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General Information

Key Personnel (in addition to PI):
  First Name: Nadine
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Degree: Master of Science
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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_2019_21.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. NCT00253201 - GAL-USA-1 - Efficacy, Tolerability and Safety of Galantamine in the Treatment of Alzheimer's Disease
2. NCT00253227 - GAL-INT-2 - Galantamine in the Treatment of Alzheimer's Disease: Flexible Dose Range Trial
3. NCT00216502 - GAL ITA-2 - Long Term Treatment With Galantamine In Dementia
4. GAL-INT-3 - Long Term Safety and Efficacy of Galantamine in the treatment of Alzheimer's Disease
5. NCT00261573 - GAL-INT-6 - The Safety and Efficacy of Galantamine in the Treatment of Vascular and Mixed Dementia
6. NCT00253188 - GAL-INT-1 - Efficacy, Tolerability and Safety of Galantamine in the Treatment of Alzheimer's Disease
7. NCT00253214 - GAL-INT-10 - Placebo-Controlled Evaluation of Galantamine in the Treatment of Alzheimer's Disease: Safety and Efficacy of a Controlled-Release Formulation
8. NCT00236574 - CR003145 // GAL-INT-11 - A Randomized Double Blind Placebo-Controlled Trial to

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

Research Proposal

Project Title

Adverse events of acetylcholinesterase inhibitors - systematic review and meta-analysis of double-blind randomized controlled trials

Narrative Summary:

Dementias are increasingly developing into a serious health problem. With proof of effectiveness, the acetylcholinesterase inhibitors donepezil, rivastigmine, galantamine and the NMDA antagonist memantine are currently approved in Germany for the treatment of mild to moderate Alzheimer's dementia and are used in clinical practice. Acetylcholinesterase inhibitors often produce different adverse events such as neuropsychiatric symptoms like headache or dizziness. The aim of this systematic review and meta-analysis is to quantify the risk of acetylcholinesterase inhibitors to cause common adverse events compared to placebo and other medications.

Scientific Abstract:

Background: Dementias are increasingly developing into a serious health problem. With proof of effectiveness, the acetylcholinesterase inhibitors donepezil, rivastigmine, galantamine and the NMDA antagonist memantine are currently approved in Germany for the treatment of mild to moderate Alzheimer's dementia and are used in clinical practice.
Objective: The aim of our study is to systematically review all available studies to extract data for psychiatric adverse events such as anxiety, depression, and insomnia, and to analyze both qualitatively and quantitatively whether or there is a particular risk for these events. Study Design: Our study is a systematic review and meta-analysis of both published and unpublished data on patients taking acetylcholinesterase inhibitors. Studies are collected after a literature search in two scientific databases (PubMed, WebOfScience) and one Clinical Trial Registries (ClinicalTrials). Data from unpublished studies are sought out by contacting study authors or manufacturers. Total numbers of exposed patients and frequencies of psychiatric and psychosomatic adverse events of these patients are extracted, categorized, and reviewed. Participants: No one, because it is a Review. Main Outcome: Frequencies for psychiatric or psychosomatic adverse events for acetylcholinesterase inhibitors. Statistical Analysis: For placebo-controlled studies, meta-analyses are calculated for adverse events during acetylcholinesterase inhibitors vs. Placebo.

Brief Project Background and Statement of Project Significance:

In 2016, 53.5 million defined daily doses (million DDD) of the group of cholinesterase inhibitors and 27.5 million DDD of the NMDA receptor antagonist memantine were prescribed in Germany. With regard to psychiatric adverse

drug reactions, information can be found sporadically in the specialist information.

Our project is to evaluate the risk of psychiatric or psychosomatic by the means of a systematic review and meta-analysis. If the results of our independent study confirm the safety of cholinesterase inhibitors regarding mental health, it may help raise awareness of the suitability of cholinesterase inhibitors therapy in patients with Dementia and comorbid psychiatric disorders of vulnerability towards a psychiatric disorder.

Specific Aims of the Project:

Aim of our project is to systematically investigate and review whether a therapy with cholinesterase inhibitors is associated with psychiatric adverse events. To evaluate or hypothesis we will extract data on psychiatric (including psychosomatic) adverse events from interventional and observational studies using cholinesterase inhibitors, determine their frequencies across studies, and meta-analytically compare the frequencies of psychiatric adverse events during cholinesterase inhibitors to those during placebo.
1. Which adverse events appear the most during therapy with acetylcholinesterase inhibitors and how is the risk compared to placebo and alternative treatments?
2. Are there differences between different acetylcholinesterase inhibitors regarding the occurence of adverse events during therapy?
3. Are there differences between patients populations or different diseases regarding the occurence of adverse events during therapy with acetylcholinesterase inhibitors. Psychiatric adverse events are the following: "Asthenia", "Fatigue", "Anorexia", "Loss of Appetite", "Decreased Appetite", "Depression", "Insomnia", "Anxiety", "Somnolence", "Depressed Mood", "Delirium", "Confusional State", "Confusion", "Metal Status Change", "Hallucination", "Decreased Libido", "Mood Swings".

What is the purpose of the analysis being proposed? Please select all that apply.
Summary-level data meta-analysis
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

For the literature search, we used two databases (PubMed/MEDLINE and WebOfScience) and one clinical trials registries (ClinicalTrials). Keyword for research was „(memantine OR donepezil OR galantamine OR rivastigmine) AND (random*). Selection of literature was performed manually using pre-defined criteria. We included observational and interventional trials on human subjects with at least one treatment arm of cholinesterase inhibitors that reported at least one psychiatric adverse events.
Terms which represent psychiatric adverse events and we are interested in, are the following: "Asthenia", "Fatigue", "Anorexia", "Loss of Appetite", "Decreased Appetite", "Depression", "Insomnia", "Anxiety", "Somnolence", "Depressed Mood", "Delirium", "Confusional State", "Confusion", "Metal Status Change", "Hallucination", "Loss of Libido", "Decreased Libido", "Mood Swings", "Amnesia", and/or "Psychiatric Disorder".

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

Prespecified primary and secondary outcomes are psychiatric adverse events (PAE) (Aggression, Agitation, Anorexia, Anxiety, Asthenia, Behavior problems , Confused thoughts, Confusion/confusional state, Decreased appetite, Depression, Dizziness, Fainted, Faintness, Fall, Fatigue, Fearful thoughts, Foot twitching, Hallucination, Hallucination visual, Headache, Hypertension, Hypotension, Insomnia, Irritation, Malaise, MS relapse, Nightmares, Parkinsonism, Poor appetite, Post traumatic stress disorder, Restless legs, Restlessness, Self serious ideation, Shakiness, Sleeping difficulties, Somnolence, Syncope, Tremor, Vertigo, Weight gain, Weightloss) and withdrawal of therapy due to PAE, respectively.

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 cholinesterase inhibitors . For the meta-analysis, the predictor for the outcome of interest is treatment (with cholinesterase inhibitors vs. Placebo). Terms which represent psychiatric adverse events and we are interested in to conduct the frequencies of, are the following: Dosage, frequency and duration of application/intake of acetylcholinesterase inhibitors, specific disease (Alzheimers dementia, OCD, Schizophrenia, Cannabis use disorder, Autism spectrum disorder, Mild cognitive

impairment, Parkinsons disease, Multiple sclerosis, PTSD, Brain tumor, Down's syndrome, Vascular dementia, Alcohol dependence), sex, age, previous illnesses of participants (HIV, High blood pressure, Metabolic syndrome).

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: "Asthenia", "Fatigue", "Anorexia", "Loss of Appetite", "Decreased Appetite", "Depression", "Insomnia", "Anxiety", "Somnolence", "Depressed Mood", "Delirium", "Confusional State", "Confusion", "Metal Status Change", "Hallucination", "Loss of Libido", "Decreased Libido", "Mood Swings", "Amnesia", and/or "Psychiatric Disorder".

Statistical Analysis Plan:

Statistical analyses are carried out using Review Manager 5.3.18 and/or R since RevMan will not be available. We perform pairwise meta-analyses, calculating odds ratios (OR) with 95% confidence intervals (CI) and respective p-values for each symptom or symptom cluster. We found that similar symptoms were reported across different studies using different terms. In such cases, symptoms were grouped into clusters. The Medical Dictionary for Regulatory Activities Terminology (MedDRA) was used as a reference throughout. As one example: Sleep disturbance, Sleeping problems, Trouble sleeping, Poor quality sleep are one cluster according to MedDRA.
I am not analyzing participant-level data / I will not be using these software for analyses in the secure platform
Software Used:
R
Project Timeline:

Our project is nearly finished. All aforementioned databases and clinical trial registries were searched and the studies were scanned, categorized and analyzed. Frequencies were extracted and evaluated. We also contacted several authors of studies that did not report adverse events in their publications. The requested studies in YODA is the last in our attempt to gain a most complete set of data.
Actual start date: 01/01/2021
Analysis completion date: 31/10/2021
Date manuscript drafted: 15/01/2022 and submitted for publication 31/01/2022
Anticipated completion date: 30/04/2022

Dissemination Plan:

Our project is part of a PhD and will be published in a journal. Potentially suitable journals for submission would be: PLoS ONE, Hypertension, Psychological Review, Psychological Medicine, Depression and Anxiety, Human Psychopharmacology-Clinical and Experimental.
If submission is succesfull you will receive a copy of the manuscript.

Bibliography:

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