

Effects of celecoxib augmentation of antidepressant or anxiolytic treatment on affective symptoms and inflammatory markers in patients with anxiety disorders: exploratory study

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Prolonged stress has been associated with elevated levels of circulating proinflammatory cytokines. Cyclo-oxygenase-2 inhibitors such as celecoxib exert anti-inflammatory effects and may enhance the response to antidepressant drug treatment in patients with depressive disorders, but their effect on anxiety symptoms in patients with anxiety disorders is uncertain. Patients with a primary diagnosis of an anxiety disorder, with stabilised symptoms, underwent either 6 weeks of celecoxib augmentation of continued treatment ($n = 18$) or continued 'treatment as usual' ($n = 9$). Assessments included the Warwick-Edinburgh mental well-being Scale (WEMWBS), Hospital Anxiety and Depression Scale (HADS), Oxford questionnaire of emotional side effects of antidepressants (OQUESA) and Clinical Global Impression of Illness Severity (CGI-S). Venous blood samples were collected for assays of inflammatory cytokines. Patients who underwent celecoxib augmentation showed significant reductions in anxiety (HADS-A -3.17) and depressive (HADS-D -2.11) symptoms and in overall illness severity (CGI-S -1.11), and improvements in mental well-being (WEMWBS 7.5) and positive changes in emotional responsiveness (OQUESA-RP -3.56 ; OQUESA-AC

-4.22): these were not seen with 'treatment as usual'. There were no significant changes in blood levels of inflammatory cytokines in either group. Celecoxib augmentation appeared associated with beneficial effects on anxiety and depressive symptoms and mental well-being. The findings from this pilot study merit further exploration within a double-blind, randomised placebo-controlled study. *Int Clin Psychopharmacol* 36: 126–132 Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

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Background

Anxiety symptoms and disorders can develop when the physiological response to actual or perceived stress becomes impaired and leads to reduced levels of functioning (Kandel *et al.*, 2012). Anxiety symptoms have been associated with decreased levels of C-reactive protein (CRP), tumour necrosis factor- α (TNF- α), certain interleukins (IL-1b, IL-6, IL-8) and neurotrophins (Zorrilla *et al.*, 1994; Janelidze *et al.*, 2015; Martin *et al.*, 2015; Priya *et al.*, 2016). Somatic anxiety symptoms have been associated with higher levels of CRP, IL-6 and TNF- α , whereas psychological anxiety symptoms have been associated with increased levels of CRP (Duivis *et al.*, 2013). Furthermore, low IL-6 levels predicted symptom resolution in a non-clinical sample of participants with psychological distress (Virtanen *et al.*, 2015). However, not all evidence is consistent; for example, a large study ($n = 1037$) found no correlation between anxiety symptoms and inflammatory markers, after adjusting for environmental and other health factors (Baune *et al.*, 2012).

A recent meta-analysis found differences in IL-10, TNF- α and interferon-gamma (IFN- γ) in patients with generalised anxiety disorder (GAD), when compared to controls (Costello *et al.*, 2019). Several published studies have detected evidence of elevated CRP, TNF- α , IL-1 and IL-2 levels in panic disorder (Rapaport *et al.*, 1994; Koh *et al.*, 2004; Hoge *et al.*, 2009; Vieira *et al.*, 2010; Wagner *et al.*, 2015; Glaus *et al.*, 2017). Only few studies have examined inflammatory markers in social phobia, specific phobia and comorbid anxiety disorders with obsessive-compulsive disorder (OCD). Social phobia has been associated with decreased levels of CRP and IL-6 (Vogelzangs *et al.*, 2013). Some studies in OCD have found decreased levels of TNF- α and IL-6 (Denys *et al.*, 2004; Konuk *et al.*, 2007; Fluitman *et al.*, 2010), whereas others found the opposite in OCD patients with comorbid depression (Monteleone *et al.*, 1998; Carpenter *et al.*, 2002).

Proinflammatory and anti-inflammatory cytokines function in complementary and competing effects in producing an overall response that determines the onset,

duration and severity of the inflammatory phase of healing. A net anti-inflammatory pattern is required for a less severe, shorter healing response (Elnazer *et al.*, 2020). Proinflammatory cytokines can induce cyclo-oxygenase enzymes (COX) (Harden *et al.*, 2015): COX-1 and COX-2 catalyse the oxidation of arachidonic acid to produce prostaglandin G2 (PGG2) and the peroxidation of PGG2 to prostaglandin H2 (PGH2), these reactions being associated with release of reactive oxygen species which can cause cell damage (Maes *et al.*, 2012).

A meta-analysis of the influence of nonsteroidal anti-inflammatory drugs (NSAID) treatment in patients with osteoarthritis suggests potential beneficial effects on depressive symptoms (Iyengar *et al.*, 2013). Meta-analysis of investigations of a range of anti-inflammatory treatments in patients with mood disorders found greater reductions in depressive symptom scores when compared to placebo (6 trials, $n = 214$), and improved manic symptoms in patients with bipolar affective disorder (3 trials, $n = 96$): additional analysis of investigations with celecoxib (11 randomised controlled trials) suggests it may be associated with antidepressant effects in patients with major depressive disorder, without conferring an additional side effect burden (Husain *et al.*, 2017). A more recent randomised clinical trial found a reduction of anxiety symptoms in patients with treatment-resistant bipolar depression ($n = 47$), during celecoxib augmentation (Halaris *et al.*, 2020). However, it remains uncertain whether celecoxib is beneficial in reducing anxiety symptoms in patients with anxiety disorders.

Methods

Study sample

Participants were recruited from general practice and secondary care mental health services. Potentially eligible patients were sent a letter with a participant information sheet, contact information return slip and stamped addressed envelope. When a potential participant contacted the research team or when a contact information slip was returned, the researcher made an appointment for clarification of study aims and procedures, and potential participants were invited to consent to a screening assessment, which included the Mini International Neuropsychiatric Interview (Sheehan *et al.*, 1998). Patients were considered eligible for the study if they were aged between 18–70 years; had the primary diagnosis of an anxiety disorder or anxiety-related disorder, defined according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria (American Psychiatric Association, 2013), and were competent to provide written consent. Patients with OCD could be included, for although OCD is now classified separately from anxiety disorders, anxiety symptoms are common and maybe the reason for seeking treatment. Patients were excluded from the study if they were outside the age range 18–70

years, did not have a primary diagnosis of an anxiety disorder, were unable to provide written informed consent, had clinically significant alcohol or substance use in the previous three months or were pregnant or breastfeeding.

Assessments and celecoxib administration

The Hospital Anxiety and Depression Scale (HADS) (Zigmond *et al.*, 1983) was used as the primary outcome measure. Patients were also assessed using the Clinical Global Impression of Illness Severity (CGI-S) (Guy *et al.*, 1976), Warwick–Edinburgh Mental Well-being Scale (WEMWEBS) (Tennant *et al.*, 2007) and Oxford questionnaire of emotional side effects of antidepressants (OQUESA) (Price *et al.*, 2012), at Baseline and after 6 weeks of being stabilised on treatment (week 6). At week 6, patients were invited to either undergo 6 weeks of open-label augmentation with celecoxib or continue ‘treatment as usual’. Further assessments were undertaken at week 12. Treatment adherence was determined by patient report and tablet count. Venous blood samples were collected at Baseline, week 6 and 12 for determination of inflammatory marker concentrations. Exclusion criteria for celecoxib augmentation were medical contra-indication for celecoxib; history of hypersensitivity to NSAIDs; presence of cardiac impairment, thromboembolic disease, renal impairment, hepatic impairment or history of recurrent gastrointestinal ulceration; concomitant use of NSAIDs, ciclosporins, coumarins, dabigatran, ketorolac, lithium, methotrexate, phenindione, quinolones or sulfonylureas. The celecoxib dosage was 200 mg twice daily, based on previous augmentation studies in depressed patients (Nery *et al.*, 2008; Akhondzadeh *et al.*, 2009; Abbasi *et al.*, 2012).

Treatment withdrawal criteria

Participants could withdraw their consent from study procedures at any point. Treatment would be stopped immediately for any patient who experienced any celecoxib serious adverse event listed in the electronic medicines’ compendium during either the preaugmentation phase or the augmentation phase. Patients were advised to access emergency help if they had shortness of breath or trouble breathing, chest pain, weakness in one part or side of the body, slurred speech, swelling of the face or throat. Patients were advised to stop celecoxib and call their general practitioner immediately if they had nausea, fatigue, pruritus, jaundice, abdominal pain, flu-like symptoms, haemoptysis, haematochezia, melena, skin rash or blisters with fever, unusual weight gain or oedematous arms, legs, hands or feet.

Inflammatory marker assay and analysis

Sampling

Venous blood samples were collected from participants at Baseline and after 6 weeks of celecoxib augmentation: 8–10 ml samples were collected by venepuncture into a

vacutainer containing no preservative (red top). Sampling was performed according to National Health Service procedures, observing sterile conditions, with infection control by either a nurse trained in phlebotomy or by a qualified medical practitioner.

Sample preparation

Samples were centrifuged at 1600g on a Capricorn 2000 bench centrifuge for 10 min. The plasma fraction created from the serum sample was transferred using a Pasteur pipette to suitably labelled vial tubes. Serum samples were placed in a ziplock bag and airtight sealed container inside a lockable box for initial storage at -20°C then transfer to a -80°C freezer for longer-term storage.

Quantification

Luminex multianalyte profiling (xMAP) technology employs proprietary bead sets which are distinguishable under flow cytometry: each bead set is coated with a specific capture antibody, and fluorescence or streptavidin-labelled detection antibodies bind to the specific cytokine-capture antibody complex on the bead set.

Multiple cytokines can be recognized and measured by the differences in both bead sets, with chromogenic or fluorogenic emissions detected using flow cytometric analysis. We used a commercially available proinflammatory panel 1 (human) kit (from V-PLEX, MESO SCALE DISCOVERY, Rockville, Maryland, USA) to measure IL-1 β ; IL-2; IL-4; IL-6; IL-8; IL-10; IL-12p70; IL-13; and TNF- α in the same sample.

Investigations of hair cortisol concentration (HCC) in this sample have been published previously (Elnazer *et al.*, 2020). As celecoxib may affect cortisol concentration in vitro and in vivo (Liu *et al.*, 2016), and because the interplay between inflammatory and neuroendocrine mechanisms modulates the response to stressors (McEwen *et al.*, 1997; Turnbull *et al.*, 1999; Elenkov *et al.*, 2002; Elenkov, 2008; Wolkow *et al.*, 2015), we examined correlations between HCC and cytokines.

Ethical and research governance considerations

The study was approved by Hampshire Research Ethics Committee (REC reference:16/SC/0038); the UK Health Research Authority (IRAS project ID: 170365); and the Medicinal Health Research Authority (EudraCT number:2016-000337-48), as part of a larger project investigating the potential influence of neuroinflammatory and endocrine factors in patients with anxiety disorders.

Results

A total of 170 referrals were received from primary care or secondary care mental health services. Of these, 135 patients dropped out following the initial explanation of the study [53 males (39%), 82 females (61%): mean age 34 years]. Thirty-five participants consented to take part and completed the Baseline assessment. Two patients dropped out before the week 6 review, and six patients dropped out before the week 12 review. All patients who expressed interest in the open-label celecoxib augmentation were carefully screened against the exclusion criteria for augmentation, and none of them met the exclusion criteria. Eighteen patients underwent open-label augmentation with celecoxib, and nine patients completed 12 weeks of treatment as usual.

Clinical characteristics at Baseline

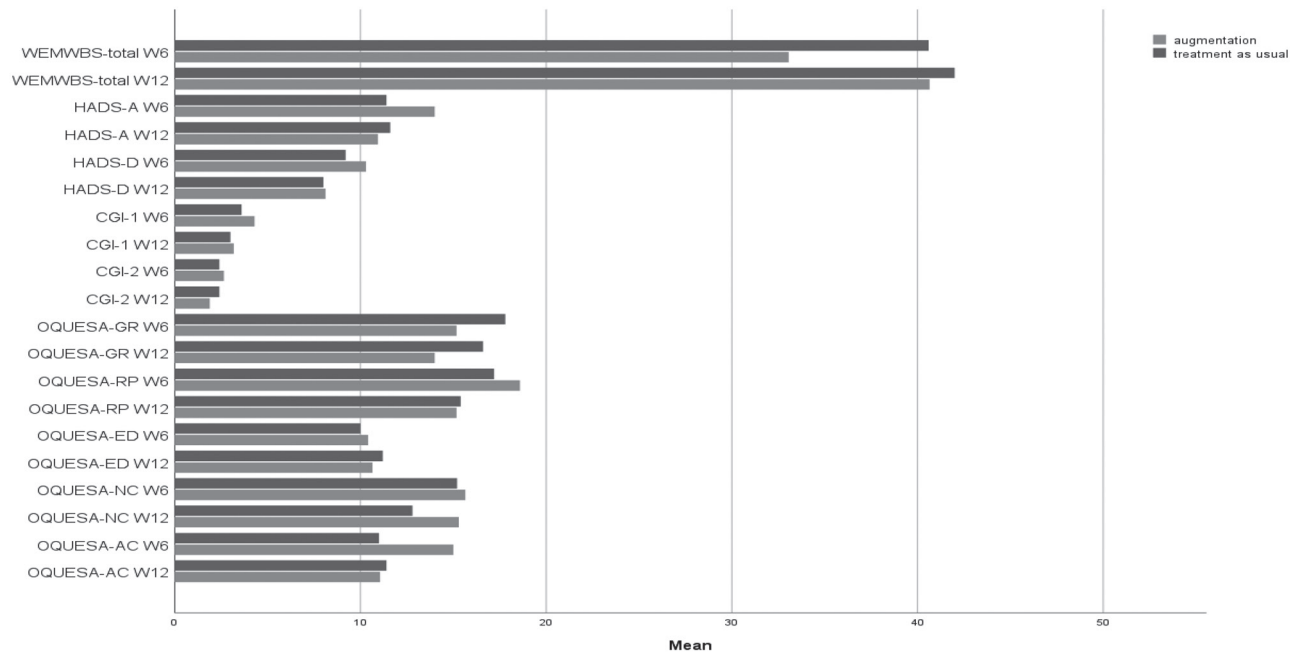
Baseline clinical characteristics for study participants are detailed elsewhere (Elnazer *et al.*, 2020). The mean scores (and standard error of the means) on rating scales were as follows: WEMWBS 27 (1.81); HADS-A 15.42 (0.88); HADS-D 13 (0.82); CGI-1 4.56 (0.22); OQUESA-GR 15.5 (1.17); OQUESA-RP 22.18 (0.75); OQUESA-ED 15.09 (3.17); OQUESA-NC 18 (1.27). Mean plasma cytokine concentrations (and HCC) were found to be within normal concentration ranges apart from a low mean concentration of IL-12p70 (0.11 pg/mL, SEM 0.04; normal range 0.26–0.38 pg/mL) and an elevated mean

Table 1 Clinical and demographic characteristics by treatment group (preaugmentation phase)

Variables	Celecoxib augmentation (n = 18)				Treatment as usual (n = 9)			
Age mean minimum–maximum	33 20–60				31.77 20–56			
Sex	Frequency		Percent		Frequency		Percent	
Men	5		27.8		4		44.4	
Women	13		72.2		5		55.6	
Total	18		100.0		9		100.0	
Diagnoses	Frequency				Frequency			
Panic disorder	1				1			
GAD	4				5			
Panic disorder with agoraphobia	6				1			
Social phobia	5				2			
OCD	2							
Total	18				9			
Antidepressant treatment	Frequency				Frequency			
SSRI	10				5			
SNRI	4				2			
NASSA	3							
β-blocker	1							
CBT					2			
Total	18				9			
Week 6 psychometric mean scores	Mean	N	SD	SEM	Mean	N	SD	SEM
WEMWBS	33.22	18	6.151	1.45	36.89	9	16.42	5.473
HADS-A W6	14.11	18	3.513	.8328	12.11	9	5.819	1.94
HADS-D W6	10.17	18	3.682	.8768	10.22	9	4.711	1.57
CGI-S W6	4.28	18	1.1327	.2766	3.78	9	1.481	0.494
OQUESA-GR W6	15.18	17	4.142	1.005	17.75	8	3.732	1.319
OQUESA-RP W6	18.89	18	5.2768	1.242	18	8	6.188	2.188
OQUESA-ED W6	10.39	18	4.0217	.9547	10.38	8	5.975	2.112
OQUESA-NC W6	15.78	18	4.360	1.032	14.5	8	5.952	2.104
OQUESA-AC W6	15.83	18	6.653	1.576	10.17	6	3.817	1.558

CBT, cognitive behavioural therapy; CGI-S, clinical global impression of illness severity; GAD, generalised anxiety disorder; HADS, hospital anxiety and depression scale; NASSA, noradrenergic and specific serotonergic antidepressant; OCD, obsessive-compulsive disorder; OQUESA, Oxford questionnaire of emotional side effects of antidepressants; SNRI, serotonin-noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; WEMWBS, Warwick-Edinburgh mental well-being scale.

Fig. 1



Rating scale scores at Week 6 and Week 12, by group.

concentration of TNF- α (2.37 pg/mL, SEM 0.43; normal range 0.10–1.75 pg/mL).

Preaugmentation phase

Participants received 6 weeks of treatment as usual, from their usual clinician. Nineteen patients had undergone treatment with a selective serotonin reuptake inhibitor; six patients with a serotonin-noradrenaline reuptake inhibitor; three patients with a noradrenergic and specific serotonergic antidepressant; two patients with cognitive behavioural therapy; and a single patient with a β -blocker: two patients had not undergone any treatment by the week 6 review.

At week 6, participants remained troubled by anxiety and other symptoms HADS-A 13.70 (SEM 0.73); CGI-S 4.27 (SEM 0.23) CGI-I 2.69 (SEM 0.16) OQUESA-GR 16.30 (SEM 0.75); OQUESA-RP 18.97 (SEM 0.95); OQUESA-ED 11.06 (SEM 0.87) and OQUESA-NC 16.10 (SEM 0.86).

Analysis of cytokine (IFN- γ , IL-1 β , IL-10, IL-12p70, IL-13, IL-2, IL-4, IL-6, IL-8, TNF- α) levels in participants who provided blood samples at week 6 ($n = 25$) found a low mean concentration of IL-2 [0.22 pg/mL (median 0.17 pg/mL), normal range 0.22–2.68 pg/mL] and a high mean concentration of TNF- α [2.16 pg/mL (median 1.60 pg/mL), normal range 0.10–1.75 pg/mL]. Paired sample t test for cytokines concentrations found no significant changes from week 0 (Baseline) to week 6.

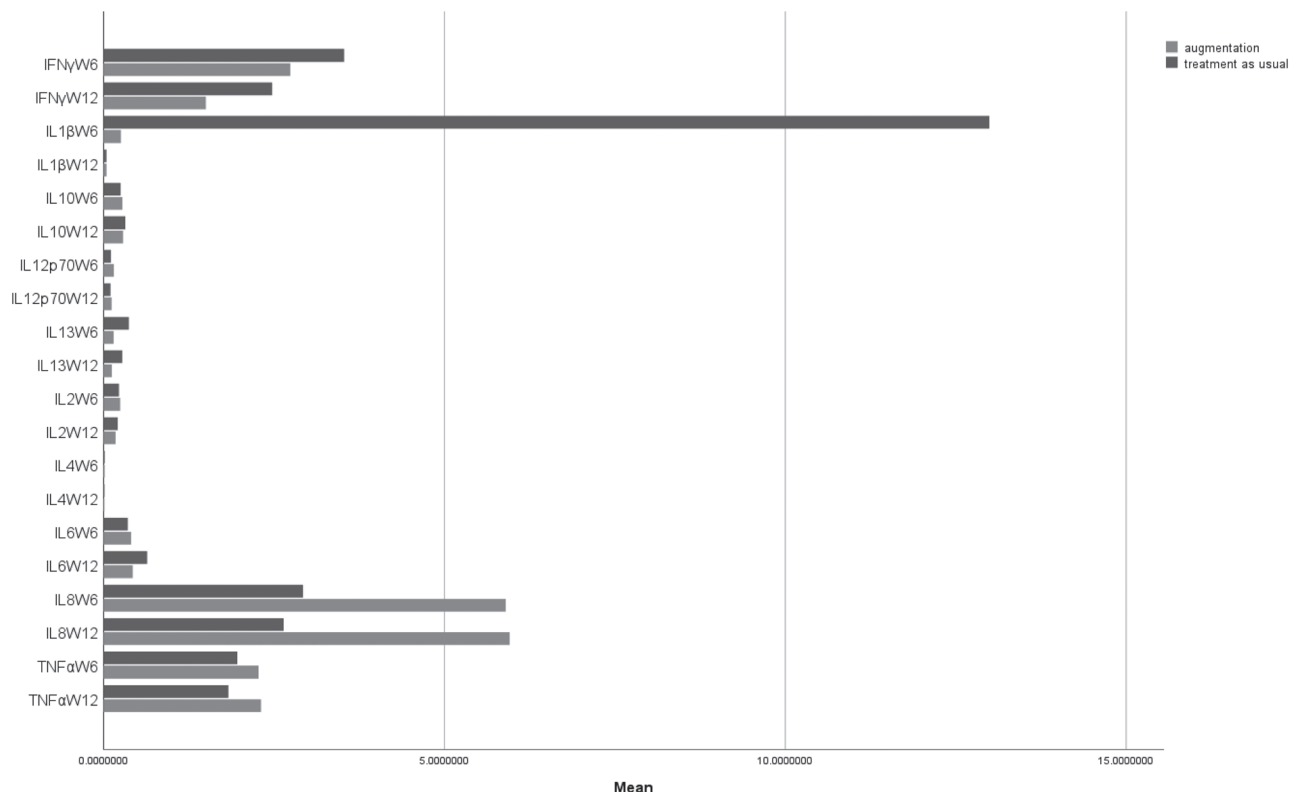
Subgroup analyses found generally comparable scores (Table 1). The treatment as usual group had a higher mean score of a general reduction in emotions (OQUESA-GR) (17.77 SEM 1.033) but lower scores on the scale for ascribing causality of emotional disturbance to antidepressants (OQUESA-AC) (12.27 SEM 1.966) when compared to the augmentation group (15.18 SEM 1.01) and (15.83 SEM 1.58), respectively.

Paired-T sample analysis showed no significant changes in rating scores from Baseline to week 6, in both groups. No significant changes in inflammatory marker concentrations were seen in either group.

Celecoxib augmentation phase

By week 12, eighteen participants had undergone augmentation with celecoxib, and nine participants had continued 'treatment as usual'. Analysis using paired t tests in the augmentation group found significant changes in mean scores from week 6 to 12: WEMWBS 7.50 increase (SEM 2.63, $P = 0.01$); HADS-A 3.17 reduction (SEM 0.52, $P = 0.00$); HADS-D 2.11 reduction (SEM 0.80, $P = 0.02$); CGI-S 1.11 reduction (SEM 0.18, $P = 0.00$); CGI-I 0.78 reduction (SEM 0.32, $P = 0.03$); OQUESA-RP 3.56 reduction (SEM 1.19, $P = 0.01$) and OQUESA-AC 4.22 reduction (SEM 1.25, $P = 0.00$). Analysis using paired sample t test in the treatment as usual group found changes in mean scores from week 6 to 12 as follows: WEMWBS 1.22 increase (SEM 2.10, $P = 0.58$); HADS-A 0.11 increase (SEM 0.82, $P = 0.90$); HADS-D 0.78 decrease (SEM 1.11,

Fig. 2



Cytokines' concentrations at Week 6 and Week 12 by group.

$P = 0.50$); CGI-S 0.33 decrease (SEM 0.28, $P = 0.28$); CGI-I 0.44 increase (SEM 0.41, $P = 0.31$); OQUESA-GR 1.12 decrease (SEM 1.80, $P = 0.55$); OQUESA-RP 2.00 decrease (SEM 0.82, $P = 0.05$); OQUESA-ED no change (SEM 1.18, $P = 1.00$); OQUESA-NC 1.87 decrease (SEM 1.09, $P = 0.13$) and OQUESA-AC 0.40 increase (SEM 1.03, $P = 0.72$) (Fig. 1).

Analysis of cytokine levels in the augmentation group found a low mean concentration of IL-1 β (0.04 pg/mL, SEM 0.024; normal range 0.11–24.3 pg/mL); low mean concentration of IL-12p70 (0.12 pg/mL, SEM 0.015; normal range 0.26–0.38 pg/mL); low mean concentration of IL-13 (0.11 pg/mL, SEM 0.05; normal range 0.60–2.78 pg/mL) and a high mean concentration of TNF- α (2.33 pg/mL, SEM 0.21; normal range 0.10–1.75 pg/mL). Paired sample t testing found a significant change from week 6 to 12 in the mean concentration of IL-2 0.06 pg/mL (SEM 0.02, $P = 0.00$). Analysis of cytokines concentration in the treatment as usual group at week 12 found low mean concentrations of IL-1 β (0.43 pg/mL, SEM 0.018; normal range 0.11–24.3 pg/mL); IL-12p70 (0.102 pg/mL, SEM 0.04; normal range 0.26–0.38 pg/mL); IL-13 (0.27 pg/mL, SEM 0.11; normal range 0.60–2.78 pg/mL); and IL-2 (0.21 pg/mL, SEM 0.03; normal range 0.22–2.68 pg/mL):

and a high mean concentration of TNF- α (2.33 pg/mL; normal range 0.10–1.75 pg/mL). Paired sample t testing, from week 6 to 12, found no significant change in this group (Fig. 2).

Predicting response to treatment

We used traditional forecasting models in an exploration of response to treatment. The analyses suggest some significant findings in the celecoxib augmentation group but not the treatment as usual group. Time series forecasting analysis, using autoregressive integrated moving average in the celecoxib augmentation group found significant predictability of emotional detachment scores (OQESA-ED) by HCC at week 6. Self-rated reduction in positive emotions at week 6 (OQESA-RP) had significant predictability of depressive symptom severity (HADS-D), clinician-rated overall severity of illness (CGI-S) and self-rated reduction in positive emotions (OQESA-RP) (Table 2).

Discussion

Patients with a diagnosis of any anxiety disorder (including OCD) at Baseline had low levels of IL-12p70 but high levels of TNF- α . A significant correlation between HADS-A and IL-6 was found after adjusting for age,

Table 2 Forecasting response to treatment, ARIMA model parameters^a

Outcome	Predictors				Estimate	SE	t	Sig.
HADS-A W12	WEMWBS-total W6	No transformation	Numerator	Lag 0	−0.332	0.078	−4.273	0.001
				Lag 3	−0.353	0.086	−4.086	0.002
HADS-D W12	HADS-A W6	No transformation	Numerator	Lag 0	0.681	0.096	7.075	0.000
	OQUESA-RP W6	No transformation	Numerator	Lag 0	0.421	0.033	12.661	0.000
CGI-1 W12	CGI-1 W6	No transformation	Numerator	Lag 0	0.740	0.096	7.739	0.000
				Lag 2	−0.342	0.102	−3.358	0.006
OQUESA-RP W12	OQUESA-RP W6	No transformation	Delay	3				
			Numerator	Lag 0	−0.081	0.029	−2.826	0.015
			Delay	2				
			Numerator	Lag 0	0.385	0.134	2.860	0.019
OQUESA-ED W12	OQUESA-ED W12 HCC W6	No transformation		Lag 5	−0.528	0.140	−3.773	0.004
			Constant		8.334	1.307	6.375	0.000
			Numerator	Lag 0	0.332	0.144	2.298	0.035

CGI-S, clinical global impression of illness severity; HADS, hospital anxiety and depression scale; HCC, hair cortisol concentration; OQUESA, Oxford questionnaire of emotional side effects of antidepressants; WEMWEBS, Warwick–Edinburgh mental well-being scale.^aFor some models, some predictor series are not considered by expert modeller, due to missing values found in the estimation period.

diagnosis and sex. At week 6, mean scores on the HADS-A 13.70 (SEM 0.73) indicate that participating patients were still troubled by substantial symptoms. Analysis of inflammatory markers found low levels of IL-2 but high levels of TNF- α , but the longitudinal analysis found no significant changes in inflammatory markers from Baseline to week 6.

At week 12, there was a significant change in questionnaire scores in the celecoxib augmentation group, with improved mental well-being (WEMWBS); reduced anxiety (HADS-A); reduced depression (HADS-D); lesser reduction in positive emotions (OQUESA-RP); and lesser attribution of antidepressants as cause (OQUESA-AC). There were no significant changes in questionnaire scores in the treatment as usual group. Nor were there significant changes in inflammatory marker concentrations in either group. The exploratory findings suggest that HCC, emotional detachment and reduction of positive emotions at week 6 might predict a positive response to 6 weeks' augmentation with celecoxib.

Limitations

The study sample had a high attrition rate. Nearly 79% of patients who expressed initial agreement to take part had dropped out before Baseline assessment. As a small number of participants consented to take part and were assessed with a large number of outcome measures, it was not possible to conduct further analyses of the findings. The augmentation group had double the number of patients compared to the treatment as usual group, as more participants preferred to opt for the augmentation group.

Conclusion

There was a significant change in questionnaire scores in the celecoxib augmentation group, reflecting improved mental well-being, reduced anxiety, reduced depression, lesser reduction in positive emotions and lesser attribution of antidepressants as the cause of altered emotions. Potential weaknesses of this study include the small

sample size, the lack of randomisation and the lack of blindness to treatment group allocation. Our findings suggest that further studies, using a more robust double-blind randomised placebo-controlled design, should be undertaken to explore these preliminary results in greater detail.

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The authors meet the criteria of authorship described by The International Committee of Medical Journal Editors (ICMJE).

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflicts of interest

There are no conflicts of interest.

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