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Authors' reply

We read with great interest the comment by Creed,¹ and the letter by Castle and Libby in this issue concerning a recent article published by our group in *Gut*.² We wish to thank the authors for their interest in our work and their remarks. In this study, we reported that treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram considerably improved irritable bowel syndrome (IBS) symptoms, including abdominal pain, compared with placebo in non-depressed patients with IBS. Moreover, this effect on core IBS symptoms was found to be independent of effects on anxiety and depression as measured by self-report questionnaires.

We agree with both Creed¹ and Castle and Libby that psychological processes including hypervigilance towards bodily sensations and abnormal attributions of these sensations (thus, abnormal illness beliefs) may play a key role in the pathophysiology of functional somatic syndromes (FSS)—somatoform disorders in general and IBS in particular.^{1–6} This hypothesis is in line with the concept of visceral-specific anxiety as a key process in IBS, as proposed by Labus *et al*.⁷ The hypothetic aetiological concept “somatisation”, which is descriptively defined as “the presence of somatic symptoms that cannot be (adequately) explained by organic findings”,⁸ may indeed be frequent and important in IBS, and a reduction in somatisation (or the psychological processes underlying it) could be hypothesised as an important mechanism of action by which SSRIs may influence FSS, as proposed by Creed.¹ However, evidence is growing that psychological processes may underlie the multidimensional phenomenon.^{3–5}

Analysis of the SCL-90R somatisation scores from our study showed significant improvement after 3 and 6 weeks of citalopram treatment, compared with run-in and placebo (table 1). Somatisation scores at the beginning of the first treatment period did not differ from those at the beginning of the second treatment period, so in contrast with IBS symptom severity, no carry-over effect of citalopram was observed for the somatisation scores. Furthermore, no significant correlation was found between changes in somatisation scores and changes in overall or specific symptom scores (all $r < 0.18$, all $p > 0.05$). Hence, as the effect of citalopram on IBS symptoms is independent of general anxiety, depression or somatisation, we do not agree that our study can be seen as directly supporting the assumptions formulated by Castle and Libby in their letter.

Table 1 Somatisation levels during treatment with citalopram or placebo, assessed using the symptom-checklist-90-revised (SCL-90R)

	Before citalopram	Citalopram 3 weeks	Citalopram 6 weeks	Before placebo	Placebo 3 weeks	Placebo 6 weeks
Somatisation (SCL-90R)	26.1 (1.9)	21.6 (1.3)*†	18.8 (0.9)*†	26.2 (2)	25.1 (2)	25.4 (1.9)

Data are presented as mean (SEM).

* $p = 0.02$ compared with placebo.

† $p < 0.001$ compared with run-in.

These observations do not exclude a primarily central action of citalopram on IBS symptomatology. As most somatisation symptoms are painful symptoms, the hypothesis that SSRIs work primarily through a central analgesic effect could be supported by our data. On the other hand, it remains conceivable that SSRIs may affect more subtle psychological processes, including (especially attention to bodily symptoms) those that may underlie somatisation. We believe that those psychological processes (especially attention to bodily symptoms) may interact in a complex way with central proanalgesic and analgesic systems⁹ and that SSRIs may influence this complex interaction. Thus, the hypotheses that SSRIs work through a central analgesic effect or through reduction in somatisation or the psychological processes underlying it may be complementary rather than contradictory.

Although we agree with several points formulated by the same authors in their recent review article,⁶ including the role of stress and abnormal illness beliefs, we do not believe that IBS can simply be seen as “an affective disorder in its own right”. Clearly, an important reciprocal interaction exists between gastrointestinal sensorimotor and emotional regulation (at the level of the brain),⁹ which may explain the observed similarities between FSS/IBS and affective disorders (high comorbidity, role of stress/life events, treatment, etc). However, as affective disorders are currently still defined on the basis of symptom criteria,¹¹ it seems contradictory to call a disorder lacking key affective symptomatology “an affective disorder in its own right”.¹¹ This does not exclude a role for affective disorders in somatic symptom generation in (large) subsets of patients with FSS/IBS. In our view, the dualistic distinction between “functional” and “organic” somatic disease is problematic,⁴ as evidence for an influence of psychological (including affective) factors on both is growing.^{5,12,13} As psychopathology (including “subthreshold” psychological disturbances) does not always explain bodily symptoms in the absence of readily identifiable bodily pathology, we support the proposal of considering bodily symptoms/syndromes in their own right. Their aetiology is likely to be multifactorial with interacting psychological, social and biological factors in all cases (see fig 1 in reference 4), consistent with the biopsychosocial model as proposed by George Engel almost 30 years ago.^{3,13,14}

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Abdominal epilepsy, an uncommon cause of recurrent abdominal pain: a brief report

Abdominal epilepsy is an uncommon cause of recurrent abdominal pain.^{1,2} It is characterised by paroxysmic episodes of abdominal pain, diverse abdominal complaints, definite EEG abnormalities and favourable response to the introduction of epilepsy drugs.¹

We describe four patients, with recurrent abdominal pain, without obvious associated symptoms suggestive of central nervous system abnormalities, but each had definite EEG

abnormalities and a striking response to anti-convulsant drugs.

A 15-year-old boy presented with recurrent episodes of abdominal pain and vomiting for the past 12 years. The pain was localised in the epigastric region and its duration varied from 30 min to 1 h. The paroxysms were sudden in onset and subsided spontaneously. The episodes occurred every 3–4 months, and were followed by lethargy.

On investigating, the gastrointestinal barium study showed features suggestive of duodenal invagination.

While performing an exploratory laparotomy, it was noted that besides having intestinal malrotation, the patient also had multiple congenital bands with adhesions. Gastrojejunostomy and adhesiolysis were carried out.

During the postoperative follow-up, the patient again developed symptoms of abdominal pain and vomiting.

A CT scan of the brain was performed, which was normal. However, the EEG recording showed right temporal focal seizure discharge with generalisation, with diffuse cortical dysfunction in the form of slowing (fig 1). An MRI of the brain was performed, which was found to be normal.

The patient started treatment with oxcarbazepine and remained asymptomatic for

6 months. He again had a relapse of his symptoms. Doubting his compliance with the drug regimen, the serum oxcarbazepine level was tested and found to be sub-therapeutic. A repeat EEG was carried out, which showed bursts of diffuse paroxysmal acute waves (fig 2). He restarted treatment with oxcarbazepine and subsequently his symptoms subsided.

He has remained asymptomatic during the past 18 months of follow-up, receiving regular drugs.

A 13-year-old girl presented with recurrent abdominal pain for the past 8 years. The pain was mainly periumbilical in distribution, colicky and paroxysmal in nature, non-radiating and had no apparent relationship with meals. Each episode of pain used to last for 10–30 min, with spontaneous resolution of symptoms, and recurred 4–5 times in a month. There was no history of associated vomiting, headache or convulsions.

Her blood analyses were normal. Ultrasonography of the abdomen and BMFT were normal. A CT scan of brain showed mild ventriculomegaly. An MRI of the brain also failed to detect any structural anomalies. EEG record showed generalised spike and wave discharges (fig 3).

The patient started treatment with oxcarbazepine and has been asymptomatic for the past 20 months.

A 50-year-old man presented with a history of intermittent abdominal discomfort associated with repeated episodes of vomiting for the past 15 years. The paroxysms occurred 3–4 times in a year and were not associated with headache or convulsions.

He underwent an exhaustive investigation (including complete blood cell count, stool examinations for ova and parasites, abdominal ultrasound, and upper and lower gastrointestinal endoscopies). However, no abnormalities were detected.

He underwent an EEG examination during a typical paroxysm, which revealed left temporal dysrhythmia in the form of slowing (fig 4). He also underwent an MRI, which was normal. He did very well receiving treatment with oxcarbazepine. In the past 14 months of follow-up, he has been asymptomatic.

A 52-year-old woman presented with paroxysmal headache, occurring 1–2 times a week, which was associated with vomiting for the past 15 years. The paroxysms were followed by increased sleep. She also complained of a vague abdominal discomfort, which occurred intermittently.

The peripheral blood picture, urine analysis, abdominal ultrasound scan, liver and renal function tests, serum amylase and urine spot test for porphyria were normal. Gastrointestinal barium and endoscopic

Figure 1 Awake EEG record showing high-voltage generalised slowing.

Figure 2 EEG record showing focal spike and wave discharges with phase reversal from right temporal.

studies were also normal. A CT scan of the brain also failed to detect any anomaly.

A provisional diagnosis of migraine was made and she started treatment with tab Ergotamine, but the symptoms persisted.

The treatment regimen was altered and she was treated with tab Flunarizine, but no improvement was noted.

An EEG was carried out, which showed right frontal focal discharge with generalisation (fig 5).

The patient has been receiving treatment with tab Oxcarbazepine and has remained asymptomatic for the past 23 months of follow-up.

Abdominal epilepsy is an uncommon syndrome in which gastrointestinal complaints result from seizure activity. It is characterised by (1) otherwise unexplained, paroxysmal gastrointestinal complaints; (2) symptoms of a central nervous system disturbance; (3) an abnormal EEG with findings specific for a seizure disorder; and (4) improvement with anticonvulsant drugs.³

A review of the history of this syndrome yielded 36 cases reported in the English literature in the past 34 years.³

Abdominal epilepsy is well documented among children, patients but is recognised only infrequently in adults.⁴ The paucity of reports in adults could be because of a lack of recognition of this syndrome in adults.

The variability of clinical presentation in abdominal epilepsy indicates a spectrum of both gastrointestinal and CNS manifestations. The gastrointestinal manifestations include all or a combination of the following: recurrent abdominal pain, nausea, vomiting, bloating and diarrhoea. A similar diversity of CNS manifestations has been reported, which includes confusion, fatigue, headache, dizziness and syncope. In our series, we found that the most common presenting symptoms were paroxysmal abdominal pain and vomiting. The CNS manifestations in our patients were subtle, with only one patient presenting with headache as a predominant symptom.⁴

Although its abdominal symptoms may be similar to those of the irritable bowel syndrome, abdominal epilepsy may be distinguished from the latter condition by the presence of altered consciousness during some of the episodes, a tendency towards tiredness after an episode, and an abnormal EEG.⁵ All our patients, had symptoms suggestive of a functional abdominal pain but with definite EEG changes.

In patients with abdominal symptoms and headache, it is often difficult to differentiate abdominal migraine from abdominal epilepsy, because of the overlap of symptoms. An EEG is a simple and non-invasive investigation, which

may be helpful to differentiate between the two entities, as patients with abdominal epilepsy usually have specific EEG abnormalities, particularly of a temporal lobe seizure disorder.⁴

Previous reports^{1,4} have suggested that the most common findings on EEG recording in patients with abdominal epilepsy are a burst of sharp waves and/or spikes from one or both temporal regions. In our series, two patients had specific EEG abnormalities of a temporal lobe seizure disorder, whereas one had an EEG recording that showed generalised spike and wave discharges and another had an EEG recording that showed right frontal focal discharge with generalisation.

A sustained response to anticonvulsants has been accepted as one of the criteria for the diagnosis of patients with abdominal epilepsy.⁴ However, there are no recommendations on the choice of anticonvulsant to be used. In our series, all patients were treated with oxcarbazepine. In these patients, the symptoms were well controlled in the average 18 months of follow-up (range 14–23 months) and there were no reported adverse events. Only one patient had a relapse of symptoms because of non-compliance with the drug regimen.

We suggest that in patients with paroxysms of abdominal pain, nausea and vomiting with

Figure 3 Awake EEG record showing generalised spike and wave discharges.

or without CNS manifestations, the possibility of abdominal epilepsy should be considered after exclusion of more common aetiologies for the presenting complaints. The investigation in these patients should proceed with an EEG. Treatment typically begins with anticonvulsant drugs; oxcarbazepine is an effective anticonvulsant in this syndrome.

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The pattern of cytokine expression determines the degree of mucosal damage

It is widely accepted that both qualitative and quantitative differences in cytokine expression determine the extent of mucosal damage in different intestinal pathologies.¹ However, few comparative analyses of these conditions have been published to date.

We analysed mRNA expression of several cytokines and effector molecules in intestinal biopsies by real time polymerase chain reaction (summary of study groups and results are shown in table 1). These included samples from healthy controls (duodenal biopsies from patients suspected of having an intestinal pathology, later ruled out), non-specific small bowel inflammation (mild histological changes in the biopsy consisting of a non-specific lamina propria infiltrate but no villous

atrophy), active coeliac disease (on a gluten containing diet) and ulcerative colitis from affected tissue areas. These pathologies show mild, moderate and severe degrees of mucosal damage, respectively, and the cytokine pattern varies significantly, from lack of cytokine upregulation in mild inflammations to the highest levels and widest array of proinflammatory cytokines in ulcerative colitis, together with a parallel increase in levels of effector molecules involved in mucosal damage (inducible nitric oxide synthase (iNOS), matrix metalloproteinase-3 (MMP-3) and granzyme B).

In tissue samples from patients with non-specific small bowel inflammations, levels of cytokines or effector molecules did not increase in any case, despite the findings of microscopic mild alterations in these tissue samples. We hypothesise that the immune activation which triggers the mucosal damage might have occurred during one or several past inflammatory episodes, although these were no longer measurable at the molecular level.

In active coeliac disease, effector molecules showed raised levels above healthy controls and, moreover, iNOS mRNA levels correlated with the degree of mucosal damage (Marsh score) ($p = 0.001$). Of the cytokines analysed, only interferon γ (IFN γ) was clearly increased