Table 1 Characteristics of patients with lamivudine-resistant and adefovir dipivoxil-resistant chronic hepatitis B virus treated with tenofovir disoproxil fumarate

				ALT (IU/l)				HBV DNA (log_{10} copies/ml)**			
Patient	HBe-Ag	HBV genotype	ADV-resistant mutation*	Baseline	4 weeks	12 weeks	24 weeks	Baseline	4 weeks	12 weeks	24 weeks
1	Negative	D	Negative	187	21	16	12	6.03	4.10	2,13	Negative
2	Negative	D	rtA181T rtN236T	358	ND	68	40	7.25	ND	4.62	3.28
3	Negative	D	rtN236T	85	76	65	63	5.57	4.54	3.59	2.30
4	Negative	D	Negative	178	183	56	30	8.63	7.64	4.37	4.44
5	Negative	D	rtA181V	34	ND	36	41	8.64	ND	6.09	3.95
6	Positive	D	rtA181V	339	275	173	92	8.04	5.46	4.54	3.17

ADV, adefovir dipivoxil; ALT; alanine aminotransferase; HBV, hepatitis B virus; Hbe-Ag, hepatitis B antigen; ND, not done.
*ADV-resistant mutations were detected as previously described[4]
**lower limit of quantification: 1.85 log_{10} copies/ml.

2 **van Bőmmel F**, Wunsche T, Mauss S, *et al*. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. *Hepatology*, 2004; 40, 1421–5.
3 **Fung SK**, Andreone P, Han SH, *et al*. Adefovir-resistant hepatitis B can be associated with viral rebound and hepatic decompensation. *J Hepatol* 2005;**43**:937–43.
4 **Benhamou Y**, Fleury H, Trimoulet P, *et al*. Anti-hepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients. *Hepatology* 2006;**43**:548–55.
5 **Stephan C**, Berger A, Carlebach A, *et al*. Impact of tenofovir-containing antiretroviral therapy on chronic hepatitis B in a cohort co-infected with human immunodeficiency virus. *J Antimicrob Chemother* 2005;**56**:1087–93.

Authors' response

We would like to thank Trojan *et al* for their interest in our paper and for supplementing interesting data of tenofovir (TDF) in lamivudine (LMV)-resistant and adefovir (ADV)-resistant chronic hepatitis B. We agree that TDF has strong antiviral activity against the hepatitis B virus (HBV) in patients infected with either wild-type or LMV-resistant strains, without major side effects, and viral resistance in short-term treatment. However, we would like to discuss several points that should be considered in this regard.

There are some differences in the definition of antiviral resistance between the data of Trojan *et al* and ours. Trojan *et al* considered that ADV resistance had occurred when serum HBV DNA level increased to >4 log_{10} copies/ml. In their study, two of six patients showed insufficient antiviral response to ADV without known drug-resistant genotypic mutation. Insufficient response to adefovir treatment in LMV-resistant patients was reported in up to 50% of treated patients.[1] In our study, insufficient antiviral response (serum HBV DNA >4 log_{10} copies/ml after 6 months of treatment), including primary treatment failure, was found in 60% of the patients.[1] Clinical consequences of the emergence of drug-resistant mutation and insufficient response may be different in long-term follow-up.

There is no standard agreement for selecting antivirals and estimating their effects in multidrug-resistant patients. In patients with chronic hepatitis B carrying ADV-resistant mutations, L-nucleoside analogues including LMV, emtricitabine, telbivudine, torcitabine and clevudine may have some effect. According to earlier reports,[2 3] the in vitro response of rtN236T, rtA181T/V and rtL180M+M204V+N236T mutations to LMV were reported to be 1.06, 2–6, and >40-fold resistant, respectively, compared with wild-type HBV. The antiviral susceptibility of these three mutations to entecavir (ETV) was 0.88-fold decreased, unknown and 6.25-fold decreased, respectively, compared with wild-type HBV. The response to TDF was 4.5-fold decreased, unknown and 4.4-fold decreased, respectively.

In our study, the longer follow-up period of the patients showed that 11 patients developed ADV-resistant genotypic mutations and viral rebound. Four patients were switched from an ADV and LMV combination (n = 3) or ADV monotherapy (n = 1) to a TDF plus LMV combination. Three patients were treated with ADV only; two patients were given an ADV LMV combination. One patient was treated with an ETV plus ADV combination. The mean duration of TDF combination therapy was 5.2 (range 4–8) months. The mean serum HBV DNA at the start of TDF treatment was 5.88 log_{10} copies/ml, which reduced to 3.35 log_{10} copies/ml. The mean ALT was reduced to normal level from TDF baseline 277 (range 71–462) IU/ml in all of the four patients. In addition, in patients treated with ADV and LMV (n = 1) and ETV and ADV (n = 1), combinations, the decrease in serum HBV DNA was 5 log_{10} copies/ml.

As TDF and ADV has the same equimolar potency in suppressing wild-type HBV, clinical studies suggested that stronger viral suppression and a lower rate of TDF resistance than ADV was possibly related to the use of a higher dose. However, a mutation at rtA194T in conjunction with LMV-resistant mutation in HIV–HBV cases indicated that long-term follow-up is needed to define the role of TDF in multidrug-resistant patients with hepatitis B. In conclusion, TDF is a useful drug in patients with insufficient antiviral response to LMV and ADV treatment. In addtion, other potent nucleotide/nucleoside analogues, in monotherapy or combination therapy, would be another useful alternative in difficult clinical situations. In selecting antiviral agents, actions (monotherapy vs combination therapy, add on vs switch to), clinical status (treatment naive vs previously treated, compensate vs decompensate liver disease) and sites of mutant selection should be considered to reduce antiviral resistance and induce potent inhibition of HBV replication in long-term treatment.

Jong Eun Yeon
Division of Gastroenterology and Hepatology, Korea University Guro Hospital, Seoul, Korea

Chang Hong Lee
Department of Internal Medicine, Konkuk University Hospital, Seoul, Korea

Correspondence to: Professor Chang Hong Lee, Department of Internal Medicine, Konkuk University Hospital, 4–12 Hwayang-dong, Kwangjin-gu, Seoul 143-729, Korea; chlee@kuh.ac.kr

Competing interests: None.

References

1 **Fung SK**, Chae HB, Fontana RJ, *et al*. Virologic response and resistance to adefovir in patients with chronic hepatitis B. *J Hepatol* 2006;**44**:283–90.
2 **Brunelle MN**, Jacquard AC, Pichoud C, *et al*. Susceptibility to antivirals of a human HBV strain with mutations conferring resistance to both lamivudine and adefovir. *Hepatology* 2005;**41**:1391–8.
3 **Delaney W**, Locarnini S, Shaw T. Resistance of hepatitis B virus to antiviral drug: current aspects and direction for future investigation. *Antivir Chem Chemother* 2001;**12**:1–35.

Further evidence supporting a psychological component to irritable bowel syndrome

We welcome the conclusion by Creed (*Gut* 2006;**55**:1065–7) that citalopram leads to clinical improvement in irritable bowel syndrome (IBS) uncomplicated by psychiatric illness[1] by targeting psychological processes. The implicit assumption is that psychological disturbance is fundamental to IBS, irrespective of psychiatric comorbidity.

This is consistent with a previously proposed disease model for functional gastrointestinal disorders,[2] which suggested that dominant, shared psychological disturbance provides the best explanation for the very high overlap between IBS, other functional disorders (gastrointestinal and otherwise) and depression/anxiety. The model also explained how depression and IBS can wax and wane independently, and predicted that the response of non-psychiatric IBS to selective serotonin reuptake inhibitor antidepressants would be similar to the response of depressive disorders to selective serotonin reuptake inhibitors.

We also welcome the author's identification of abnormal illness beliefs as the principal psychological pathology. Evidence suggesting that these beliefs are causative in IBS[3] has recently been supported by the demonstration that cognitive behaviour therapy, which targets these beliefs, leads to clinical improvement. Further scrutiny of these beliefs could be the key to understanding the nature and importance of the central pathology of IBS and other functional disorders.

M Castle, G W Libby
Departments of Gastroenterology and Psychiatry, Barts and the London National Health Services Trust and the Wingate Institute of Neurogastroenterology, London, UK

Correspondence to: Dr G W Libby, Departments of Gastroenterology and Psychiatry, Barts and the London National Health Services Trust and the Wingate Institute of Neurogastroenterology, 9 Upper Wimpole Street, London W1G 6LJ, UK; Gerald.libby@btconnect.com

Competing interests: None.

References

1 **Tack J**, Broekaert D, Fischler B, *et al*. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. *Gut*, 2006;*55*, 1095–103.
2 **Castle MZD**, Silk DBA, Libby GW. The rationale for antidepressant therapy in functional gastrointestinal disorders. *Aliment Pharmacol Ther* 2004;**19**:969–79.
3 **Gomborone J**, Dewsnap P, Libby G, *et al*. Abnormal illness attitudes with Irritable Bowel Syndrome. *J Psychosom Res* 1996;**39**:227–30.

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 Creed[1] 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 3–6] 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'',[5] 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 systems[8] 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]

Lukas Van Oudenhove*, Jan Tack
Department of Pathophysiology, Gastroenterology Division, University Hospital Gasthuisberg, University of Leuven, Belgium

Correspondence to: Dr J Tack, Department of Pathophysiology, Gastroenterology Section—Center for Gastroenterological Research, University Hospital Gasthuisberg–University of Leuven, Herestraat 49, Leuven B-3000, Belgium; jan.tack@med.kuleuven.be

*Research Fellow of the Research Foundation–Flanders

Competing interests: None.

References

1 **Creed F**. How do SSRIs help patients with irritable bowel syndrome? *Gut* 2006;**55**:1065–7.
2 **Tack J**, Broekaert D, Fischler B, *et al*. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. *Gut* 2006;**55**:1095–103.
3 **Mayou R**, Kirmayer LJ, Simon G, *et al*. Somatoform disorders: time for a new approach in DSM-V. *Am J Psychiatry* 2005;**162**:847–55.
4 **Kirmayer LJ**, Looper KJ. Abnormal illness behaviour: physiological, psychological and social dimensions of coping with distress. *Curr Opin Psychiatry* 2006;**19**:54–60.
5 **De Gucht V**, Maes S. Explaining medically unexplained symptoms: Toward a multidimensional, theory-based approach to somatization. *J Psychosom Res* 2006;**60**:349–52.
6 **Castle MZD**, Silk DBA, Libby GW. The rationale for antidepressant therapy in functional gastrointestinal disorders. *Aliment Pharmacol Ther* 2004;**19**:969–79.
7 **Labus JS**, Bolus R, Chang L, *et al*. The Visceral Sensitivity Index: development and validation of a gastrointestinal symptom-specific anxiety scale. *Aliment Pharmacol Ther* 2004;**20**:89–97.
8 **Villemure C**, Bushnell MC. Cognitive modulation of pain: how do attention and emotion influence pain processing? *Pain* 2002;**95**:195–9.
9 **Van Oudenhove L**, Demyttenaere K, Tack J, *et al*. Central nervous system involvement in functional gastrointestinal disorders. *Best Pract Res Clin Gastroenterol* 2004;**18**:663–80.
10 **American Psychiatric Association**. *Diagnostic and statistical manual of mental disorders*, 4th edn., Washington, DC: American Psychiatric Association 1994.
11 **Lipowski ZJ**. Somatization and depression. *Psychosomatics* 1990;**31**:13–21.
12 **Persoons P**, Vermeire S, Demyttenaere K, *et al*. The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. *Aliment Pharmacol Ther* 2005;**22**:101–10.
13 **Sharpe M**, Mayou R, Walker J. Bodily symptoms: New approaches to classification. *J Psychosom Res* 2006;**60**:353–6.
14 **Engel GL**. The need for a new medical model: a challenge for biomedicine. *Science* 1977;**196**:129–36.

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 paroxystic 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