Probiotic formulation for patients with schizophrenia or bipolar disorder who have screened positive for increased intestinal permeability

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON53363

Source
ToetsingOnline

Brief title
GUTS

Condition

- Other condition
- Manic and bipolar mood disorders and disturbances

Synonym
Schizophrenia en bipolar disorder

Health condition

Schizophrenia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Stanley Medical Research Institute - SMRI

Intervention

Keyword: Bipolar disorder and Probiotics, Gut, Schizophrenia

Outcome measures

Primary outcome

Primary outcome is psychiatric symptoms severity as assessed with the Brief

Psychiatric Rating Scale (BPRS).

Secondary outcome

secondary outcomes are cognition , functional disability as assessed with the

World Health Organization*s Disability Schedule (WHO-DAS II), quality of life,

recovery, and side-effects together with peripheral immune markers and markers

of intestinal barrier function. Stool and blood samples are analysed to

identify optimal biomarkers for response to probiotics.

Study description

Background summary

Schizophrenia and bipolar disorder are severe mental disorders, both placing significant burden on global health (WHO 2006). Although the introduction of antipsychotic medications in the 1950s has substantially improved clinical symptoms of schizophrenia (Tandon et al., 2010), the disease is still causing considerable morbidity and mortality (Saha et al., 2007). In bipolar disorder, lithium is since many years the first-choice maintenance-treatment, with anticonvulsants and antipsychotics as major alternatives. However, up to 50% of patients with bipolar disorder do not respond adequately to these treatments

and still suffer from manic and/or depressive episodes, often severely affecting functioning (Perlis et al., 2006). The pathogenesis of these disorders is still far from elucidated, but quite certainly multifactorial, with immune dysregulation being one of many contributing factors.
Abnormal immune responses have been reported in patients with schizophrenia and bipolar disorder, of varying disease stages and medication status (Muller & Schwarz, 2010; Horvath & Mirnics, 2014; Munkholm et al., 2013; Beumer et al., 2012). For example, adult schizophrenia patients as a group have elevated serum levels of pro-inflammatory cytokines compared to controls (Francesconi et al., 2011; Kunz, et al., 2011; Pedrini, et al., 2012; Song et al., 2013). Both disorders are associated with an increased pro-inflammatory gene expression in circulating monocytes (Drexhage et al., 2010). Symptom severity is found to correlate with levels of inflammatory markers (Fan et al., 2007; Fan et al., 2010; Hope et al., 2013). It has therefore been hypothesized that schizophrenia and bipolar disorder can originate from early exposure to microbial infections, contributing to the aetiology, through chronic neuro-inflammatory and autoimmune processes (Yolken & Torrey, 2008).
Autoimmunity, atopic disorders, early infection and, more recently, *leaky gut* resulting from microbiome imbalance, have all been associated with schizophrenia and bipolar disorder (Severance et al., 2014). It is interesting to see that also intestinal microbiota imbalance is associated with schizophrenia and bipolar disorder (Fond et al., 2014; Nemani et al., 2015; Dickerson et al., 2017), as this may offer a non-invasive and relatively simple strategy to improve symptoms and condition of the brain. An increased incidence of gastrointestinal barrier dysfunction, food antigen sensitivity, inflammation and the metabolic syndrome are observed in patients with schizophrenia and bipolar disorder, suggesting a potential deficit in gut microbiota.

Another reason to consider probiotic supplementation in patients with schizophrenia and bipolar disorder, is the high prevalence of gastro-intestinal symptoms. In schizophrenia, constipation is a prevalent symptom (De Hert, Dockx et al., 2011; De Hert, Hudyana et al., 2011; Koizumi et al., 2013). Probiotic supplementation has been shown to improve constipation in different populations but has not yet been studied in schizophrenia (Chmielewska & Szajewska, 2010; Miller & Ouwehand, 2013; Dimidi et al., 2014). Bipolar disorder, in contrast, is associated with diarrhoea and satiety, a gastro-intestinal symptom for which probiotics are recognized to be efficacious (Sherwin et al., 2016). Several studies have been published describing gastro-intestinal inflammation in schizophrenia and bipolar disorder. Already back in 1953, gastro-intestinal inflammation was associated with schizophrenia in a post-mortem study of 82 individuals with schizophrenia, where researchers found that 50% had gastritis, 88% enteritis and 92% colitis (Buscaino, 1953). Conversely, prevalence estimates for any psychiatric comorbidity in patients diagnosed with irritable bowel syndrome (IBS), range from 54 to 94% (Whitehead et al., 2002), and estimates for a schizophrenia-spectrum or bipolar comorbidity approaching 20% (Gupta et al., 1997).
There have been several studies of the fecal microbiome in healthy children and

adults (Collado et al., 2015; Lozupone et al., 2012; Zhernakova et al, 2016). However, collection and processing of fecal samples from individuals with severe psychiatric disorders is difficult. Up till now, studies analyzing the fecal microbiome of individuals with schizophrenia are largely lacking. In bipolar disorder, one study analyzing the fecal microbiome has been published recently, providing the first detailed analysis of the gut microbiome relationships with multiple psychiatric domains in this disorder (Evans et al. 2017). In this study, the stool microbiome from 115 individuals with bipolar disorder and 64 control subjects were compared, using 16S ribosomal RNA (rRNA) gene sequence analysis, revealing global community case-control differences. Operational Taxonomical Unit (OTU) level analysis demonstrated significantly decreased fractional representation of Faecalibacterium. In individuals with bipolar disorder, the fractional representation of this bacterium was associated with better self-reported health outcomes based on the Short Form Health Survey (SF12); the Patient Health Questionnaire (PHQ9); the Pittsburg Sleep Quality Index (PSQI); the Generalized Anxiety Disorder scale (GAD7); and the Altman Mania Rating Scale (ASRM). This data thereby provides support for the hypothesis that targeting the microbiome may be an effective treatment paradigm for bipolar disorder.

Probiotics are live organisms, which can confer a health benefit for the host when administered in adequate amounts (Hill et al., 2014). Probiotics are shown to have immune modulatory effects as well as effects on the epithelial barrier in healthy adults (Ohland & Macnaughton, 2010; Klaenhammer et al., 2012). Probiotic bacteria can manipulate brain functioning from the intestine by multiple mechanisms (Forsythe et al., 2012; Dinan et al., 2013; Galland, 2014), for example by changing immune system signals to the brain. Recent research in a mouse model shows that probiotics can improve abnormal behaviours associated with inflammation (D'Mello et al., 2015). They also have the capacity to increase plasma levels of neurotransmitters, such as the GABA and serotonin precursor tryptophan (Lesniewska et al., 2006; Desbonnet et al., 2008; Barrett et al., 2012). Probiotic bacteria can also produce bacterial metabolites, such as short chain fatty acids (SCFA), which can be carried by monocarboxylate transporters, expressed at the blood-brain barrier (Maurer et al., 2004). The vagus nerve is another important mechanism for signalling between brain and gut and has been shown to be involved in the antidepressant effects of probiotics in mice (Bravo et al., 2011). Although the exact mechanisms are not yet known in human, it is likely that a combination of different pathways convey the effects of probiotics on the brain.
Given the accumulating evidence for abnormal immune responses which are seen in schizophrenia and bipolar disorder patients, and the observation that intestinal microbiota and the intestinal epithelial barrier can play a role in both diseases, probiotic therapy can be viewed as a potential candidate for treatment in these patients, especially in those known to have signs of decreased epithelial barrier function.
Immunomodulatory effects of probiotics (combination of Lactobacillus rhamnosus GG and bifidobacterium animalis subsp. Lactis BB12) have already been shown in

patients with schizophrenia and the authors speculated that supplementation of probiotics for schizophrenia patients may improve control of gastrointestinal leakage (Tomasik et al., 2015). Patients in the probiotic arm of the intervention study were less likely to develop severe bowel difficulty, but this trial did not show significant differences in symptom severity between probiotic and placebo supplementation (Dickerson et al., 2014). Possible reasons for not finding an effect on symptom severity could be the relatively short duration of the intervention, the daily dose of the probiotic product, or the selection of patients with long-term schizophrenia. In addition, probiotics may be effective for a subpopulation only. When given to an unselected sample, efficacy in this subgroup may be obscured by inefficacy in the majority. In a recent study of Dickerson et al. (2018) in patients with bipolar disorder they found that administration of probiotic supplementation is associated with a lower rate of hospitalization in patients who have been recently discharged following hospitalization for mania.

In this study we will examine the effect of the probiotic product Ecologic Barrier on symptom improvement, cognition and peripheral immune parameters in patients with schizophrenia and bipolar disorder. Limited effects on symptom severity and cognition are expected, when given to an unselected sample. Therefore, patients will be screened using serum LPS-binding protein (LBP) levels in blood as an indication of intestinal permeability (Only patients with LPB >= 9 ng/ml will be included in the intervention.) and C reactive protein (CRP) as measurement for intestinal inflammation. In this selected sample, larger effect sizes are expected.

Study objective

The primary objective of this trial is to investigate the effects of probiotics, as compared to placebo, when given in addition to antipsychotic/mood stabilizing medication to a selected patient sample. Our aim will be to lower symptom severity as measured with the BPRS to assess if probiotics can form an effective treatment paradigm for both schizophrenia and bipolar disorder.

We will also assess improvements in cognition and disability in the probiotic and the placebo-treated group. In addition, we expect that probiotics will improve immune parameters which are abnormal in schizophrenia and bipolar patients.

Study design

The current monocenter study has a randomized, placebo-controlled double-blind study.

Intervention

Treatment period of 12 weeks in which they are randomized 1: 1 in either 2 grams of probiotic formulation (1x10 ^ 10 colony forming units / day) or placebo twice daily twice a day.

Study burden and risks

There is no potential harmful dose of probiotics known. Probiotics are already on the market as a food supplement. There are little known risks for using probiotics. Previous studies with probiotics in patients without life-threatening somatic illnesses have not resulted in adverse events, besides incidental sensations of bloating and change in stool consistency.

The risk and burden from such blood samples drawings are low and risks well known (e.g. irritation). Stool samples will be collected at start and end of treatment. The burden and risks are acceptable while the benefits are expected to be considerable.

Contacts

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Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.Age 18-65 years;2.The participant understands the study and is capable of providing written informed consent;3.The participant has a DSM-IV-R or DSM-5 diagnosis of: 295.x

(schizophrenia, schizophreniform disorder or schizo-affective disorder) or bipolar disorder 296.x;4.Serum LPS-binding protein (LBP) values of 9 ng/ml or higher

Exclusion criteria

1.Pregnancy or breastfeeding;2.Mental retardation (IQ score <60);3.Active liver-, kidney- or pancreas disease as defined by ALAT > two times the upper boundary of normal levels;4.Any clinically significant or unstable medical disorder as determined by the investigators, including IBD, short-bowel syndrome or acute/chronic pancreatitis

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-05-2019
Enrollment:	145
Type:	Actual

Ethics review

Approved WMO

Date:	22-03-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	03-12-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 24444
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL67848.042.18
OMON	NL-OMON24444