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Short Report

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Fluoxetine for Maintenance of Remission and to Improve Quality of Life in Patients with Crohn's Disease: a Pilot Randomized Placebo-Controlled Trial

Antonina Mikocka-Walus,[a,b,c,d] Patrick A. Hughes,[e] Peter Bampton,[f] Andrea Gordon,[a] Melissa A. Campaniello,[e] Chris Mavrangelos,[e] Benjamin J. Stewart,[c] Adrian Esterman,[a,i] Jane M. Andrews[g,h]

[a]School of Nursing and Midwifery, University of South Australia, Adelaide, Australia [b]Department of Health Sciences, University of York, York, UK [c]School of Psychology, University of Adelaide, Adelaide, Australia [d]School of Psychology, Deakin University, Burwood, Australia [e]Centre for Nutrition and Gastrointestinal Diseases, School of Medicine, University of Adelaide and South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia [f]Department of Gastroenterology and Hepatology, Flinders Medical Centre, Bedford Park, Australia [g]Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, Australia [h]School of Medicine, Faculty of Health Sciences, University of Adelaide, Adelaide, Australia [i]Australian Institute of Tropical Health and Medicine, James Cook University, Townsville, Australia

Corresponding author: A. Mikocka-Walus, Senior Lecturer, School of Psychology, Deakin University, 221 Burwood Highway, Burwood, 3125, Victoria, Australia. Tel: +61 3 924 68575; email: antonina.mikockawalus@deakin.edu.au

Abstract

Background and Aims: Previous studies have shown that antidepressants reduce inflammation in animal models of colitis. The present trial aimed to examine whether fluoxetine added to standard therapy for Crohn's disease [CD] maintained remission, improved quality of life [QoL] and/or mental health in people with CD as compared to placebo.

Methods: A parallel randomized double-blind placebo controlled trial was conducted. Participants with clinically established CD, with quiescent or only mild disease, were randomly assigned to receive either fluoxetine 20 mg daily or placebo, and followed for 12 months. Participants provided blood and stool samples and completed mental health and QoL questionnaires. Immune functions were assessed by stimulated cytokine secretion [CD3/CD28 stimulation] and flow cytometry for cell type. Linear mixed-effects models were used to compare groups.

Results: Of the 26 participants, 14 were randomized to receive fluoxetine and 12 to placebo. Overall, 14 [54%] participants were male. The mean age was 37.4 [SD=13.2] years. Fluoxetine had no effect on inflammatory bowel disease activity measured using either the Crohn's Disease Activity Index [$F(3, 27.5)=0.064$, $p=0.978$] or faecal calprotectin [$F(3, 32.5)=1.08$, $p=0.371$], but did have modest effects on immune function. There was no effect of fluoxetine on physical, psychological, social or environmental QoL, anxiety or depressive symptoms as compared to placebo [all $p>0.05$].

Conclusions: In this small pilot clinical trial, fluoxetine was not superior to placebo in maintaining remission or improving QoL. [ID: ACTRN12612001067864.]

Key Words: Antidepressants; Crohn's disease; disease activity; mental health; quality of life

1. Introduction

There is ongoing debate regarding the efficacy of antidepressants for mental disorders;[1] however, antidepressants have been increasingly studied in the context of physical health and, in particular, the immune system. Although studies with healthy volunteers have demonstrated that antidepressants can improve immunoregulatory activity,[2] lead to a reduction in the need for steroids in asthma sufferers[3] and to further possible improvements in overall immune function,[4] little research has been conducted on antidepressants in inflammatory bowel disease [IBD].

It has been documented that up to 30% of IBD patients use antidepressants.[5] In the initial systematic review conducted on the topic,[6] the low quality of available evidence made it impossible to provide a definitive statement on their efficacy in IBD. The most recent update to this review[7] suggested a positive impact of antidepressants [desipramine and fluoxetine] on inflammation in IBD. This evidence originates from randomized controlled trials [RCTs] in animal models of IBD where desipramine and fluoxetine reduced the severity of intestinal inflammation. Most recently, a small 12-week RCT compared duloxetine [60 mg/day] to placebo in patients with IBD and demonstrated a slight improvement in anxiety and depression [p=0.049 and 0.041, respectively], improvements in physical, psychological and social quality of life [QoL] [p=0.001, 0.038 and 0.015, respectively] and decreased IBD severity [p=0.02], with mild to moderate effect sizes.[8] However, the long-term impact of antidepressant treatment on IBD course or other clinical outcomes is largely unknown. Additionally, there is no experimental study using objective measures of inflammation such as faecal calprotectin [FC] or inflammatory markers in blood. Thus, the aim of the present study was to examine the impact of a low-dose antidepressive agent, fluoxetine, in addition to standard therapy as compared to placebo on disease activity, QoL and mental health in patients with Crohn's disease [CD] over 12 months.

2. Methods

The study was approved by the hospitals' and university research ethics committees. The protocol was registered with the Australian New Zealand Clinical Trials Registry [ID: ACTRN12612001067864]. Adult patients from two major South Australian hospitals with clinically established diagnosis of CD, in clinical remission but who flared CD in the last 12 months were included in this parallel double-blind placebo RCT involving intention to treat analyses. We excluded those with serious uncontrolled mental illness, those alcohol/substance-dependent or cognitively impaired; those taking antidepressants or receiving psychotherapy; those taking steroids [prednisolone >15 mg or equivalent]; those pregnant/breastfeeding or planning to become pregnant; and those taking any medications listed as contraindicated with fluoxetine.[9] Participants were randomly [using a computer-generated sequence] assigned to receive either fluoxetine 20 mg daily or placebo [i.e. gelatin capsules filled with microcrystalline cellulose]. Fluoxetine was selected based on previous research showing its anti-inflammatory properties in humans,[10,11] and in relation to IBD based on animal models of colitis.[7,12] While desipramine has shown similar effects with respect to reduced inflammation, fluoxetine is a better tolerated medication, with fewer adverse events. Previous human studies have recommended a dose of 20 mg daily when looking for anti-inflammatory effect and the length of the study to be at least 3–8 weeks.[10,11,13–15] Patients in both treatment arms remained on their current IBD medication. Treatment was delivered via hospital pharmacies to ensure double blinding. Participants were asked to provide blood and stool samples and complete questionnaires on four occasions [baseline, 3, 6 and 12 months] [Appendix 1]. Screening for mental disorders was undertaken using the Structural Clinical Interview for DSM disorders [SCID].[16] The primary outcome measures were a significant group difference in the CD remission rate as measured on the Crohn's Disease Activity Index [CDAI][17] [cut-off <150] and the difference in means on the World Health Organisation Quality of Life questionnaire [WHOQoL].[18] Secondary measures were differences in: remission rates as measured by FC;[19] means on the Hospital Anxiety Depression Scale [HADS];[20] and mean cytokine and chemokine levels between the experimental and control groups at 6 months. Peripheral blood mononuclear cells [PBMCs] were isolated from fresh blood by density centrifugation as previously described.[21,22] Power calculations were prepared for two main outcome measures of disease activity and QoL, using the PASS 11 software package:

[a] Disease activity on CDAI at 12 months: a sample size of 26 in each group yields 80% power to detect a difference in means of 65 assuming a common standard deviation of 70 using a two group t-test with a 0.025 two-sided significance level. A value of p=0.025 was used to allow for multiple testing.
[b] Quality of life on WHOQoL at 12 months: a sample size of 23 in each group yields 80% power to detect a difference in means of 19 assuming a common standard deviation of 20 using a two group t-test with a 0.025 two-sided significance level. A value of p=0.025 was used to allow for multiple testing.

Groups were compared on the outcome measures [except for immune studies] using the linear mixed effects, with time, group and time–group interaction terms included, adjusting for stratifying variables [sex, HADS score]. Immune cell proportion and cytokine secretion were compared by paired Student's t-test.

3. Results

The CONSORT flow diagram [Figure 1] presents study recruitment. Overall, 26 patients were randomized: 14 to fluoxetine and 12 to placebo groups. In each group, three participants withdrew from the study at some point, resulting in an overall attrition of 23%. Table 1 presents demographic, clinical and treatment characteristics of the study's population. The mean age was 37.4 [SD=13.2] years. Throughout the trial, the fluoxetine group received numerically more biologics than controls [at 6 months: n=9 vs n=3 and at 12 months: n=8 vs n=3, respectively, p=n.s.]. The numbers of patients taking immunomodulators were similar between the fluoxetine group and controls [at 6 months: n=9 vs n=6 and at 12 months: n=8 vs n=7]. The use of steroids was low, with only one control group participant taking them at 6 months and no participants taking them at 12 months.

3.1. Fluoxetine and disease activity

There was no statistically significant difference in the proportion of participants in remission at any time point [p<0.05] [Table 2]. Putting the CDAI into the linear mixed-effects model as a continuous variable likewise showed no group difference [$F(3, 27.5)$=0.064, p=0.978].

While numerically the fluoxetine group had slightly better disease control during the study, as assessed by FC, multivariate group comparions showed no group difference in FC scores during the 12-month treatment period [$F(3, 32.5)$=1.08, p=0.371].

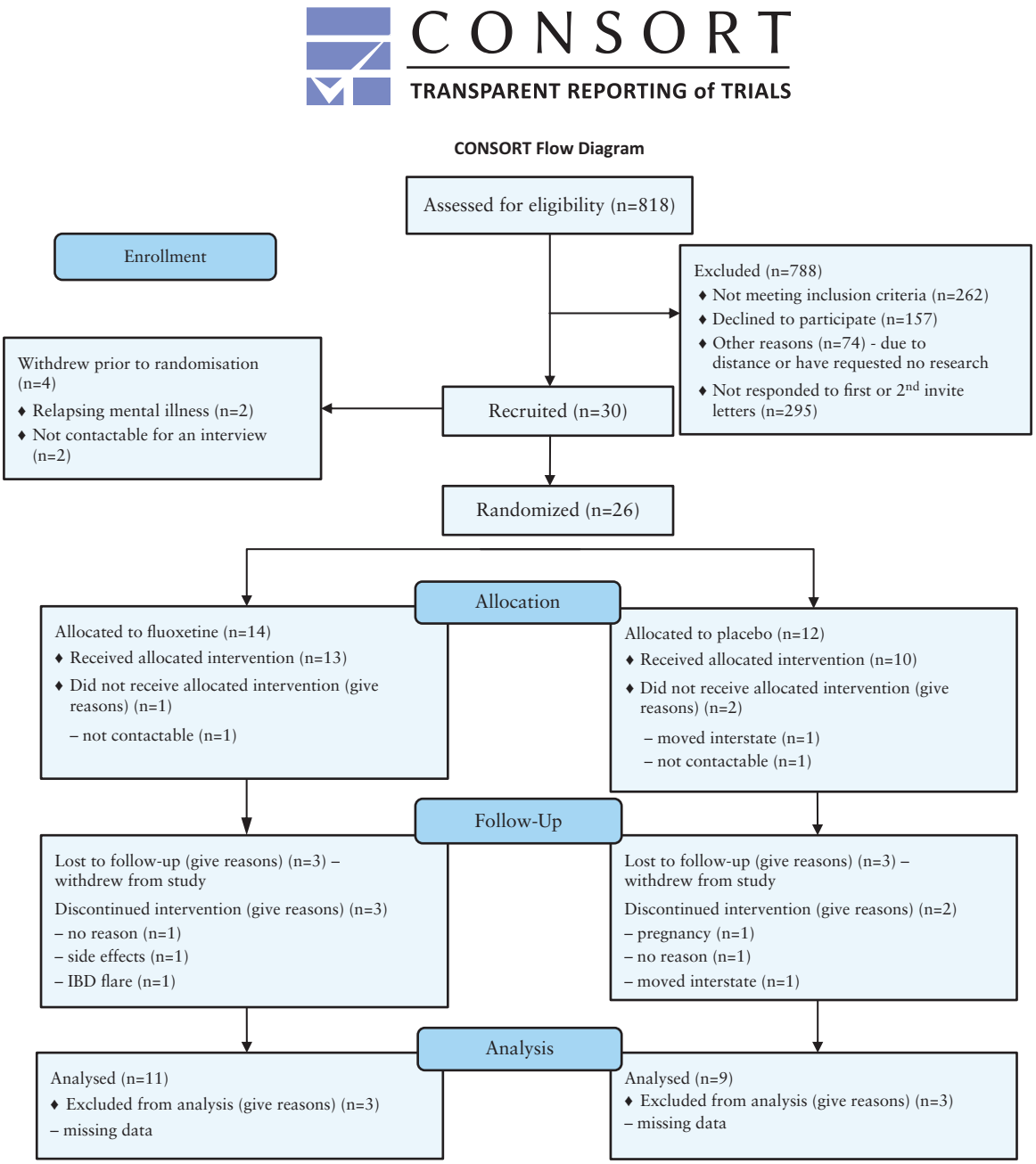

Figure 1. CONSORT flow diagram of study recruitment.

Live PBMC single cells were gated [Table 3]. Fluoxetine treatment significantly increased the proportion of $T_{H\ Effector\ Memory}$ and decreased the proportion of $T_{C\ Effector\ Memory\ RA}$ cells at the 6-month visit, while placebo treatment had no effect [Table 4]. Other T cell subpopulations in the peripheral blood, including T_H and T_C gut homing and T_{REG}, did not vary in response to either fluoxetine or placebo between baseline and 6 months. Placebo patients had significantly reduced interleukin-10 [IL-10] secretion from PBMCs at 6 months compared to baseline, while fluoxetine patients had no such effect [Table 5]. No other cytokine stimulation response was affected by fluoxetine or placebo.

3.2 Fluoxetine, QoL and metal health

There was no significant group difference in physical QoL [$F(3, 34.9)=0.560, p=0.645$], psychological QoL [$F(3, 33.5)=0.217, p=0.884$], social relationships QoL [$F(3, 33.7)=0.553, p=0.649$] or environmental QoL [$F(3, 36.1)=0.031, p=0.992$] over the 12 months. There was no significant group difference in anxiety [$F(3, 33.9)=0.063, p=0.979$] or depression [$F(3, 36.1)=0.106, p=0.956$] over the 12 months.

3.3. Safety

Overall, eight [57%] fluoxetine group participants versus three [25%] controls reported side-effects. These all resolved during the first 2 weeks of treatment. In the fluoxetine group, side-effects included: fatigue [$n=4$], episode of low mood/anxiety [$n=2$]; nausea/diarrhoea/vomiting [$n=2$], dry mouth [$n=1$] and hot flushes [$n=1$] [n adds to >8 as some participants reported more than one side-effect]. In the placebo group, these were muscle spasms [$n=2$] and nausea/diarrhoea/vomiting [$n=1$].

Table 1. Demographic, clinical and treatment characteristics by group: *n* [%]

		Fluoxetine (*n*=14)	Placebo (*n*=12)
Gender	Male	8 [57]	6 [50]
Marital status	Married/*de facto*	8 [57]	9 [75]
Employment status	Working full- or part-time	10 [71]	9 [75]
Education	University degree	5 [36]	6 [50]
	Year 12	4 [29]	2 [17]
Operations for IBD		7 [50]	7 [58]
Medication for IBD	Complementary	7 [50]	5 [42]
	Mesalazine	4 [29]	3 [25]
	Prednisolone	1 [7]	0 [0]
	Immunomodulators	9 [64]	10 [83]
	Biologics	9 [64]	4 [33]
	Analgesics	5 [36]	5 [42]
Currently smoking		3 [21]	2 [17]
Previous antidepressant use		3 [21]	1 [8]
Previous psychotherapy use		3 [21]	3 [25]
Any overnight hospital admissions for IBD		11 [79]	9 [75]
		Mean [SD]	
Age, years		38.07 [13.6]	36.67 [13.2]
Years since diagnosis with CD		14.98 [13.1]	12.21 [8.1]
No. of hospital admissions in last 5 years		3.44 [2.3]	3.08 [4.1]

Table 2. Disease activity over time by group: *n* [%]

		Fluoxetine (*n*=14)				Placebo (*n*=12)			
		Baseline (*n*=14)	3 months (*n*=12)	6 months (*n*=11)	12 months (*n*=10)	Baseline (*n*=12)	3 months (*n*=10)	6 months (*n*=10)	12 months (*n*=8)
CDAI	Active >150	0 [0]	0 [0]	0 [0]	1 [10]	0 [0]	1 [10]	0 [0]	0 [0]
Calprotectin	Active >200	0 [0]	3 [25]	1 [9.1]	1 [10]	2 [16.6]	4 [40]	5 [50]	0 [0]
		Mean [SD]							
CDAI		63.8 [44.4]	54.92 [37.3]	52.36 [43.3]	84.40 [82.5]	66.4 [44.7]	53.1 [59.7]	48.50 [39.2]	60.63 [46.5]
Calprotectin		46.4 [33.2]	125.5 [106.6]	91.4 [86.1]	76.9 [90.5]	98.1 [94.4]	178.3 [108.9]	185.4 [111.8]	67.9 [45.6]
Physical QoL		24.8 [5.3]	25.4 [3.4]	25.7 [4.5]	26.3 [3.7]	26 [4.3]	27.2 [2.9]	26 [4.6]	25.7 [6.1]
Psychological QoL		22.3 [4.1]	24.5 [2.6]	23.7 [4.2]	24.1 [3.6]	22.8 [3.7]	24.3 [2.2]	23.9 [2.3]	23.3 [4.1]
Social QoL		10.4 [2.9]	11.1 [3.1]	11.4 [2.4]	11.8 [2.2]	12.3 [2.1]	12.3 [1.1]	12.3 [1.1]	12 [2.8]
Environmental QoL		31.5 [4.8]	31.7 [4.1]	32.3 [4.6]	31.6 [4.6]	32.2 [4.4]	32.2 [3.8]	32.8 [4.5]	32.2 [3.1]
HADS Anxiety		5.3 [4.1]	3.2 [2.5]	3.2 [2.6]	3.8 [2.6]	4.9 [3.4]	2.9 [2.1]	3.3 [2.9]	4.2 [4.9]
HADS Depression		3.8 [2.9]	2 [1.6]	2.7 [2.9]	2.9 [2.8]	3.6 [3.1]	1.7 [1.8]	2 [1.9]	3.1 [3.4]

Table 3. Flow cytometry gating strategy

Cell type	Gating strategy
T	CD3+
T_{HELPER} [T_H]	CD3+ CD4+ CD8–
T_H gut homing	CD3+ CD4+ CD8– CD45RA– CD49d+ β_7+
$T_{H\ Effector\ Memory}$ [$T_{H\ EM}$]	CD3+ CD4+ CD8– CD45RA– CD197–
$T_{H\ Central\ Memory}$ [$T_{H\ CM}$]	CD3+ CD4+ CD8– CD45RA– CD197–,
$T_{H\ Effector\ Memory\ RA}$ [$T_{H\ EMRA}$]	CD3+ CD4+ CD8– CD45RA– CD197–
T_{REG}	CD3+ CD4+ CD8– CD25+ $CD127^{DIM}$
$T_{CYTOTOXIC}$ [T_C]	CD3+ CD4– CD8+
T_C gut homing	CD3+ CD4– CD8+ CD45RA– CD49d+ β_7+
$T_{C\ Effector\ Memory}$ [$T_{C\ EM}$]	CD3+ CD4– CD8+ CD45RA– CD197–
$T_{C\ Central\ Memory}$ [$T_{C\ CM}$]	CD3+ CD4– CD8+ CD45RA– CD197–,
$T_{C\ Effector\ Memory\ RA}$ [$T_{C\ EMRA}$]	CD3+ CD4– CD8+ CD45RA– CD197–

4. Discussion

This study is the first longitudinal trial on the effect of fluoxetine on CD activity, QoL and mental health.

While a previous trial of a similar size to ours demonstrated short-term effectiveness of duloxetine in improving anxiety, depression, QoL and severity of symptoms measured on a disease activity index,[8] the present trial demonstrated no benefit of fluoxetine on disease activity [assessed with CDAI and FC], QoL or mental health over 12 months compared to placebo. This may mean that selective serotonin reuptake inhibitors such as fluoxetine offer no IBD-specific benefit while other newer antidepressants could be a more promising treatment pathway. Given the success of tricyclic antidepressants in managing functional gut disorders,[23,24] they are certainly an interesting option to explore. Similarly, atypical medications such as mirtazapine, which resemble tricyclics in their mechanism of action but have fewer side-effects, could also be tested. However, it should be noted that this result could also be due to a small sample size. In addition, participants were allowed to receive their usual treatment [steroids, biologics, etc.] and these could be increased during the trial, if needed. While relapse of CD meant withdrawal from the study, some patients had mildly active disease throughout the trial and may have received more aggressive treatment for it [e.g. at baseline and throughout the trial numerically more patients in the fluoxetine group received biologics], which could impact our results, particularly that biologics are known to improve QoL in IBD and thus also potentially mood.[25] Further, clinical depression

Table 4. Flow cytometry analysis ofT cell populations in PBMCs from subjects who received placebo and active treatment. Study entry and 6-month visit relative proportions compared by paired *t*-test. n.s. = $p>0.05$, *$p<0.05$. Populations gated as outlined in Table 3.

Cell type	Fluoxetine			Placebo		
[%]	Study entry	6 months	Significance	Study entry	6 months	Significance
T	71.2 ± 3.3	70.9 ± 2.8	n.s.	72.4 ± 1.9	66.2 ± 1.74	n.s.
T_H	65.1 ± 3.4	66.6 ± 3.6	n.s.	63.1 ± 3.2	61.3 ± 3.7	n.s.
$T_H\ \alpha_4\beta_7$	10.7 ± 1.2	11.2 ± 1.3	n.s.	12.3 ± 2.3	14.0 ± 2.1	n.s
$T_{H\ EM}$	6.7 ± 0.6	7.2 ± 0.9	n.s.	8.1 ± 1.8	6.8 ± 1.1	n.s.
$T_{H\ CM}$	2.5 ± 0.4	2.5 ± 0.37	n.s.	3.3 ± 0.7	3.3 ± 0.8	n.s.
$T_{H\ EMRA}$	42.8 ± 4.5	45.8 ± 4.5	* ↑	44.0 ± 2.9	39.7 ± 3.1	n.s.
T_{REG}	3.6 ± 0.53	4.3 ± 0.7	n.s.	4.2 ± 0.7	3.6 ± 0.4	n.s.
T_C	23.5 ± 2.1	23.5 ± 1.9	n.s.	20.3 ± 2.8	22.3 ± 3.9	n.s.
$T_C\ \alpha_4\beta_7$	27.5 ± 2.4	29.2 ± 2.3	n.s.	32.8 ± 2.8	32.2 ± 3.8	n.s.
$T_{C\ EM}$	3.9 ± 0.4	3.9 ± 0.4	n.s.	3.2 ± 0.5	3.3 ± 0.9	n.s.
$T_{C\ CM}$	27.6 ± 2.5	27.0 ± 2.0	n.s.	27.3 ± 4.3	27.8 ± 5.3	n.s.
$T_{C\ EMRA}$	3.9 ± 0.5	3.5 ± 0.48	* ↓	4.4 ± 0.9	4.75 ± 0.9	n.s.

Table 5. Comparison of CD3/CD28 stimulated cytokine concentrations in PBMC supernatants from subjects who received placebo and active treatment. Visit 1 [V1] and visit 2 [V2] concentrations compared by paired *t*-test. n.s. = $p>0.05$, *$p<0.05$.

Cytokine [pg/ml]	Fluoxetine			Placebo		
	Study entry	6 months	Significance	Study entry	6 months	Significance
IFN-γ	33 677 ± 10 741	25 074 ± 7565	n.s.	19 576 ± 6946	6364 ± 2012	n.s.
IL-2	16 052 ± 1199	13 542 ± 2234	n.s.	10 477 ± 2640	9961 ± 2788	n.s.
IL-4	0.875 ± 0.142	0.641 ± 0.09	n.s.	0.471 ± 0.14	0.299 ± 0.06	n.s.
IL-5	1256 ± 230.7	952.6 ± 175.3	n.s.	711.2 ± 214.3	553.7 ± 176.5	n.s.
IL-6	783.3 ± 212.2	1075 ± 615	n.s.	675.1 ± 257.3	206.1 ± 79.43	n.s.
IL-10	801.52 ± 171.2	525.3 ± 93.2	n.s.	633.6 ± 163.3	222.9 ± 63.2	* ↓
IL-13	9289 ± 1064	6697 ± 970.7	n.s.	4369 ± 1091	3182 ± 885.8	n.s.
TNF-α	6649 ± 541.7	5671 ± 730.9	n.s.	4593 ± 1113	3269 ± 929.3	n.s.

was not necessary to enter the trial and it could be argued that if the pathway to controlling disease activity in CD leads via improving mood, as could be supposed based on the current brain–gut–microbiome research reviewed elsewhere,[26–28] to show the effect we should have included only those CD patients with established depression. The mechanism behind the antidepressants' effect on inflammation is, however, as yet unclear. Similarly, it could be easier to show antidepressants' effect on inflammation had we included people during flares. However, in the present trial we were interested in the maintenance of remission and thus that was not considered appropriate.

Adaptive T cell immune responses have a central role in IBD, and fluoxetine treatment had modest, but significant, effects on effector memory RA cells, increasing T_H and decreasing T_C populations. These cells have important roles in immune responses to virus and vaccine, and while they are yet to be definitively characterized in IBD they are likely to play an important role.[29] There was no effect on the proportions of T_{REG} or the proportions of T_H or T_C expressing integrins that direct T cells to migrate to the gut. Interestingly, T-cell secreted IL-10 decreased in the placebo group but not the fluoxetine group. IL-10 plays an important anti-inflammatory role, and the sustained IL-10 secretion that occured in the fluoxetine-treated group but not placebo group suggests that fluoxetine activates anti-inflammatory mechanisms. However, as there was little difference between clinical symptoms associated with placebo or fluoxetine treatment, other compensatory immune mechanisms may be in play, potentially involving T_{EMRA} cells.

Finally, the current study showed that the intervention was acceptable to patients and was well tolerated. Clinicians may thus use fluoxetine in the IBD population.

4.1. Limitations

While attrition was not particularly high, recruitment proved challenging and the study was underpowered. In order to be successful with the trial of antidepressants in IBD, a multi-centre approach with a large pool of patients not exposed to antidepressants is required. Future studies should utilize objective measures of inflammation such as FC and inflammatory markers in blood and follow patients for at least 12 months. If the sample size allows for it, confounders such as concurrent depression, previous use of antidepressants and current CD treatment [e.g. biologics] should be controlled for.

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Conflict of Interest

We have not identified any competing interests in relation to this trial. However, JMA has served as a consultant for AbbVie, Abbott, Ferring, Janssen, Pfizer, Takeda, MSD, Shire. PB has served as an advisory board member for Abbvie Australia and Janssen Australia.

Author Contributions

AMW designed the study, contributed to data analysis, drafted the paper and approved its final version. PAH contributed to conception and design of the study and PAH, MAC, CM conducted immune analysis, provided comments on drafts, and approved the final version of the manuscript. PB contributed to conception and design of the study, was involved in patient recruitment, provided comments on drafts, and approved the final version of the manuscript. AG contributed to conception and design of the study, managed the administrative side of the study, provided comments on drafts, and approved the final version of the manuscript. BJS contributed to conception and design of the study, was involved in patient recruitment, provided comments on drafts, and approved the final version of the manuscript. AE contributed to conception and design of the study, contributed to the analysis, provided comments on drafts, and approved the final version of the manuscript. JMA contributed to conception and design of the study, was involved in patient recruitment, provided comments on drafts, and approved the final version of the manuscript.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Kirsch I. *The Emperor's New Drugs: Exploding the Antidepressant Myth*. New York: Basic Books; 2009.
2. Szuster-Ciesielska A, Tustanowska-Stachura A, Slotwinska M, Marmurowska-Michalowska H, Kandefer-Szerszen M. In vitro immunoregulatory effects of antidepressants in healthy volunteers. *Pol J Pharmacol* 2003;**55**:353–62.
3. Brown ES, Vigil L, Khan DA, Liggin JD, Carmody TJ, Rush AJ. A randomized trial of citalopram versus placebo in outpatients with asthma and major depressive disorder: a proof of concept study. *Biol Psychiatry* 2005;**58**:865–70.
4. Krommydas G, Gourgoulianis KI, Karamitsos K, Krapis K, Kotrotsiou E, Molyvdas PA. Therapeutic value of antidepressants in asthma. *Med Hypotheses* 2005;**64**:938–40.
5. Mikocka-Walus AA, Gordon AL, Stewart BJ, Andrews JM. The role of antidepressants in the management of inflammatory bowel disease (IBD): a short report on a clinical case-note audit. *J Psychosom Res* 2012;**72**:165–7.
6. Mikocka-Walus AA, Turnbull DA, Moulding NT, Wilson IG, Andrews JM, Holtmann GJ. Antidepressants and inflammatory bowel disease: a systematic review. *Clin Pract Epidemiol Ment Health* 2006;**2**:24.
7. Mikocka-Walus A, Clarke D, Gibson P. Can antidepressants influence the course of inflammatory bowel disease? The current state of research. *Eur Gastroenterol Hepatol* 2009;**5**:48–53.
8. Daghaghzadeh H, Naji F, Afshar H, *et al*. Efficacy of duloxetine add on in treatment of inflammatory bowel disease patients: a double-blind controlled study. *J Res Med Sci* 2015;**20**:595–601.
9. *Australian Medicines Handbook*. Adelaide: Australian Medicines Handbook Pty Ltd; 2012.
10. O'Brien SM, Scott LV, Dinan TG. Antidepressant therapy and C-reactive protein levels. *Br J Psychiatry* 2006;**188**:449–52.
11. Sluzewska A, Rybakowski JK, Laciak M, Mackiewicz A, Sobieska M, Wiktorowicz K. Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. *Ann N Y Acad Sci* 1995;**762**:474–6.
12. Koh SJ, Kim JM, Kim IK, *et al*. Fluoxetine inhibits NF-κB signaling in intestinal epithelial cells and ameliorates experimental colitis and colitis-associated colon cancer in mice. *Am J Physiol Gastrointest Liver Physiol* 2011;**301**:G9–19.
13. Maes M. The immunoregulatory effects of antidepressants. *Hum Psychopharmacol* 2001;**16**:95–103.
14. Maes M, Delange J, Ranjan R, *et al*. Acute phase proteins in schizophrenia, mania and major depression: modulation by psychotropic drugs. *Psychiatry Res* 1997;**66**:1–11.
15. Maes M, Song C, Lin AH, *et al*. Negative immunoregulatory effects of antidepressants: inhibition of interferon-γ and stimulation of interleukin-10 secretion. *Neuropsychopharmacology* 1999;**20**:370–9.
16. First MB, Williams JBW, Spitzer RL, Gibbon M. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinical Trials Version (SCID-CT)*. New York: Biometrics Research; 2007.
17. Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976;**70**:439–44.
18. WHO. *WHOQOL User Manual*. Geneva: WHO; 1998 [cited 2010]. Available from: http://www.who.int/mental_health/resources/evidence_research/en/index.html.
19. Tibble J, Teahon K, Thjodleifsson B, *et al*. A simple method for assessing intestinal inflammation in Crohn's disease. *Gut* 2000;**47**:506–13.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.
21. Hughes PA, Moretta M, Lim A, *et al*. Immune derived opioidergic inhibition of viscerosensory afferents is decreased in irritable bowel syndrome patients. *Brain Behav Immun* 2014;**42**:191–203.
22. Hughes PA, Harrington AM, Castro J, *et al*. Sensory neuro-immune interactions differ between irritable bowel syndrome subtypes. *Gut* 2013;**62**:1456–65.
23. Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut* 2009;**58**:367–78.
24. Ford AC, Luthra P, Tack J, Boeckxstaens GE, Moayyedi P, Talley NJ. Efficacy of psychotropic drugs in functional dyspepsia: systematic review and meta-analysis. *Gut* 2015; doi: 10.1136/gutjnl-2015-310721.
25. Feagan BG, Reinisch W, Rutgeerts P, *et al*. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. *Am J Gastroenterol* 2007;**102**:794–802.
26. Mayer EA, Bradesi S, Gupta A, Katibian DJ. The brain–gut axis and psychological processes in IBD. In: Knowles SR, Mikocka-Walus A, editors. *Psychological Aspects of Inflammatory Bowel Disease: A Biopsychosocial Approach*. London: Routledge; 2015: 20–9.
27. Sexton KA, Bernstein CN. Stress, distress and IBD. In: Knowles SR, Mikocka-Walus A, editors. *Psychological Aspects of Inflammatory Bowel Disease: A Biopsychosocial Approach*. London: Routledge; 2015: 10–19.
28. De Cruz P. Microbiota and psychological processes in IBD. In: Knowles SR, Mikocka-Walus A, editors. *Psychological Aspects of Inflammatory Bowel Disease: A Biopsychosocial Approach*. London: Routledge; 2015: 30–9.
29. Mueller SN, Gebhardt T, Carbone FR, Heath WR. Memory T cell subsets, migration patterns, and tissue residence. *Ann Rev Immunol* 2013;**31**:137–61.