Journal of Psychiatric Research 118 (2019) 1–6

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Higher prevalence of irritable bowel syndrome and greater gastrointestinal symptoms in obsessive-compulsive disorder

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ARTICLE INFO

Keywords:
Obsessive-compulsive disorder
Anxiety
Mood
IBS
Gut-brain axis
Gastrointestinal

ABSTRACT

Background: Anxiety and mood symptoms often co-occur with gastrointestinal problems, such as irritable bowel syndrome (IBS). The extent to which these relate to Obsessive-Compulsive Disorder (OCD) is unclear, despite anxiety being a prominent symptom of this disorder. The purpose of this analysis was to examine gastrointestinal symptoms in unmedicated, non-depressed adult OCD patients compared to age- and sex-matched community controls.

Methods: Twenty-one OCD patients and 22 controls were recruited from the community (Hamilton, ON, Canada) and enrolled in this cross-sectional study. In addition to a standardized psychiatric assessment, participants completed clinician- and self-rated psychiatric and gastrointestinal symptom severity measures. Presence of IBS was assessed using Rome III criteria.

Results: Gastrointestinal symptom severity (GSRS total; OCD = 8.67 ± 6.72 vs. controls = 2.32 ± 2.12) and prevalence of IBS (OCD = 47.6%; Controls = 4.5%) was higher in OCD patients than in controls. A comparison of OCD patients based on IBS status revealed greater depressive symptom severity (total MADRS: 12.60 ± 1.89 vs 6.91 ± 2.77), $p < 0.001$) among those with IBS.

Conclusions: High prevalence and severity of gastrointestinal symptoms may be an important clinical consideration when treating OCD patients. More specifically, assessment of IBS and gastrointestinal symptoms may be useful when considering pharmacotherapeutic treatments options for patients. Given the high comorbidity noted with IBS, a disorder of the "gut-brain axis", results may suggest a shared pathophysiological mechanism between psychiatric and gastrointestinal disorders which should be explored in future research.

1. Introduction

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder. Meta-analytic evidence has suggested a global prevalence of 11.2% (Lovell and Ford, 2012), with North American rates ranging between 3.0% and 20.1% (Canavan et al., 2014). IBS pathophysiology is not well understood; however, it is hypothesized to be a disorder of the "gut-microbiota-brain axis" (Dinan and Cryan, 2017). This axis describes a bi-directional communication pathway linking the enteric and central nervous systems and is thought to be regulated by pathways including the immune system via cytokine release, gut hormones activating the enteric nervous system, brain signalling via ascending neural pathways and production of neurotransmitters by the gut microbiota (reviewed in Collins et al., 2012). Dysfunction in some of these pathways have been implicated in IBS (reviewed in Dinan and Cryan, 2017) and such disruptions may also be relevant to anxiety and related conditions. Similarly, it is well-established that individuals with IBS have higher levels of anxiety and depression compared to controls (Fond et al., 2014; Palsson and Drossman, 2005) which has led to the suggestion that these conditions may share a pathophysiological mechanism.

Anxiety is prominent component of other disorders like Obsessive-

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https://doi.org/10.1016/j.jpsychires.2019.08.004
Received 19 May 2019; Received in revised form 2 August 2019; Accepted 8 August 2019

Compulsive Disorder (OCD). OCD is a chronic and debilitating disorder often comorbid with mood and anxiety disorders. While several lines of evidence suggest that the gut-brain axis might be relevant to OCD (previously reviewed in Turna et al., 2017, 2016), the relationship between OCD and IBS is less explored. However, a limited literature suggests that OCD may be relevant to gastrointestinal function. For instance, in a small cohort of patients with functional bowel disorders, OCD was reported to be the second most common psychiatric co-morbidity (20%), following dysthymia (25%) (Fakhraei et al., 2015). Similarly, in cohorts of OCD patients, gastrointestinal diseases are also quite common (20.5%) (Aguglia et al., 2018).

To date, rates of IBS in OCD cohorts have only been examined in only two studies. Masand et al. (2006) reported that 35.1% of their OCD patients met Rome I criteria for IBS (compared to 2.5% of patients from an outpatient family practice). The second study reported IBS (based on Rome II criteria) in 16% of OCD patients in an outpatient specialized anxiety clinic which was comparable to community rates (Gros et al., 2009). Since these studies were published, the criteria for diagnosis of functional gastrointestinal disorders, including IBS, have undergone two revisions. As such, this limits the clinical relevance and interpretation of these findings within the context of current research. Further, these studies lack appropriate control groups potentially skewing the reported prevalence rates. Some patients in these studies were also on medication, making it difficult to delineate whether IBS symptoms were possible side effects of these treatment. Finally, they are limited in scope as they do not provide any measure of gastrointestinal and psychiatric symptom severity. Considering these limitations, the current study examined gastrointestinal symptom severity and rates of IBS in a sample of non-depressed, unmedicated OCD patients compared to sex- and age-matched non-psychiatric community controls. Biological markers suggestive of pro-inflammatory mechanisms were also examined to comment on the role of inflammation in OCD and IBS.

2. Methods

The results reported in this study represent a sub-analysis of data from a single-site, cross-sectional pilot examination of the gut microbiome profile and inflammatory markers of non-depressed, medication-free patients with OCD and a sex- and age-matched control group comparator. Gastrointestinal symptom severity and prevalence of IBS were secondary outcomes associated with this study and are the focus of the current report.

2.1. Participants

Men and women aged 18–65 years were recruited from the community to the MacAnxiety Research Centre (McMaster University, Hamilton, ON Canada) (Fig. 1). This included a group of non-depressed, unmedicated individuals with a primary DSM-5 diagnosis of OCD as per the Mini International Neuropsychiatric Interview (MINI). At least moderate OCD (Yale-Brown Obsessive-Compulsive Scale [Y-BOCS] score ≥ 20) and no more than mild depressive symptoms (Montgomery-Åsberg Depressive Symptom Rating Scale [MADRS] score < 16) were permitted. Those with significant suicidal ideation (MADRS item $10 \geq 3$) or suicidal behaviours in the last 6 months were excluded. Lifetime bipolar disorder, substance abuse, schizophrenia or other psychotic disorders, delirium, dementia and amnesic and other cognitive disorders were excluded. Similarly, lifetime autoimmune disorders (i.e. rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, etc.), inflammatory bowel disease, and diabetes were excluded. Age- and sex-matched controls with no clinically significant psychiatric symptoms were also recruited. Participants were recruited from the community through online advertisements (online classified sites, research centre website, etc.), community posters, public transit ads and word of mouth. Recruitment was completed between January 2015 and April 2017.

All study participants provided written informed consent prior to administration of any study assessments. This project was approved by the Hamilton Integrated Research Ethics Board at McMaster University (Hamilton, ON, Canada) and posted on clinicaltrials.gov (NCT02285699).

2.2. Procedures

All participants attended 1–2 in-person study visits where a detailed medical and psychiatric history was collected; the MINI was administered by a trained doctoral student. Medical history, and OCD and co-morbid psychiatric diagnoses were confirmed with a formal psychiatric consultation. Self- and clinician-rated measures detailing diet, psychiatric and gastrointestinal symptomatology were also completed.

Morning blood samples were drawn by standard venipuncture technique to examine levels of plasma C-Reactive Protein (CRP) and serum Tumor Necrosis Factor (TNF)-α and Interleukin (IL)-6. Plasma CRP levels were determined by immunoturbidimetry (MULTIGENT CROP Vario assay; Abbott Laboratories Inc., Abbott Park, Illinois, USA). IL-6 and TNF-α levels were determined using Quantikine heparin sulfate enzyme-linked immunosorbent assay (HS ELISA) (Human IL-6 and TNF- α Immunoassay; R&D Systems, Inc., Minneapolis, MN, USA). All analyses were performed simultaneously on the same assay.

2.3. Measures

IBS diagnosis was determined as per Rome III criteria for IBS (Drossman and Dumitrascu, 2006). Individuals were classified as

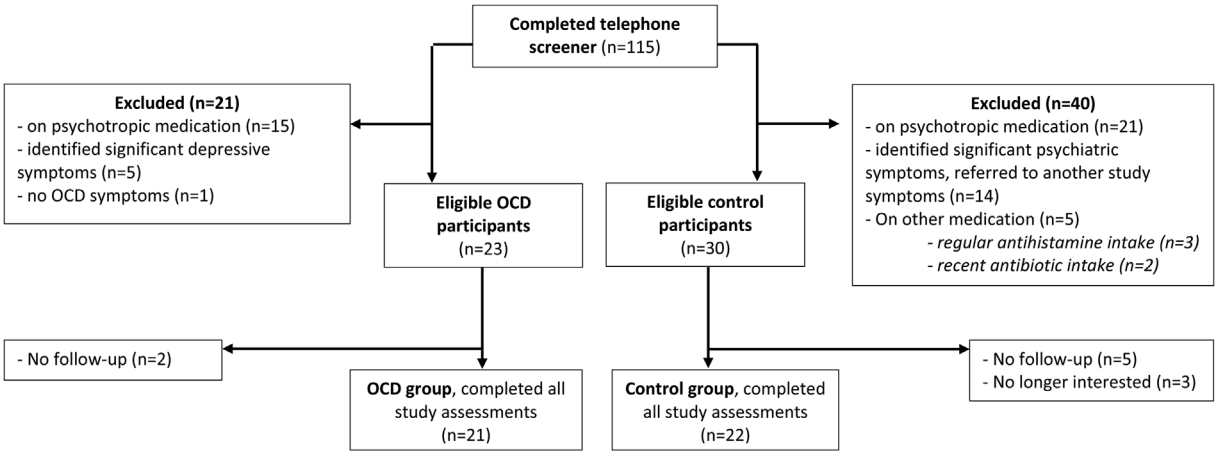

Fig. 1. Flow chart of participant screening and enrollment.

having IBS if they reported recurrent abdominal pain or discomfort associated with two or more of the following: improvement with defecation; and/or onset with a change in frequency; and/or onset with change in form of stool. These symptoms needed to be present at least one day/week for the previous three months, with onset at least six months prior (Drossman and Dumitrascu, 2006).

Participant gastrointestinal symptoms and bowel functioning were assessed using the clinician-rated Gastrointestinal Symptom Rating Scale (GSRS) (Svedlund et al., 1988) and self-rated Short-form Leeds Dyspepsia Questionnaire (SF-LDQ) (Fraser et al., 2007). Several clinician- and self-rated psychiatric symptom severity measures were also administered. Clinician-rated measures included the Y-BOCS (Goodman et al., 1989), Dutch Dimensional Obsessive-Compulsive Scales (DDOCS) and MADRS (Montgomery and Åsberg, 1979), which assessed OCD and depression symptom severity respectively. Self-report measures included the Obsessive-Compulsive Inventory (Revised) (OCI-R) (Foa et al., 2002), and the Depression Anxiety and Stress Scale (DASS-21) (Henry and Crawford, 2005). All data was collected through Research Electronic Data Capture (REDCap) (Harris et al., 2009), a secure web tool which was programmed to confirm completion of all questionnaires prior to submission to reduce likelihood of missing data.

2.4. Statistical analysis

All data were tested for normality using a Shapiro-Wilk's test and Levene's test to examine homogeneity of variance. A χ^2 test was used to compare prevalence of IBS among OCD patients and controls. Differences in means of demographic, gastrointestinal and psychiatric symptom severity data were examined using an independent/Welch's *t*-test or Mann-Whitney test where applicable.

Post-hoc analyses were conducted to characterize the OCD-IBS group. Specifically, differences in mean comorbid disorders, psychiatric and gastrointestinal symptom severity and cytokine data were examined using an independent/Welch's *t*-test or Mann-Whitney test where relevant.

Descriptive statistics, such as number of subjects, means and standard deviation are provided to summarize group characteristics. Missing data were not relevant in the current analysis as study participants completed all study measures. All analyses were conducted using IBM SPSS Statistics 25 (IBM, 2017) with a conservative significance level of 0.005 (Benjamin et al., 2018).

3. Results

Twenty-one OCD outpatients and 22 age- and sex-matched controls were enrolled in the gut microbiome study. No demographic differences were noted between the two groups (Supplementary Table 1). Overall, gastrointestinal symptom severity, assessed by the GSRS was higher in the OCD group than in controls (Table 1). Though dyspepsia (SF-LDQ) scores did not differ, nausea (n = 5, 23.8%) and indigestion (n = 5, 23.8%) were the most commonly reported problems in the OCD group.

Table 1
Gastrointestinal symptom severity in OCD patients versus non-psychiatric controls.

Measure	OCD (n = 21) (Mean ± SD)	Controls (n = 22) (Mean ± SD)
*GSRS total	8.67 ± 6.72	2.32 ± 2.12
*GSRS (abdominal)	0.86 ± 0.79	0.14 ± 0.35
GSRS (reflux)	1.62 ± 2.06	0.32 ± 0.65
*GSRS (indigestion)	2.43 ± 2.29	0.86 ± 0.94
*GSRS (bowel dysfunction)	3.76 ± 3.32	1.00 ± 1.38
SF-LDQ total	5.25 ± 6.24	2.14 ± 2.33

GSRS = Gastrointestinal Symptom Severity Scale; OCD = obsessive-compulsive disorder; SF-LDQ = Short form Leeds Dyspepsia Questionnaire.
t-test to compare means, significance level: *p < 0.005.

Table 2
Demographic characteristics of patients with and without IBS.

Characteristic	OCD-IBS (n = 10) N (%)	OCD-noIBS (n = 11) N (%)
Age (mean ± SD)	33.50 ± 8.36	28.73 ± 9.31
Sex		
Male	5 (50.0)	6 (54.5)
Female	5 (50.0)	5 (45.5)
Body Mass Index (mean ± SD)	27.61 ± 6.31	21.83 ± 2.56
Race		
White	5 (50.0)	7 (63.6)
South Asian	3 (30.0)	1 (9.1)
East Asian	0 (0.0)	1 (9.1)
West Asian	1 (10.0)	1 (9.1)
Mixed race	1 (10.0)	1 (9.1)
Education		
High school or less	1 (10.0)	1 (9.1%)
Some college/university	1 (10.0)	3 (27.3)
Technical/non-university	2 (20.0)	3 (27.3)
University degree	2 (20.0)	3 (27.3)
Graduate degree	4 (40.0)	1 (9.1%)
Employment		
Full-time	4 (40.0)	4 (36.4)
Part-time	1 (10.0)	1 (9.1)
Unemployed	1 (10.0)	2 (18.2)
Retired	0 (0.0)	1 (9.1)
Student	4 (40.0)	3 (27.3)
Relationship		
Never Married	3 (30.0)	8 (72.7)
Married/Common-law	7 (70.0)	1 (9.1)
Divorced/Separated	0 (0.0)	2 (18.2)

OCD-IBS = Patients with Obsessive-compulsive disorder and irritable bowel syndrome; OCD-noIBS = Obsessive-compulsive disorder patients without irritable bowel syndrome.
Age compared using *t*-test, remaining categorical outcomes compared using χ^2 test, significance level: *p < 0.005.

3.1. Prevalence of IBS

Almost half (47.6%, n = 10) of OCD patients met Rome III criteria for IBS (OCD-IBS) compared to 4.5% (n = 1) of controls (χ^2 (1) = 10.47, p = 0.001). Of those in the OCD-IBS group, diarrhea-predominant IBS was most common (n = 6, 60%), with the remaining meeting criteria for either constipation-predominant (n = 2, 20%) or mixed IBS (n = 2, 20%). Demographic characteristics of OCD patients based on IBS status is presented in Table 2.

3.2. Post-hoc analyses: Differences in OCD-IBS group

The number of comorbid disorders were equivalent in both groups [OCD-IBS mean = 3.10 ± 1.37) vs OCD-noIBS mean = 2.73 ± 1.35, t (19) = 0.62, p > 0.005). GAD was the most common comorbidity in OCD patients with IBS (Table 3). Neither self-report nor observer-rated OCD symptom severity differed between the two groups (Table 3). However, results were suggestive of fewer, and likely less severe, compulsions among OCD-IBS patients [mean compulsions subscale: 13.40 ± 1.78 vs 15.45 ± 2.29; t (19) = -2.27, p = 0.035]; no difference was noted with obsessions [mean obsessions subscale: 13.50 ± 2.17 versus 11.73 ± 3.52; t (19) = 1.20, p > 0.005].

Higher MADRS scores were noted in OCD-IBS patients, however self-report mood problems were not different (Table 3). GAD was common among all OCD patients; self-reported levels of anxiety and stress did not differ statistically between groups (Table 3).

As expected, gastrointestinal symptoms were higher in OCD-IBS patients compared to OCD-noIBS patients (Fig. 2). Gastrointestinal symptom severity in the OCD-IBS group, would be considered clinically

Table 3
Psychiatric symptom severity and common comorbid conditions in the OCD-IBS group.

	OCD-IBS group	OCD-noIBS group
Comorbidity N (%)		
Generalized Anxiety Disorder	8 (80.0)	8 (72.7)
Past Major Depressive Disorder (last episode ended > 5 years ago)	7 (70.0)	5 (45.4)
Attention Deficit/Hyperactivity Disorder	7 (70.0)	2 (18.2)
Presence of tics	6 (60.0)	4 (36.4)
Social Anxiety Disorder	4 (40.0)	6 (54.5)
Body Dysmorphic Disorder	3 (30.0)	2 (18.2)
Psychiatric Symptom Severity (mean ± SD)		
Observer-Rated Measures		
Y-BOCS	27.60 ± 2.41	27.18 ± 5.15
DDOCS	21.40 ± 4.62	22.45 ± 7.92
*MADRS	12.60 ± 1.89	6.91 ± 2.77
Patient-Rated Measures		
OCI-R	29.80 ± 5.90	27.18 ± 12.38
DASS-21		
DASS-depression	17.80 ± 9.36	7.40 ± 11.12
DASS-anxiety	14.40 ± 8.48	7.40 ± 8.5
DASS-stress	24.20 ± 7.87	16.80 ± 10.758

OCD-IBS = Patients with Obsessive-compulsive disorder and irritable bowel syndrome; OCD-noIBS = Obsessive-compulsive disorder patients without irritable bowel syndrome.
Mean psychiatric symptom severity of groups compared using *t*-test, significance level: *p < 0.005.

significant (GSRS total > 9) (Fig. 2).

Based on IBS criteria, levels of IL-6 were not significantly different, however they were suggestive of increased inflammation in OCD-IBS patients (OCD-IBS; mean IL-6 = 1.46 ± 0.86 pg/mL vs OCD-noIBS; mean IL-6 = 0.98 ± 0.98 pg/mL; $U = 85.0$, $p = 0.03$). CRP (t (18.78) = 0.36, p = 0.65) and TNF-α (U = 61.50, p = 0.51) levels did not differ based on IBS status of OCD patients.

4. Discussion

Existing studies examining gastrointestinal symptoms and IBS in OCD are limited by their reliance on outdated IBS diagnostic criteria, absence of clinician-rated measures and confounding variables (e.g. concomitant psychotropic or immunomodulating medications, non-clinical or lack of controls, etc.). Whereas the current study included OCD patients who denied intake of concurrent medications, appropriate non-psychiatric controls and measures of psychiatric and gastrointestinal symptom severity. Compared to controls, OCD patients reported significantly higher gastrointestinal symptoms and almost half of OCD patients (47.6%) met Rome III criteria for IBS (OCD-IBS group). Rates of IBS in the current OCD group were higher than reported in previous studies. When comparing OCD patients based on IBS status, no difference was noted in OCD or anxiety symptom severity and stress. However, OCD-IBS patients reported more mood problems with scores ranging from normal to mild depression on the MADRS. Finally, levels of serum IL-6 suggested elevations in the OCD-IBS group, however the difference was not statistically different. To our knowledge, this is the first study to examine gastrointestinal symptom severity, IBS and inflammatory markers in a sample of OCD patients.

Gastrointestinal symptom severity of the overall OCD group (total, reflux, indigestion and bowel dysfunction) exceeded previously reported community scores (Dimenäs et al., 1996). Despite the significant symptoms, these patients were not undergoing any treatment, nor were they diagnosed with any gastrointestinal condition (aside from IBS in some). While this highlights the question of perceived versus actual symptom severity, it is possible that these symptoms may be characteristic of an undiagnosed condition or part of the patients' OCD. Alternatively, "bowel obsessional syndrome" is a condition characterized by overwhelming and irrational severe fear of fecal incontinence, ideation over bowel habits, compulsive behaviours at maintaining body control (Porcelli and Leandro, 2007). Parallels between this condition and OCD have been proposed (Porcelli and Leandro, 2007), with some suggesting that it may be a subtype of OCD (Beidel and Bulik, 1990; Hatch, 1997; Porcelli and Leandro, 2007). Interestingly, bowel dysfunction was the highest scoring subscale of the GSRS in OCD patients

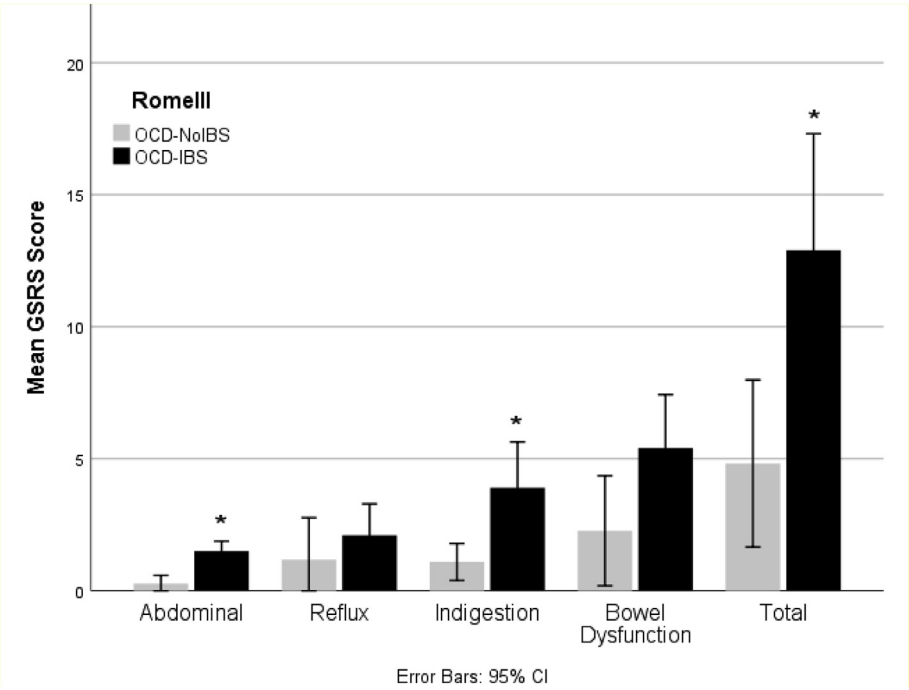

Fig. 2. Gastrointestinal symptom severity in patients with IBS (OCD-IBS) and those without (OCD-NoIBS). Mean gastrointestinal scores compared using t-tests, significance level: *p < 0.005.

and was characterized by urgency (describing lack of control over bowel movements). Perhaps, the gastrointestinal problems noted in this sample relate to this potential syndrome; however, given that criteria of bowel obsessional syndrome were not examined in the study we cannot comment on this.

Alternatively, rates of IBS in the current OCD group were elevated compared to both controls and North American prevalence rates using population-based samples (3.0%–21.0%) (Canavan et al., 2014). Although this may offer a partial explanation for elevated GSRS scores in the overall OCD group, GSRS scores of the OCD-noIBS group were also elevated compared to previous community reports and controls in the current study. Therefore, gastrointestinal problems may be evident in OCD irrespective of IBS status, albeit IBS status was associated with more gastrointestinal problems. A previous study also revealed an elevated rate of IBS in a sample of OCD patients (Masand et al., 2006), and theorized this finding to be related to the putative role of serotonin not only in both IBS and OCD, but also in the gut-brain axis dysfunction. The immune system by way of inflammation is another strongly supported theoretical pathway of the altered gut-brain axis. Given the potential role for immune dysregulation in OCD and also IBS (Petra et al., 2015), the trend towards elevated levels of the pro-inflammatory cytokine IL-6 in OCD-IBS patients, may provide further support for this shared pathophysiology. However, the small sample size and limited power in the current study suggest that this finding should be interpreted cautiously. Further, previous studies have suggested that low grade inflammation in IBS may be subtype-specific, with an increased inflammatory profile associated with diarrhea-predominant IBS (Martin-Viñas and Quigley, 2016). While this was the most common IBS-subtype in the current sample, the small sample size of our current IBS subset limited our ability to look differences amongst IBS subtypes.

Gastrointestinal problems are a common side effect associated with first-line pharmacological treatments for OCD. Non-adherence to pharmacological treatments in OCD has also been related to side effects associated with such treatments (Taylor et al., 2012). Given that this was an unmedicated sample with prominent gastrointestinal difficulties, clinicians may benefit in discussing gastrointestinal symptoms with OCD patients prior to initiating treatment. This information may advise selection of a treatment regimen whose side effect profile does not involve gastrointestinal symptoms, potentially improving treatment compliance and consequently treatment outcomes. For instance, clomipramine with its anticholinergic effects may be better suited as an OCD treatment for patients with IBS-D while SSRI's be recommended for those with IBS-C (Fujishiro et al., 2002). Further, meta-analyses support the use of antidepressants in treating IBS with the antidepressant treatment to be based on IBS-subtype (Ford et al., 2014, 2009). Given the high prevalence of IBS in OCD and comorbidity with psychiatric disorders in general, clinicians should consider IBS status or existing gastrointestinal problems when choosing a treatment for OCD, treating potentially both conditions with one treatment.

While the study design has strengths in its inclusion of an appropriate control condition and in the administration of clinician- and self-rated measures, there are limitations. For instance, the sample size of the current study is quite small, limiting the power of our analyses. The control group was recruited looking for “healthy adults”, as such the low rate of IBS in the control group may have been prone to selection bias. Similarly, the high IBS rate in the OCD group may have also been subject to recruitment or self-selection biases. Specifically, recruitment strategies indicated the study was exploring involvement of the gut microbiome as such, given public knowledge of the gut microbiome's involvement in gastrointestinal disorders, perhaps this resulted in recruitment of OCD outpatients who suffered from gastrointestinal issues. It is also possible the high rate of IBS in the OCD group may be driven by the high GAD comorbidity in this study sample, given that gastrointestinal distress is a symptom of GAD. Further, since initiating data collection, the newer Rome IV criteria were published. Although IBS criteria were altered, a recent study revealed that most patients who previously met criteria for Rome III IBS continue to meet criteria for Rome IV IBS(Aziz et al., 2018). The two primary modifications from Rome III to Rome IV IBS criteria involved: (1) removal of the term “abdominal discomfort”, leaving only “abdominal pain” and (2) symptom frequency has increased from 3 days/month to at least 1 day/week (Aziz et al., 2018). Based on these new criteria, the rate of IBS in OCD patients may be lower than what is reported in the current study. While we are unable to preclude whether elevated IBS rates in the current sample are simply due to modifications in Rome criteria, it is unlikely that this is the case. It has been suggested that the evolving Rome criteria have resulted in trends towards reduced rates of diagnostic criteria among patients (Sperber et al., 2007). However, the studies comparing prevalence from Rome I to II or Rome II to III have been mixed, making it unclear what rates of IBS may be like with older criterion. Given these limitations, a larger observational trial, perhaps in an outpatient clinic where consecutive OCD patients are recruited could appropriately inform these findings.

Overall, these results inform future lines of research, particularly those related to the role of the gut-brain-microbiome axis in OCD. As demonstrated with research in autism spectrum disorder, prominent gastrointestinal difficulties fueled exploration of the gut microbiome. Further, a possible role of the HPA axis may be of interest. As the central stress-response system, it is interesting to note that stress not only worsens symptoms of IBS (Fadgyas-Stanculete et al., 2014), but also symptoms of OCD (Rosso et al., 2012). Both of these conditions have been independently associated with hyperactivity of the HPA axis (Dinan et al., 2006). Clinically, whether patients with pre-existing gastrointestinal problems or IBS are more susceptible to side effects of current first-line psychopharmacological treatments or less compliant with treatment may also be of interest. Further exploration of the relationship between OCD and IBS would also be of interest, particularly by examining efficacy of interventions that may concurrently treat both conditions. Given that OCD is a disorder where the pathophysiological mechanism remains unclear, high prevalence of IBS and elevated inflammation suggest the gut-brain axis may be a pathway of interest for future exploration with the gut microbiome as a prime target for research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.08.004.

Conflicts of interest

Dr. Michael Van Ameringen is on the Advisory Boards of Purdue and Allergan; and the Speaker's Bureau for Lundbeck, Purdue and Allergan. He has received research support from Janssen-Ortho Inc, Pfizer and Shire Canada. Dr. Noam Soreni reports research funding from Lundbeck. The remaining authors have nothing to disclose.

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