ALTERING THE GUT MICROBIOME TO MODULATE BEHAVIOR MANIFESTATIONS IN AUTISM SPECTRUM DISORDERS: A SYSTEMATIC REVIEW

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Review question / Objective: How do probiotics and prebiotics influence the gut-brain axis to therapeutically modulate the behavioral manifestations of autism spectrum disorders?

Condition being studied: Autism spectrum disorders.

Main outcome(s): The main outcomes sought will include behavioral manifestations of autism spectrum disorders as measured by validated questionnaires like ATEC, GSI, Autism-spectrum quotient, as well as measures of specific symptoms like constipation and frequency of bowel movements.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 September 2020 and was last updated on 15 November 2020 (registration number INPLASY202090011).

INTRODUCTION

Review question / Objective: How do probiotics and prebiotics influence the gut-brain axis to therapeutically modulate the behavioral manifestations of autism spectrum disorders?

Rationale: Dysfunction along the gut-brain axis is increasingly implicated in the pathogenesis of autism spectrum disorders (ASD). In addition to its neurodevelopmental deficits, ASD is also characterized by a range of gastrointestinal...
symptoms, which increase in proportion to the severity of ASD. Moreover, many studies have found that those with ASD have an altered intestinal microbiome composition. Current evidence appears inconsistent; therefore, we aim to conduct a review to analyze this.

**Condition being studied:** Autism spectrum disorders.

**METHODS**

**Search strategy:** This study will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and supplemented by guidance from the Cochrane Collaboration Handbook. For this systematic review, MEDLINE-PubMed, Science Direct, Web of Science and Scopus databases will be used to search for relevant studies conducted in previous years. Three separate searches will be performed and subsequently combined using a 10-year and human only filter and the following MeSH terms: ("Dietary Fiber"[Mesh] AND "Autism Spectrum Disorder"[Mesh]), ("Fecal Microbiota Transplantation"[Mesh] AND "Autism Spectrum Disorder"[Mesh]) and ("Probiotics"[Mesh] OR "Symbiotics"[Mesh]) OR "Fecal Microbiota Transplantation"[Mesh] AND "Autism Spectrum Disorder"[Mesh]).

**Participant or population:** Children with Autism spectrum disorders.

**Intervention:** Probiotic and prebiotic supplementation.

**Comparator:** Behavioral manifestations of ASD, e.g. ATEC and GSI questionnaire.

**Study designs to be included:** RCTs, open-label trials, crossover studies, observational studies, prospective cohort, and retrospective cohort studies.

**Eligibility criteria:** All searched titles, abstracts, and full-text articles will be independently reviewed by two reviewers (C.D. and D.M.). Disagreements over inclusion and exclusion criteria will be resolved through a consensus between the reviewers or discussion with other investigators of this study. The following inclusion criteria will be used: clinical trials, human studies, prebiotic use, probiotic use, and subjects with autism spectrum disorders. Studies will be excluded based on the following exclusion criteria: studies that did not fit the above characteristics, review articles, meta-analyzes, abstracts only, conference proceedings, editorials/letters, case reports, published over 10 years ago. Selected abstracts and, later, selected full-text articles will be brought to full-text analysis. Key criteria for full text analysis will include availability of ASD outcome measurements and probiotic/prebiotic intervention or use.

**Information sources:** MEDLINE-PubMed, Science Direct, Web of Science, Scopus databases and via authors own knowledge of the field.

**Main outcome(s):** The main outcomes sought will include behavioral manifestations of autism spectrum disorders as measured by validated questionnaires like ATEC, GSI, Autism-spectrum quotient, as well as measures of specific symptoms like constipation and frequency of bowel movements.

**Data management:** COVIDENCE will be used to manage and track data.

**Quality assessment / Risk of bias analysis:** The risk of bias will be assessed according to the Cochrane guidelines for Randomized Controlled Trials (RCTs). Six areas will be evaluated: sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias). Risk of bias will be rated as low, unclear, or high according to established Cochrane guidelines (Higgins et al., 2020). The overall impression is a gestalt score based on the study’s strengths and risk of bias per Cochrane guidelines (Higgins et al., 2020).
Two investigators independently (C.D. and D.M.) will conduct this assessment and any disagreements will be resolved by consensus between the reviewers or discussion with other investigators of this study.

**Strategy of data synthesis:** A systematic narrative synthesis will be presented in the text to summarize and explain the findings and characteristics of the included studies. Studies will be qualitatively analyzed, compared, and discussed based on the strength of their study design and risk of bias.

**Subgroup analysis:** Qualitative analysis only.

**Sensibility analysis:** Qualitative analysis only.

**Language:** English only.

**Country(ies) involved:** USA.

**Keywords:** Prebiotics, Probiotics, Fiber, Gut-Brain Axis, Gut Microbiota, Autism Spectrum Disorders, ASD, Autism, Gastrointestinal Problems, Quality of Life.

**Contributions of each author:**

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