5 in order to identify the risks for adverse events across populations as wekk as perfoming sub group analyses of risks for adverse events. For that matter, frequencies of PAE will be taken from the CSR-data and pooled with data already collected (for examples see section data source) and supplemented with the data provided by YODA. No IPD will be used in our analyses. We consider the analyses taken to be a substantial contribution in order to describe the safety profile of TPM.
Software Used:
I am not analyzing participant-level data / I will not be using these software for analyses in the secure platform
Project Timeline:

Our project is in the midst of completion. All aforementioned databases and clinical trial registries were searched and the studies were scanned and categorized and will be analysed further. Frequencies will extracted and evaluated. We will also contact several authors of studies that did not report adverse events in their publications. The requested studies in YODA are among the last in our attainment of white literature to gain a most complete set of data. We agree that it's a long term project and would adopt our time frame, but we'd like you to consider that we already performed the searches for published literature and clinical databases and extracted the data.

Project start date: 01.11.2019
Analysis completion date: 01.09.2020 (but still waiting for additional and more detailed data from YODA)
Manuscript drafted date: 30.11.2020
Results reported back date: 01.12.2020
Publication date: 01.02.2021

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Dissemination Plan:

Our project is part of a master thesis for a M.Sc. in Psychology. It was agreed with the supervisors of the project that the thesis will from the start be written in style of a scientific paper as per the submission guidelines of our target journal: "Human Psychopharmacology: Clinical and Experimental".
Before submission, you will receive a copy of the manuscript.

Bibliography:

A short selected enumeration of included studies:

Anthenelli, R. M., Heffner, J. L., Wong, E., Tibbs, J., Russell, K., Isgro, M., ... & Doran, N. (2017) / Pubmed ID: 28029173
de Brito, A. M. C., de Almeida Pinto, M. G., Bronstein, G., Carneiro, E., Faertes, D., Fukugawa, V., ... & Tavares, H. (2017) / Pubmed ID: 27256372
Johnson, B. A., Ait-Daoud, N., Wang, X. Q., Penberthy, J. K., Javors, M. A., Seneviratne, C., & Liu, L. (2013) / Pubmed ID: 24132249
Elkashef, A., Kahn, R., Yu, E., Iturriaga, E., Li, S. H., Anderson, A., ... & Serpi, T. (2012) / Pubmed ID: 22221594
Yeh, M. S., Mari, J. J., Costa, M. C. P., Andreoli, S. B., Bressan, R. A., & Mello, M. F. (2011) / Pubmed ID: 21554564
Jankovic, J., Jimenez-Shahed, J., & Brown, L. W. (2010) / Pubmed ID: 19726418
Rosenstock, J., Hollander, P., Gadde, K. M., Sun, X., Strauss, R., & Leung, A. (2007). / Pubmed ID: 17363756
Muehlbacher, M., Nickel, M. K., Kettler, C., Tritt, K., Lahmann, C., Leiberich, P. K., ... & Loew, T. H. (2006) / Pubmed ID: 16788338
Ondo, W. G., Jankovic, J., Connor, G. S., Pahwa, R., Elble, R., Stacy, M. A., ... & Hulihan, J. F. (2006) / Pubmed ID: 16436648
Loew, T. H., Nickel, M. K., Muehlbacher, M., Kaplan, P., Nickel, C., Kettler, C., ... & Bachler, E. (2006) / Pubmed ID: 16415708