

# Clinical Response to Tricyclic Antidepressants in Functional Bowel Disorders is not Related to Dosage

Albena Halpert, M.D., Christine B. Dalton, P.A.-C., Nicholas E. Diamant, M.D., Brenda B. Toner, Ph.D., Yuming Hu, Ph.D., Carolyn B. Morris, Ph.D., Shrikant I. Bangdiwala, Ph.D., William E. Whitehead, Ph.D., and Douglas A. Drossman, M.D.

*UNC Center for Functional GI and Motility Disorders, Chapel Hill, North Carolina; and University of Toronto, Toronto, Ontario, Canada*

- BACKGROUND:** As shown in the per protocol analysis of a recent randomized, controlled trial, when tolerated, Desipramine (DES) is effective over placebo (PLA) in treating moderate-to-severe functional bowel disorders (FBD). Clinical experience suggests that the benefit from tricyclic antidepressants (TCA) in FBD can be achieved at doses lower than those used to treat major depression. Within psychiatry, when using higher dosage of TCAs, plasma levels can be used to adjust daily dosage to optimize a treatment response. However, in FBD, it is not known whether plasma levels at the lower dosage are similarly related to a clinical response.
- AIM:** To determine in treating FBD, whether DES blood levels or dose taken can predict a clinical response.
- METHODS:** As part of a study of 12 wk of antidepressant and psychological treatment in 431 patients with FBD at UNC and U of Toronto, we studied those participants who completed treatment (per protocol analysis) taking DES (N = 97, dose 50–150 mg/day) or pill placebo (PLA) (N = 55 1–3 pills/day). The primary outcome measure was defined as a composite score (Satisfaction with Treatment, McGill Pain Questionnaire, Global Well-being, and IBS-QOL). The composite score was correlated with: (i) DES plasma levels at week 6, and (ii) number of pills taken over the duration of the 12-wk treatment period. In addition, we also compared DES dose with DES plasma levels.
- RESULTS:** There was a modest correlation between mean DES dose at weeks 5 and 6 and DES blood level at week 6 ( $R = 0.2$   $p < 0.07$ ). However, there were no significant correlations between the composite score either with DES dose or with DES blood levels.
- CONCLUSIONS:** Detectable blood levels of DES are associated with a clinical response in FBD. However, with dosages up to 150 mg, there is no relationship between total dose or plasma level and the clinical response.

(Am J Gastroenterol 2005;100:664–671)

## INTRODUCTION

Tricyclic antidepressants (TCA) are frequently used to treat various chronic pain syndromes including postherpetic and other neuralgias, fibromyalgia, headaches, and functional bowel disorders (FBD) (1–7). Although their efficacy in the treatment of FBD has been reported (7–10), almost all published studies have had design limitations. Recently, a well-designed, multicenter placebo-controlled study using 50–150 mg/day of the TCA Desipramine was conducted among women with moderate-to-severe FBD. This study demonstrated no difference in treatment response between Desipramine (DES) and PLA in the intention-to-treat analysis, but DES was statistically and clinically effective in the per protocol analysis of subjects who tolerated the medication and completed treatment. Furthermore, the presence of detectable blood level was associated with a good clinical

response (10, 11). These findings provide further supportive evidence that DES may be effective for patients with FBD who stay on the medication. Clinical experience favors the use of lower than full psychiatric doses of TCA for the treatment of FBD (25–150 mg/day for FBD vs 150–300 mg/day for treating major depression) (7, 12).

Generally, when used in the higher “psychiatric” dose ranges (150–300 mg/day) for treating major depression, there is a linear relationship between DES plasma concentration and therapeutic response in the majority of patients, with a lower limit of response at a plasma level of 116 ng/ml (13). This observation provides the rationale within psychiatry practice for monitoring drug levels and adjusting dosages to reach a therapeutic range, prevent toxicity, and monitor compliance. The question then arises as to whether blood levels can also be used to monitor clinical response in FBD even when lower dosages (25–150 mg/day) are used.

Currently, there are no data on the optimal dose of TCA in the treatment of FBD, and it is uncertain if blood levels can predict a clinical response.

The aim of this study was to test among women with moderate-to-severe FBD who are treated with DES, whether there is a correlation between: (i) DES dose and blood level, (ii) DES dose and clinical outcome, and (iii) DES blood levels and clinical outcome. A significant association between blood levels or dose with outcome would permit the use of blood levels or dosage of medication to predict a clinical response. However, no association would support the premise that lower dosages can still be effective in treating FBD.

## METHODS

The study is a subanalysis involving study subjects in the medication arm (DES vs PLA) of the per protocol analysis (*i.e.*, only study subjects who completed treatment) of a multicenter study on cognitive-behavioral therapy *versus* education and DES *versus* placebo for moderate-to-severe FBD (10). Since DES blood levels were obtained at week 6 and the clinical outcome was evaluated at the end of treatment (week 12), those participants who did not complete the DES arm of the study (N = 40, 29.6%) could not be evaluated. We selected the per protocol analysis in order to achieve the study aims with a complete patient sample. Furthermore, even if the needed data were available, there is no *a priori* evidence that subjects who did not complete the study would have different findings (*i.e.*, a significant correlation) related to study aims.

### Participants and Study Design

Between 1996 and 2001, females aged 18–70 yr with moderate-to-severe FBD (abdominal pain, with or without altered bowel habits for at least 2 days/week, symptoms present for over 6 months) were recruited from two medical centers: UNC at Chapel Hill, and the University of Toronto, Canada. Using the Rome I diagnostic criteria, confirmed by a physician diagnosis, patients were categorized as IBS, painful functional constipation, chronic functional abdominal pain, and unspecified functional bowel disorder. Enrolled patients were randomized in a 2:1 ratio (2 patients assigned to DES for each patient assigned to PLA).

A battery of clinical and psychosocial questionnaires was administered before treatment to assess prognostic variables and at the end of treatment to assess the predictors of the treatment. These are described elsewhere (10).

### Intervention

This paper reports clinical response at the end of the 12-wk treatment period specifically for patients allocated to the DES treatment arm and, when comparison was needed, for patients in the placebo arm. The first visit (45–60 min) occurred 1 wk after randomization. Each subsequent visit lasted 20–30 min. DES was administered as 1 pill (50 mg)/day at bedtime for

the first week, 2 pills (100 mg)/day at bedtime for the second week, and then 3 pills (150 mg)/day at bedtime from week 3–12. The placebo regimen was identical. The drug study coordinator was blinded as to the treatment allocation (DES vs PLA). When clinically appropriate, the dosage level was held or reduced and reevaluated on subsequent weeks with the goal of achieving a maintenance dose of 3 pills/day (150 mg/day). At each visit, the following occurred: (i) the diaries and current symptoms were reviewed, (ii) the remaining pills were counted, and (iii) a medication bottle for the next week was dispensed. Provided there were no side effects of at least moderate severity the DES dose was increased up to the target dose of 150 mg/day (3 pills a day) within the first 3 wk. However if needed further adjustments were made during week 3–12 to achieve the target maintenance dose. A DES plasma level was obtained at week 6. (Emit R Desipramine Immunoassay; Syva Co., Palo Alto, CA).

### Objectives and Outcomes

The primary outcome measure was a composite of four clinically meaningful variables assessed at the end of treatment (week 12): (i) Satisfaction with Treatment (14), (ii) Global Well-being (15), (iii) 2-wk averaged diary card scores of the Pain Rating Index (the average of the intensity score of all pain items endorsed for up to 20 pain descriptors) of the McGill Pain Questionnaire (16), and (iv) health-related quality of life using a 34-item condition-specific measure (IBS-QOL) (17, 18).

The composite score and its individual components for these four outcome variables were correlated with the DES average doses for weeks 1–12. DES plasma levels (done at week 6) were correlated with the DES dose at weeks 5 and 6, and the composite score (week 12). Finally, a secondary subanalysis of clinically relevant subgroups was performed as related to severity of illness (FBDSI) (19), depression (Beck Depression Inventory-II), and consistency of stool (Bristol Stool Scale Score) (20). This was done to determine if within these subgroups there would be differences in the correlation between the components of the composite score and DES dosage or blood levels.

### Data Analysis

Because the DES blood levels were taken at two different sites using two different assays, the levels were standardized between the two sites by subtracting the site-specific mean from each patient value and dividing by the site-specific standard deviations. This transformation made the blood levels comparable for purposes of analysis. Therefore, all data from UNC and University of Toronto were combined. The natural logs of drug blood levels were used in all subsequent analyses as these data permitted linear statistical comparisons when values for the groups are skewed. Average daily dose was calculated for the total study by dividing the total number of pills taken by the subject by the number of days the subject was in the study. Spearman correlation coefficients were calculated to determine the relationship between (i) DES blood

levels and average daily dose at weeks 5 and 6, (ii) average daily dose throughout the study (weeks 1–12) and the composite score, and (iii) DES blood levels and the composite score. We also compared correlations between dosages and blood levels using analysis of variance as a validation analysis. Subsequent analyses considered the individual scales that comprised the composite score (IBS-QOL, McGill Pain, Global Well-being, and Satisfaction) to determine which aspects, if any, of the composite score were significantly correlated with either the average daily dose (weeks 1–12) or DES blood levels. Subgroups for depression, defined as a Beck Depression Index-II score greater than 16 at baseline, and severity, determined from the FBDSI scale (severe if FBDSI greater than 110) (19) were also tested to determine the relationships within the particular subgroups for each of the three primary correlations. Lastly, correlation coefficients between stool characteristics (consistency by Bristol stool scale and frequency) and each of blood level, average daily dose (all 12 wk), and composite score were calculated to see if any relationship with stool characteristics existed. SAS version 8.02 was used for all analyses. Correlations were also performed after subjects in the DES arm with a nondetectable DES blood levels were excluded. Correlation analysis was also performed for the PLA arm relating dose to clinical outcome (blood levels were undetectable in PLA subjects, as expected).

## RESULTS

A total of 97 participants were included in the per protocol analysis, which is the group of interest given the aims of this study. For the analysis of DES blood levels subjects with undetectable blood levels were excluded ( $n = 13$ ), based on evidence from the psychiatry and other literature that about 30% of subjects who claim to take their medications do not we assumed that these subjects were not taking the medication and would not qualify for this analysis (21–23).

### Baseline Demographic and Clinical Data

The demographic characteristics of the study participants in the per protocol analysis are summarized in Table 1. The majority of the participants were Caucasian women in their late 30s, with an average of 15 yr formal education, and married or cohabiting. Their clinical diagnosis was predominantly IBS (80%) with two-thirds of the sample having moderate disease severity with moderate abdominal pain (38.5 on VAS) and an average of two bowel movements per day. A history of physical or sexual abuse was reported by 57% of the participants.

The baseline demographic and clinical variables were not significantly different by site (UNC and University of Toronto) except that UNC had more African-Americans.

### DES Dosage

The mean dosage of DES in the per protocol analysis over the 12-wk duration of the study was 109.0 mg/day (SD 29.9)

**Table 1.** Baseline Demographic and Clinical Characteristics

Characteristic of Patients on DES (Per Protocol)	DES (N = 97)
Age, n = 431 (years $\pm$ SD)	39.85 $\pm$ 12.1
Education, n = 431 (years $\pm$ SD)	14.64 $\pm$ 2.6
Ethnicity, n = 431 (%)	
Caucasian	85.1
African-American	8.9
Asian-American	2.2
Hispanic	1.8
Other	1.8
Native American/Canadian	0.7
Marital status, n = 431 (%)	
Single	33.3
Married/cohabitating	51.8
Divorce/Separated	11.8
Widowed	3
FBDSI, n = 431 (%)	
Mild (0–36)	4.4
Moderate (37–110)	62.2
Severe (> 110)	33.3
FBD diagnosis (%)	
Rome diagnosis, n = 431	
IBS	81.4
Functional constipation	8.5
CFAP	7.41
Characteristic of patients on DES (per protocol analysis)	DES (N = 97)
VAS Pain (0–100 VAS, mean $\pm$ SD/14 days) n = 429	38.3 $\pm$ 21.9
#Stools/day (mean $\pm$ SD/14 days) n = 431	2.3 $\pm$ 1.6
Stool consistency (Bristol Stool Form) mean $\pm$ SD	4.1 $\pm$ 1.3
McGill Pain n = 427	
Average of Pain Rating Index (PRI) mean $\pm$ SD	13.5 $\pm$ 10.3
IBS-QOL (mean $\pm$ SD) N = 431	62.6 $\pm$ 20.3
Global Well-Being (% good, very Good, or excellent), N = 431	39.2

The mean number of pills/day was for DES was 2.2  $\pm$  0.60 and PLA 2.4  $\pm$  0.35. The distribution of doses taken was as follows: 46% took the full dosage of 3/day, 36% averaged at least 2 pills/day, but less than 3 pills, 16% averaged at least 1 pill/day but less than 2 pills, and 1% took no medication.

### Adherence to Treatment

The mean number of pills taken in the ITT analysis over the 12-wk duration of the study was 162.3 ( $\pm$ 82.4), compared to 193.8 ( $\pm$ 82.1) prescribed (84% adherence). Fewer pills were prescribed in the active drug group (148.1  $\pm$  87.4) than the placebo group (191.6  $\pm$  61.8), and adherence was also poorer in the active drug (80.5%) compared to the placebo group (89.5%). Dose adjustments by the coordinator and adherence rates were related primarily to side effects.

### Treatment Response

The parent study demonstrated no difference in treatment response between DES and PLA in the intention-to-treat

analysis. However, patients in the per protocol analysis who stayed on the medication, had statistically significantly higher composite outcome scores and responder rates when compared to placebo, 0.55 ( $\pm 0.02$ ) for DES *versus* 0.48 ( $\pm 0.02$ ) for PLA ( $p = 0.03$ ). The proportion of treatment responders (defined as a score  $>28$  on an 8-question satisfaction scale, each scored 1–5) (14) was 68.5% for DES *versus* 49.1% for PLA ( $p = 0.021$ ; NNT = 5.2) (10).

### Adverse Events

There were no adverse reactions requiring emergency evaluation or hospital admission. The most common side effects for DES were related to the anticholinergic and antihistaminic effects of the drug, (*e.g.*, dry mouth, sleep disturbance, dizziness, and constipation). In the placebo group, the same effects were seen and adjustments for any side effects occurred at about half of the frequency of the DES arm. One of the participants on DES had a potentially toxic blood level of over 800 ng/ml, and the medication was temporarily discontinued.

### Correlation Analyses

There was a modest correlation between DES mean dose at weeks 5 and 6 of treatment and DES blood level obtained at week 6 ( $R = 0.2$   $p = 0.07$ ) (Fig. 1). There was no significant correlation between DES mean dose for weeks 1–12 and the composite score at week 12 (Fig. 2), or between DES blood level at week 6 and the composite score at week 12 (Fig. 3). There was no correlation between number of placebo pills taken with the composite score or blood levels (the latter being nondetectable).

Ancillary analysis for the total sample correlating DES plasma levels at 6 wk with each of the four components of the composite outcome measure at the end of 12 wk was also done. There was an association between DES blood

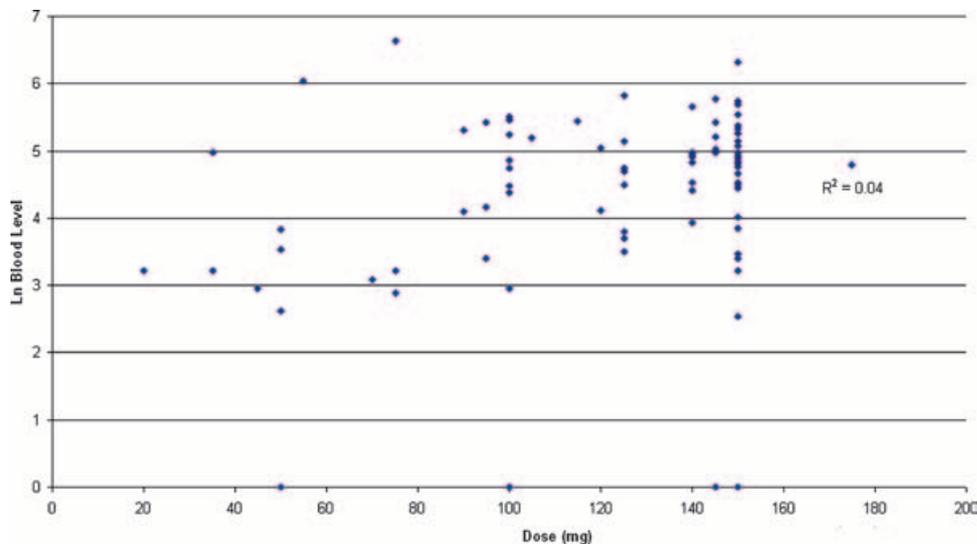
level and Global Well-being, that is, higher DES levels corresponded with a greater score of the well-being ( $R = 0.23$ ,  $p = 0.03$ ). In addition we correlated DES plasma levels with the four components of the composite score for study subjects subgroups—moderate (FBDSI 37–110;  $n = 55$ ) and severe (FBDSI  $> 110$ ;  $n = 31$ ) symptoms, and depressed (BDI-II  $> 16$ ;  $n = 17$ ) *versus* nondepressed ( $n = 68$ ) patients. We found modest correlations between DES plasma levels and the following variables in the expected direction: (i) the Global Well-being score with moderate, but not severe FBDSI ( $R = 0.28$ ,  $p = 0.04$ ), (ii) the Global Well-being score with no depression ( $R = 0.29$ ,  $p = 0.02$ ), and (iii) DES blood levels and McGill Pain score for subjects with moderate but not severe symptoms ( $R = -0.31$ ,  $p = 0.03$ ). There were no correlations between dose or blood level and the individual components of the outcome score in the study subject subgroups by stool consistency or frequency. Finally, there were no correlations between DES level with mean dose or with the composite score, or between mean dose and composite score for the study subject subgroups.

### Variance Analysis

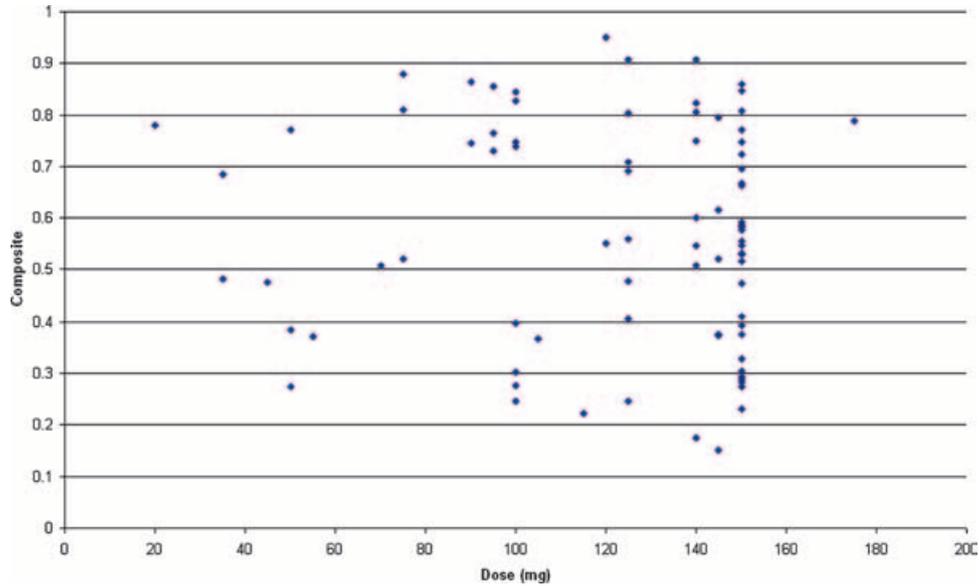
Also, when we compared dosages and blood levels by group between responders and nonresponders we found no difference between the groups' average dose for responders 106.6 (30.4) *versus* nonresponders 112.9 (31.1),  $p = 0.36$ , and mean blood levels for responders 142.1 (130.7) *versus* nonresponders 115.1 (109.9),  $p = 0.38$ , which further supports our findings.

## DISCUSSION

TCA have been widely used in the treatment of FBD. However, evidence of their effectiveness has been inconclusive



**Figure 1.** Scatter plot of log of Desipramine blood levels (week 6) and dose (week 5 and 6 mean) blood level was standardized between sites and then retransformed to U.S. levels so that a natural log could be calculated. Negative retransformed values were assigned a value of 1. Spearman correlation coefficient  $r = 0.20$ ,  $p = 0.07$ .

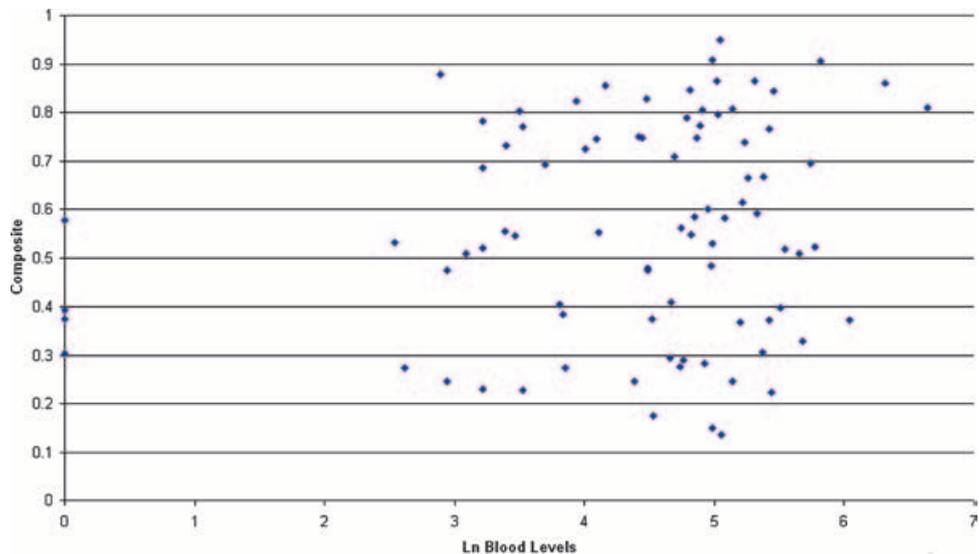


**Figure 2.** Scatter plot of mean Desipramine dose (12 wk) and composite score. Spearman correlation coefficient  $r = -0.04, p = 0.7$ .

because of poor definitions of IBS, small sample size, short treatment duration, use of different assessment variables or drug combinations, and at times, evaluation of atypical study populations (7). Recently, a large placebo-controlled, randomized study on TCA in FBD found that in the per protocol analysis DES (50–150 mg) was effective over placebo in treating women with moderate-to-severe FBD, though the results were not significant in the intention-to-treat analysis (10, 11). Furthermore, it was also noted that when subjects in the DES arm who had nondetectable blood levels (presumably due to nonadherence) were removed from the analysis the clinical and statistical benefit was enhanced. Therefore, a clinical response appears dependent on the presence of detectable blood

levels. However, it is not known whether clinical response is influenced by the magnitude of the blood level, or the amount of DES taken.

In the psychiatry literature, larger dosages of medication are taken to treat depression (*e.g.*, 150–250 mg/day DES). For these patients, the available evidence supports a relationship between TCA plasma levels and efficacy in TCA-responsive depressed patients, but it is not clear if this is a linear or curvilinear relationship (24–26). Nevertheless, an estimate of the sensitivity and specificity of different TCA plasma concentrations as a predictor of clinical response in depression has been established (27), and plasma levels are used in psychiatry practice for both adjusting the dose and monitoring for



**Figure 3.** Scatter plot of log of Desipramine blood levels (week 6) and composite score blood level was standardized between sites and then retransformed to U.S. levels. Negative retransformed values were assigned a value of 1 so that a natural log could be calculated. Spearman correlation coefficient  $r = 0, p = 0.13$ .

toxicity. For DES, the threshold concentration in plasma for therapeutic response is 116 ng/ml (sensitivity 81%, specificity 59%) (28). A metaanalysis comparing standard psychiatric TCA doses to low doses (75–100 mg) in treating major depression showed that standard dosage TCA outperformed the low dosage TCA at week 4 of treatment, but the side effects were also more frequently reported with the higher dose (29). There have been no studies examining the dose–response relationship of TCA in FBD where lower dosages are traditionally used. Therefore, it is not known whether high doses of TCA are more effective than low doses, or if monitoring TCA blood levels is useful in assessing clinical response.

To address this question, we did a per protocol subanalysis of the medication arm (DES vs placebo) of our multicenter study of female subjects with moderate-to-severe FBD (10). The per protocol study group was chosen to assess blood levels at 6 wk, and clinical response as determined by a composite score of four variables, at the end of 12 wk of treatment. We found, in agreement with the psychiatric literature, that there is a modest correlation between DES plasma levels and dose. However, we found no correlation between DES dose or plasma levels and the composite score clinical response. This finding indicates that higher dosages or higher blood levels are not predictive of a better clinical response, and supports the contention that lower doses of TCA may be sufficient to treat FBD (12). Interestingly, subjects with moderate-to-severe FBD, or with higher depression scores (Beck > 16) were previously found to have a poorer clinical response to DES, at least in the 150 mg/day dose range (10). This observation is likely also reflected in the subanalysis of our DES data where there was in fact a correlation between plasma levels of DES and the Global Well-being component of the composite score and the McGill Pain score in patients with moderate FBD and patients without depression.

Several potential mechanisms to explain the benefit of TCAs in FBD have been proposed including:

- (i) Alteration of gut motility: TCAs in low doses slow the progress of the MMC in the small bowel and reduce oro-cecal transit time, while SSRI's increase oro-cecal transit time (30, 31);
- (ii) Alteration of visceral sensitivity: TCAs may also modulate central pain perception by reducing the afferent signals originating in the gut. In animal studies, the pelvic nerve signals were reduced with increasing dosages of three TCAs (32);
- (iii) Central analgesic action: In IBS there is dysfunction of a pain control mechanism that may relate to increased activation of the anterior mid-cingulate cortex (33), therefore CNS modulation of pain is a major site of pain regulation and TCA may reverse this dysfunctional pain regulatory system (34, 35); and
- (iv) Treatment of psychiatric comorbidity (anxiety and depression). However, existing evidence supports that

TCAs are effective in the treatment of FBD with lower doses than needed to treat psychiatric comorbidity (36).

With regard to side effects and adherence to treatment, patients with FBD discontinued DES at a similar frequency (24%) despite the lower dosage used (50–150 mg/day for FBD compared to the 150–300 mg/day dose range for depression) (37, 38). Considering these results, it seems that it is not just the efficacy of TCA in FBD that is important, but also the patient's adherence to treatment that determines the effectiveness of the treatment (7). Compliance with TCAs may then be enhanced by first assessing patient's understanding of the role of antidepressants, including misconceptions, and then providing an explanation of the mechanisms of action of antidepressants in FBD (*e.g.*, as different from mood alteration), an explanation of delayed onset of action and recovery from possible side effects in 1–2 wk. Although not formally assessed in this study, we found that early follow-up (with a phone call in the first week of treatment done by the physician or physician extender) is vital in improving adherence. Notably a detectable DES blood level regardless of the value may help assess adherence to treatment in selected cases and if a blood level is present, increases the likelihood of a clinical response (10).

Our study has several limitations. First, as a *post hoc* per protocol subanalysis, the results can only provide preliminary information to be later confirmed by prospective testing. However, per protocol testing was required to evaluate subjects who stayed on treatment long enough to assess blood levels and treatment response. Second, these results apply specifically to females with moderate-to-severe FBD, and cannot be generalized for males or patients with milder symptom severity. However, with mild or less infrequent symptoms of IBS, there is generally no need to consider daily treatment with antidepressants. Third, the dose of DES was limited to a maximum 150 mg/day and averaged about 100 mg/day. The design of the study does not allow us to comment on the time needed prior to onset of action of DES in FBD nor to determine if there is a dose–response relationship when DES is used in higher “psychiatric” doses. Fourth, we would note that the positive correlations in the subgroup analyses that related one specific outcome measure (*e.g.*, global well-being or pain) to a particular subgroup of symptom severity or depression can only be viewed as preliminary since the main analysis outcome was not significant and sample size of the subgroups was small. However, these data do provide preliminary information to be further studied that may help identify which outcome variables are most responsive to TCA blood levels. Fifth, although the majority of the DES dose adjustments were done in the first 2 wk of treatment the correlation between DES blood levels (week 6) and outcome composite score (week 12) could have been potentially different if DES blood levels were obtained at the time of the outcome score assessment (week 12). However, by week 6, blood levels have reached a steady state (consistent with DES half life of 6–72 h)

and we would expect similar blood levels at 12 wk. Finally, both study centers were academic institutions comprised of study subjects who may be potentially different from those seen in private practices.

Although monitoring blood levels to assess clinical response does not relate immediately to the degree of response, assessing a blood value has potential management benefits. For example, when nondetectible blood levels are found, a clinical response is less likely and efforts to understand the reasons for possible nonadherence are needed. Obviously, a blood level is indicated if toxicity is suspected. Finally, our results indicate that DES plasma levels could potentially be a guide to dosing for some clinical parameters such as general well-being and pain. This observation requires further study.

In conclusion, DES was found to be beneficial for treating females with moderate-to-severe FBD, provided they stay on the medication (10). However when used in low dosages (50–150 mg/day), treatment benefit does not relate to blood levels or dosage. Patients with moderate disease severity and no depression may respond better to DES, when used up to 150 mg/day, than those with severe disease or depression. Importantly, the clinical outcome is dependent upon adherence to treatment, and we believe this may be improved with proper education and support.

---

**Reprint requests and correspondence:** Alben Halpert, M.D., UNC Center for Functional GI and Motility Disorders, CB#7080, UNC-Chapel Hill, Chapel Hill, NC 27599-7080.

*Received August 20, 2004; accepted September 6, 2004.*

---

## REFERENCES

- Maxton DG, Whorwell PJ. Use of medical resources and attitudes to health care of patients with 'chronic abdominal pain'. *Br J Med Econ* 1992;2:75–9.
- Onghe P, Houdenhove BV. Antidepressant-induced analgesia in chronic non-malignant pain: A meta-analysis of 39 placebo-controlled studies. *Pain* 1992;49:205–19.
- Magni G. The use of antidepressants in the treatment of chronic pain: A review of the current evidence. *Drugs* 1991;42(5):730–48.
- Pilowsky I, Barrow CG. A Controlled study of psychotherapy and amitriptyline used individually and in combination in the treatment of chronic intractable, 'psychogenic' pain. *Pain* 1990;40:3–19.
- Egbunike IG, Chaffee BJ. Antidepressants in the management of chronic pain syndromes. *Pharmacotherapy* 1990;10(4):262–70.
- France RD, Houpt JL, Ellinwood MD. Therapeutic effects of antidepressants in chronic pain. *Gen Hosp Psychiatry* 1984;6:55–63.
- Drossman DA, Camilleri M, Mayer E, et al. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002;123(6):2108–31.
- Jackson JL, O'Malley PG, Tomkins G, et al. Treatment of functional gastrointestinal disorders with anti-depressants: A meta-analysis. *Am J Med* 2000;108:65–72.
- Wald A. Psychotropic agents in irritable bowel syndrome. *J Clin Gastroenterol* 2002;35(Suppl):S53–7.
- Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy vs. education and desipramine Vs. placebo for moderate to severe functional bowel disorders. *Gastroenterology* 2003;125(1):19–31.
- Clouse RE. Managing functional bowel disorders from the top down: Lessons from a well-designed treatment trial. *Gastroenterology* 2003;125(1):249–53.
- Clouse RE, Lustman P, Geisman RA. Antidepressant therapy in 138 patients with irritable bowel syndrome: A five-year clinical experience. *Aliment Pharmacol Ther* 1994;8:409–16.
- Perry PJ, Zeilmann C, Arndt S. Tricyclic antidepressant concentrations in plasma: An estimate of their sensitivity and specificity as a predictor of response. *J Clin Psychopharmacol* 1994;14(4):230–40.
- Toner BB, Segal ZV, Emmott S, et al. Cognitive behavior group therapy for patients with irritable bowel syndrome. *Int J Group Psychother* 1998;48(2):215–43.
- Drossman DA, Li Z, Leserman J, et al. Health status by gastrointestinal diagnosis and abuse history. *Gastroenterology* 1996;110(4):999–1007.
- Melzack R. The McGill pain questionnaire: Major properties and scoring methods. *Pain* 1975;1:277–99.
- Patrick DL, Drossman DA, Frederick IO, et al. Quality of life in persons with irritable bowel syndrome: Development of a new measure. *Dig Dis Sci* 1998;43(2):400–11.
- Drossman DA, Patrick DL, Whitehead WE, et al. Further validation of the IBS-QOL: A disease specific quality of life questionnaire. *Am J Gastroenterol* 2000;95(4):999–1007.
- Drossman DA, Li Z, Toner BB, et al. Functional bowel disorders: A multicenter comparison of health status, and development of illness severity index. *Dig Dis Sci* 1995;40(5):986–95.
- Heaton KW, Gosh S. Relation between stool form on a seven point scale and symptoms of urgency, straining, and incomplete evacuation: A new way of looking at irritable bowel syndrome. *Gut* 1989;30:A1465.
- Demyttenaere K, Enzlin P, Dewe W, et al. Compliance With antidepressants in a primary care setting, 1: Beyond lack of efficacy and adverse events. *J Clin Psychiatry* 2001;62(Suppl 22):30–3.
- Demyttenaere K. Compliance during treatment with antidepressants. *J Affect Disord* 1997;43(1):27–39.
- Demyttenaere K, Haddad P. Compliance With antidepressant therapy and antidepressant discontinuation symptoms. *Acta Psychiatr Scand Suppl* 2000;403:50–6.
- Levine RR. The role of plasma concentrations in the use of tricyclic antidepressant drugs. *Prog Neuropsychopharmacol* 1979;3(1–3):211–22.
- Risch SC, Kalin NH, Janowsky DS, et al. Indications and guidelines for plasma tricyclic antidepressant concentration monitoring. *J Clin Psychopharmacol* 1981;1(2):59–63.
- Risch SC, Huey LY, Janowsky DS. Plasma levels of tricyclic antidepressants and clinical efficacy: Review of the literature—part II. *J Clin Psychiatry* 1979;40(2):58–69.
- Perry PJ, Zeilmann C, Arndt S. Tricyclic antidepressant concentrations in plasma: An estimate of their sensitivity and specificity as a predictor of response. *J Clin Psychopharmacol* 1994;14(4):230–40.
- Perry PJ, Zeilmann C, Arndt S. Tricyclic antidepressant concentrations in plasma: An estimate of their sensitivity and specificity as a predictor of response. *J Clin Psychopharmacol* 1994;14(4):230–40.
- Furukawa TA, McGuire H, Barbui C. Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: Systematic review. *Br Med J* 2002;325(7371):991.

30. Gorard DA, Libby GW, Farthing JG. Influence of antidepressants on whole gut oro-caecal transit times in health and irritable bowel syndrome. *Aliment Pharmacol Ther* 1994;8:159–66.
31. Gorard DA, Libby GW, Farthing MJG. Effect of a tricyclic antidepressant on small intestinal motility in health and diarrhea-predominant irritable bowel syndrome. *Dig Dis Sci* 1995;40:86–95.
32. Gebhart GF. Visceral nociception: Consequences, modulation and the future. *Eur J Anaesthesiol Suppl* 1995;10:24–7.
33. Naliboff BD, Derbyshire SWG, Munakata J, et al. Cerebral activation in irritable bowel syndrome patients and control subjects during rectosigmoid stimulation. *Psychosom Med* 2001;63(3):365–75.
34. Mertz H; Pickens D, Morgan V. Amitriptyline reduces activation of the anterior cingulate cortex in irritable bowel syndrome patients during rectal pain. *Gastroenterology* 2003;124(4):A-47.
35. Drossman DA. A case of irritable bowel syndrome that illustrates the biopsychosocial model of illness. *Biopsychosocial Med* 2003:15–25.
36. O'Malley PG, Jackson JL, Santoro J, et al. Antidepressant therapy for unexplained symptoms and symptom syndromes. *J Fam Pract* 1999;48(12):980–90.
37. Furukawa TA, McGuire H, Barbui C. Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: Systematic review. *Br Med J* 2002;325(7371):991.
38. Hollister LE. Plasma concentrations of tricyclic antidepressants in clinical practice. *J Clin Psychiatry* 1982;43(2):66–9.