Short Report

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; 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, lead to a reduction in the need for steroids in asthma sufferers and to further possible improvements in overall immune function, 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. In the initial systematic review conducted on the topic, 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 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 \(p=0.02\), with mild to moderate effect sizes. 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 biologics than controls [at 6 months: \(n=8\) 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.

2.1. 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 comparisons showed no group difference in FC scores during the 12-month treatment period \(F(3, 32.5)=1.08, p=0.371\).
Live PBMC single cells were gated [Table 3]. Fluoxetine treatment significantly increased the proportion of T\textsubscript{H} Effector Memory and decreased the proportion of T\textsubscript{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\textsubscript{H} and T\textsubscript{C} gut homing and T\textsubscript{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 mental 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]         |
| 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]         |
|                          | Prednisolone      | 1 [7]          |
|                          | Immunomodulators  | 9 [64]         |
|                          | Biologics         | 9 [64]         |
|                          | Antalgescs        | 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=11)| 6 months (n=10)| 12 months (n=10)| Baseline (n=12) | 3 months (n=10)| 6 months (n=10)| 12 months (n=8) |                |
|                          | 0 [0]             | 0 [0]          | 1 [10]          | 0 [0]               | 0 [0]             | 0 [0]          |                |
| CDAI                     | Active >150       |                |                |                    |                  |                |                |
| Calprotectin             | Active >200       | 0 [0]          | 3 [25]          | 1 [9.1]             | 1 [10]           | 0 [0]          | 2 [16.6]         | 4 [40]          | 5 [5]          |
|                          | Mean [SD]         | 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] |
| CDAI                     |                   | 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] |
| Calprotectin             |                   | 24.8 [5.3]     | 25.4 [3.4]      | 25.7 [4.3]          | 26.3 [3.7]       | 26 [4.3]      | 27.2 [2.9]     | 26 [4.6]        | 25.7 [6.1] |
| Physical 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] |
| Psychological 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 [2.8]        | 12 [2.8]    |
| Social 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] |
| Environmental QoL        |                   | 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 Anxiety             |                   | 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 [3.4]    |
| HADS Depression          |                   |                |                |                    |                  |                |                |                |                |

Table 3. Flow cytometry gating strategy

| Cell type                  | Gating strategy |
|---------------------------|-----------------|
| T                         | CD3+            |
| T<sub>helper</sub> [T<sub>H</sub>] | CD3+ CD4+ CD8<sup>-</sup> |
| T<sub>H</sub> effector memory [T<sub>H</sub>EM] | CD3+ CD4+ CD8<sup>-</sup> CD45RA<sup>-</sup> CD49δ<sup>+</sup> CD197+ |
| T<sub>H</sub> central memory [T<sub>H</sub>CM] | CD3+ CD4+ CD8<sup>-</sup> CD45RA<sup>-</sup> CD197+ |
| T<sub>C</sub> effector memory RA [T<sub>C</sub>EMRA] | CD3+ CD4+ CD8<sup>-</sup> CD45RA<sup>-</sup> CD197+ |
| T<sub>C</sub> cytotoxic [T<sub>C</sub>CTO] | CD3+ CD4+ CD8<sup>+</sup> CD127<sup>+</sup> |
| T<sub>C</sub> beta [T<sub>C</sub>BET] | CD3+ CD4+ CD8<sup>-</sup> CD45RA<sup>-</sup> CD49δ<sup>+</sup> |
| T<sub>C</sub> effector memory [T<sub>C</sub>EM] | CD3+ CD4+ CD8<sup>-</sup> CD45RA<sup>-</sup> CD197+ |
| T<sub>C</sub> central memory [T<sub>C</sub>CM] | CD3+ CD4+ CD8<sup>-</sup> CD45RA<sup>-</sup> 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,<sup>a</sup> 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,<sup>b,c</sup> 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 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.<sup>d</sup> Further, clinical depression
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 TEm and decreasing Tec 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.29–32 They were also more prevalent in CD patients than healthy controls. However, 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.

### Funding

This work was supported by the Broad Medical Research Program at the Crohn’s & Colitis Foundation of America [grant number: IBD-0352]. PAH is supported by NHMRC R.D. Wright Biomedical Fellowship.

### 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.

---

**Table 4.** Flow cytometry analysis of T 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 [%] | Significance |
|-------------|----------------|-------------|--------------|
|              | Study entry 6 months |                  | Significance |
| T            | 71.2 ± 3.3 | 70.9 ± 2.8 | n.s. |
| TEm         | 65.1 ± 3.4 | 66.6 ± 3.6 | n.s. |
| Tec         | 10.7 ± 1.2 | 11.2 ± 1.3 | n.s. |
| TEm αβ7     | 6.7 ± 0.6 | 7.2 ± 0.9 | n.s. |
| Tec, αβ7    | 2.5 ± 0.4 | 2.5 ± 0.37 | n.s. |
| TEm αβ8    | 42.8 ± 4.5 | 45.8 ± 4.5 | * ↑ |
| Tec, αβ8   | 3.6 ± 0.53 | 4.3 ± 0.7  | n.s. |
| TEm         | 23.5 ± 2.1 | 23.5 ± 1.9 | n.s. |
| Tec         | 27.5 ± 2.4 | 29.2 ± 2.3 | n.s. |
| TEm αβ7     | 3.9 ± 0.4 | 3.9 ± 0.4  | n.s. |
| Tec, αβ7   | 27.6 ± 2.5 | 27.0 ± 2.0 | n.s. |
| TEm αβ8    | 3.9 ± 0.5 | 3.5 ± 0.48 | * ↓ |
| Tec, αβ8  | 27.3 ± 4.3 | 27.8 ± 5.3 | n.s. |
| TEm αβ8 | 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 | Significance |
|------------------|------------|---------|--------------|
|                  | Study entry | 6 months | Significance |
| IFN-γ            | 33.677 ± 10.741 | 25.074 ± 7.565 | n.s. |
| IL-2             | 16.052 ± 1199 | 13.342 ± 2.234 | n.s. |
| IL-4             | 0.875 ± 0.142 | 0.641 ± 0.09 | n.s. |
| IL-5             | 1256 ± 230.7 | 952.6 ± 175.3 | n.s. |
| IL-6             | 783.3 ± 212.2 | 1075 ± 615 | n.s. |
| IL-10            | 801.52 ± 171.2 | 525.3 ± 93.2 | n.s. |
| IL-13            | 9289 ± 1064 | 6697 ± 970.7 | n.s. |
| TNF-α            | 6649 ± 541.7 | 5671 ± 730.9 | n.s. |
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. AE 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. 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.

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, Mar-murowska-Michalowska H, Kandefer-Szerszen M. In vitro immunoregulatory effects of antidepressants in healthy volunteers. Pol J Pharmacol 2003;55:335–62.
3. Brown ES, Vigil I, Khan DA, Liggins 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. Krommysas G, Gourgoulionis KI, Karamitos K, Kraps K, Kottoriou E, Molydas 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 Hand- book 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, Sobieszka M, Wiktorkowicz K. Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. Ann NY 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 interleu-kin-10 secretion. Neuropsychopharmacology 1999;20:370–9.
16. First MB, Williams JBW, Spitzer RL, Gibbon M. Structured Clinical Inter- view 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, Teahan K, Thjoldleifsson B, et al. A simple method for assessing intestinal inflammation in Crohn’s disease. Gut 2000;47:506–13.
20. Zigmond AS, Snith 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 inhibi- tion 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. Effi- cacy of psychotropic drugs in functional dyspepsia: systematic review and meta-analysis. Gut 2015; doi: 10.1136/gutjnl-2015-310721.
25. Feagan BG, Reinsch 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, Karibian 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: 30–9.