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Not All "Side Effects" of Tricyclic Antidepressants are True Side Effects

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Abstract

Objectives—Patients with functional gastrointestinal (GI) disorders treated with tricyclic antidepressants may report non-GI symptoms. It is unclear whether these symptoms are side effects of the medication or reflect a general behavioral tendency to report symptoms. This study 1) evaluated whether a checklist of symptoms reported by patients prior to taking desipramine increased in number or worsened in severity after being on a tricyclic antidepressant (desipramine), and 2) assessed baseline factors that predispose patients to report symptoms.

Methods—Female patients in the drug arm of a multi-center NIH treatment trial for functional bowel disorders completed a 15 item symptom questionnaire at baseline before randomization and at 2 weeks after starting Desipramine (n=81), or placebo (n=40) and at study completion 12 weeks later. Patients were asked on each occasion if they experienced any of 15 Symptoms and its level of severity and frequency, and the results were compared.

Results—A total of 57 patients in the desipramine arm who completed the questionnaire at both week 0 and week 2 comprised the study sample. Certain symptoms reported as side effects: dizziness, dry mouth/thirstiness, lightheadedness, feeling jittery or tremors and flushing not only were reported more often but also worsened at week 2 indicating a drug effect. Conversely, other symptoms that were also reported as side effects: feeling tired in AM, nausea, blurred vision, headaches, decreased appetite, and trouble sleeping either did not change in severity or showed improvement at week 2 (tiredness). All these symptoms except trouble sleeping were reported less often at Week 2 than at baseline (Week 2). Psychological distress but not desipramine level significantly correlated with symptom reporting.

Conclusions—The majority of symptoms often attributed to side effects of desipramine were present prior to treatment, and only a few related to its anticholinergic effects worsened 2 weeks after beginning treatment, suggesting that most symptoms considered as side effects were not related to drug *per se*. Clinicians should consider that "Side effects" may relate more to psychological distress than to drug effects.

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INTRODUCTION

The Functional Gastrointestinal Disorders (FGID), which are clusters of symptoms not explained by observable morphological abnormalities, are determined by the interaction of biological and psychosocial factors [1–3]. Given this understanding, tricyclic antidepressants (TCAs) have potential value in treating these disorders because of their central and peripheral effects on pain modulation and motility. Data supports their use in treating functional GI disorders including irritable bowel syndrome [3–6]. However, the physician's limited knowledge of their value, plus patient misconceptions about their mechanisms of action, and societal stigma relating to taking medications perceived to be solely for psychiatric disorders, may lead to reluctance to prescribe or take this type of medication. Furthermore, these potential limitations to prescribing are compounded when patients have concerns regarding medication side effects. If these factors and concerns are not elicited and addressed properly, these medications either may not be prescribed or may be prematurely discontinued without the opportunity to achieve benefit [4].

In addition to concerns about side effects, patients with FGIDs report more GI and non-GI symptoms than do comparison groups [7, 8]. This may relate to co-morbidities related to the disorder[9, 10] or the influence of psychosocial distress enhancing the intensity, frequency or even the numbers of symptoms via central amplification [3, 8, 11, 12]. Thus, differentiating side effects of TCAs from other somatic symptoms often reported by these patients becomes a difficult task as this may either reflect patient's general tendency to report somatic symptoms, or amplification of this tendency by the underlying psychosocial distress [13]. This phenomenon, first reported among depressed patients seen in psychiatry [14, 15] and primary care[13, 16, 17] has not been adequately studied in patients with functional GI disorders. This distinction is clinically relevant since it may affect the patient's adherence to treatment and the physician's prescribing behaviors. Thus, there is a need to clarify whether the "side effects" reported by IBS patients after taking TCAs are medication-related or not.

In our NIH-sponsored trial comparing among women with functional bowel disorders treated with desipramine vs. placebo and CBT vs. education[4], we found that tiredness and headaches, symptoms usually attributed to desipramine, were in fact worse in the placebo groups. By analogy, this raised concern as to whether some of the symptoms attributed to desipramine, might in fact not be a side effect of this medication.

The aims of this study were: (1) to determine whether symptoms that were reported after taking desipramine were present before taking TCA; (2) whether there is a change in the number and severity of symptoms over time when taking this medication; and (3) what factors predicted symptom reporting.

METHODS

We studied females with functional bowel disorders (IBS, painful constipation, functional abdominal pain or unspecified functional bowel disorder) who were participating in the active medication arm or the placebo arm of an NIH treatment trial at the University of North Carolina and the University of Toronto (RO1DK49334) [4]. In the primary study, patients were also randomized to either cognitive behavior therapy or education (used as a control for cognitive behavior therapy). However, patients randomized to cognitive behavior therapy or education groups are not included in this report and we only include data on the subjects used in the final data analysis. Patients in the current study were blinded as to treatment allocation (Desipramine or placebo).

Figure 1 provides the flow chart for questionnaire distribution as discussed below. Prior to randomization (week 0), a 15-item symptom questionnaire was given to all subjects asking

whether they were: 1) *currently experiencing*, or b) *had in the past experienced* any of 15 symptoms. Thirteen of the fifteen symptoms in the questionnaire have previously been described as side effects of tricyclic antidepressants: *dizziness, nausea, feeling lightheaded, trouble sleeping, headaches, dry mouth/thirsty, feeling jittery or tremors, decreased appetite, tired in morning, blurred vision, rash, flushing and slurred speech*. The two items definitely not considered side effects of tricyclic antidepressants are *earache and fever*. If a symptom was reported, a Total Severity Score was determined by its intensity (5-point Likert scale rated very mild to severe) and frequency (number of episodes per day, week or month) at Week 0.

On day one of the treatment phase, each subject in the medication arm was asked to begin taking one pill (desipramine 50 mg or placebo) at bedtime every night. For the second week, the dose was increased to 2 pills (100mg. desipramine or 2 placebo pills). The dosage remained at one pill (50mg desipramine or placebo) for the second week only if the subject reported side effects during the first week that were at least moderate in severity. Thereafter, desipramine dose was increased to 150mgm if tolerated and patients were maintained on the same tolerated dose for the remainder of the 12 weeks.

After receiving treatment for two weeks, subjects in both the desipramine and placebo groups again completed the symptom questionnaire, and were asked only if they were *currently* experiencing any of the same fifteen symptoms. As before, a Total Severity Score for each current symptom was also recorded at Week 2.

The symptom questionnaire was given a third time to all subjects remaining in the study at Week 12 (end of treatment phase) and the same symptom variables were obtained. Therefore, subjects completed the Symptom Questionnaires three times; Week 0, Week 2 and Week 12 (Figure 1).

DATA ANALYSIS

For demographic data, descriptive statistics were calculated and compared between groups (means, standard deviations and t-tests for continuous variables, frequencies and chi-square tests for categorical variables). For the first objective, which included only the subjects on desipramine, McNemar's test was used to test the agreement between the Week 0 and Week 2 symptom questionnaires to determine symptoms that were most probably 'true' side effects. For the second analysis, linear regression was used to compare the mean number of symptoms reported at each time point between groups. The frequency of each symptom was multiplied by its severity score to arrive at a Total Severity Score for each symptom. The Total Severity Score was compared between weeks 0 and 2 with Wilcoxon signed rank tests. For the third aim, blood desipramine levels were standardized by site and Pearson correlation coefficients were used to test the relationship between symptoms and blood levels. The mean number of symptoms reported was also compared between groups with and without psychological impairment, as determined by SCL-90 GSI scores, using t-tests.

RESULTS

Between September 1997 and October 2001, out of the eligible 245 female study participants, 93 subjects in the medication arm completed questionnaires at both week 0 and week 2 (57 in desipramine group and 36 in the placebo group). The 57 patients in the desipramine group form the study group for all of the analyses except for the analysis of mean number of symptoms over time, for which subjects randomized to receive placebo tablets were also included. Of the 24 desipramine arm patients who were not included in the study, twelve dropped out of the study (including 5 who discontinued due to side effects) and 12 did not complete the Week 2 questionnaire.

Demographics & Baseline Symptom Reports

The mean age of desipramine-treated subjects was 39.1 and mean years of education was 14.7 years. About 58% were married and 84% were white. The remainder of the demographic data for desipramine and placebo are given in Table-1. There were no difference in the mean age, years in school, race and mean number of symptoms (data not shown) between patients who completed only the Week 0 questionnaire (excluded from analysis; n=24) and patients (analysis group) who completed both Week 0 and Week 2 questionnaires (n=57) except for marital status and the site as the study group had more patients from the US (68%, p=0.0015) and were more likely to be married (58%, p=0.10). For patients in the overall study 19% were rated as clinically depressed at baseline using a cutoff of >16 with the Beck Depression Inventory.

At baseline, the proportion of the patients reporting the symptoms are: *tired in am* (47%), *nausea* (47%), *trouble sleeping* (46%), *headaches* (42%), *decreased appetite* (37%), *dry mouth* (35%), *lightheadedness* (25%), *dizziness* (18%), *blurred vision* (16%), *flushing* (12%), *feeling jittery or tremors* (11%), *rash* (7%), *ear ache* (5%), *fever*(4%), *and slurred speech* (4%). Because of the low frequency of the last four symptoms (<10%), they were omitted from most analyses.

Symptom Assessment

Number of symptoms reported at week 2 relative to symptoms prior to starting treatment—Five symptoms (*dry mouth, lightheadedness, dizziness, flushing, and jittery or tremors)* were reported by more subjects only at Week 2 (after taking desipramine) compared to reporting at both times (week 0 before starting desipramine and at week 2 after starting desipramine; $p<0.002$ to $p<0.0001$); see Figure 2, last five symptoms on right). This suggests that these symptoms may be related to the known anticholinergic effects of the medication.

However, six other symptoms (*tired in the AM, trouble sleeping, nausea, blurred vision, headaches and decreased appetite)* were reported more by subjects at both times (Week 2 and Week 0) than only at Week 2 (p=ns; see figure 2, first 6 symptoms on left) indicating that these symptoms pre-existed the start of the medication. Thus, these symptoms could not be attributed to the side effects of tricyclic antidepressants, as they were not reported more after starting the desipramine. Though the symptom trouble sleeping was statistically significant, it was most common the symptom reported by a highest proportion of subjects at baseline (23/57 (40%) at week 0 and 36/57 (63%) at week 2) indicating the drug effect could have only played a minor in reporting of this particular symptom.

Number of symptoms reported among subjects taking desipramine and placebo over time (Figure 3)—There were no differences in the number of symptoms reported between all active and control conditions during the enrollment period and prior to randomization (i.e., "baseline"). When asked: "*Did you ever* have any of these symptoms" subjects in the medication arm (n=121) reported a mean of 6.4 ± 3.9 symptoms (Desipramine 6.5 ± 3.6, Placebo 6.2 ± 3.8). When asked, "*Are you currently* having any of these symptoms", subjects reported a mean of 3.9 ± 3.4 symptoms (Desipramine 3.7 ± 3.3, Placebo 3.9 ± 3.5).

At week 2, there was a significant difference between the number of side effects reported in the Desipramine group compared to placebo, presumably due to effects from the active agent, desipramine (p=0.03), but this difference was no longer significant at week 12 due primarily to a drop in the mean number of symptoms in the desipramine group at that time. This may relate to the beneficial effects of the drug on raising symptom threshold. Furthermore, there was no statistical association at week 12 between the dose of desipramine taken daily and the number of side effects (data not reported).

Total Severity Score—In addition to increasing the number of symptoms, taking desipramine could also make a particular symptom more severe. To evaluate this, we compared the Total Severity Score of the individual symptom within the desipramine group at two weeks compared to pre-treatment. The Total Severity score for *dizziness, feeling lightheaded, dry mouth/thirsty, flushing* and *jittery or tremors* significantly increased (Fig. 4, items to the right of 0). The increased severity of these individual symptoms is consistent with the high proportion of subjects reporting these symptoms at week 2 compared to week 0, thus supporting them as true drug effects, and clinically seem related to the known anti-cholinergic actions of desipramine. Conversely, *tiredness* decreased in severity at Week 2 (Fig 4, to left of 0), possibly suggesting a therapeutic response to desipramine. All other symptoms (*nausea, poor sleep, headaches, poor appetite, and blurred vision*) did not get worse at week 2 suggesting that a symptom reporting tendency was present at baseline as many of these symptoms were reported by more subjects at baseline and it continued at week 2, rather than being a drug effect.

Determination of factors contributing to symptom reporting

Analyses were done to determine whether desipramine drug level or psychosocial distress as measured by SCL-90 related to symptom reporting.

Correlation of symptoms with Desipramine level—Blood was drawn to obtain desipramine levels at week 6, a time where the effect of desipramine could be considered therapeutic. Results were available for 33 subjects. Correlation coefficients were calculated to determine the strength of the relationship between mean blood levels of desipramine and the mean number of symptoms at week 2 and week 12 and these were not significant (r=.08, r=. 19 respectively). When correlating the individual symptoms with mean drug blood level, only dizziness at Week 12 was significant ($p<.05$). When correlating the frequency of individual symptoms with mean drug blood levels only nausea (Week 12) was significant ($p<0.05$). This suggests that overall; the symptoms attributed to the side effects of desipramine were not explained by their blood level, which traditionally is presumed to be a measure of treatment effect.

Relation of the symptom reporting to psychological impairment—To understand the role psychosocial factors play in the tendency to report symptoms, the mean number of symptoms reported was correlated with SCL-90 Global Symptom Index (GSI) scores, a summary measure of psychological distress [18]. Notably high GSI scores were associated with greater reporting of symptoms (r=.27, p=.01). We also compared the mean number of symptoms reported among subjects who were considered psychologically distressed to those who were not. Groups were defined based on the female non-patient norms reported by the SCL-90 for the GSI. For the GSI scale, those desipramine patients with higher scores (i.e., psychologically distressed) reported significantly more symptoms at baseline (2.5 mean for clinically non-distressed group, and .3 mean for clinically distressed group, p=0.01). Because of possible concern that the GSI items, which include a few somatic symptom items (including 3 that are GI related), could confound the responses, we also evaluated the relation of the anxiety and depression subscales of the GSI with number of symptoms, since they did not contain GI symptoms. The results using these two subscales mirrored the GSI results showing greater reporting of symptoms for subjects in the clinically abnormal range (Figure-5).

DISCUSSION

We found that many symptoms reported by females with FGIDs that are presumed to be side effects after two weeks of treatment with desipramine were actually present before starting treatment. In fact, only four on the checklist of 15 symptoms that seem to be related to the known anticholinergic effects of the drug got worse at two weeks while most others stayed the

same or improved with continued treatment. This effect does not appear to be related to desipramine blood levels, a measure of treatment effect, but was found to be associated with high levels of anxiety and depression.

Our results are consistent with the evidence that patients with moderate to severe FGIDs rather than patients with milder FGIDs report more symptoms possibly due to a greater tendency to set higher sensory thresholds; this has been reported for other conditions in the primary care [13, 16] and psychiatric literature [14]. Possibly, some patients may not even be aware that the symptoms they attribute to the medication often were present before initiation of therapy.

While drug induced side effects are expected to develop after starting treatment, non-drug related symptoms persist or may improve. In fact, in our study, many symptoms occurred at a higher rate at baseline than at week 2 after being on desipramine and did not get worse either at Week 2. *Tiredness* improved after being on medication only for two weeks. Similar findings have been reported for desipramine used in a depression treatment trial by Nelson et al [14]. In their study, three out of 24 symptoms, namely dry mouth, blurred vision and excessive sweating got worse with treatment and eight others significantly improved. In our study, *dizziness, feeling lightheaded, tremors, dry mouth/thirsty, and flushing* got worse at Week 2 and only the last 2 symptoms were still worse at week compared to baseline (data not shown). Our study differs from the Nelson study in terms of the patient population, indications for desipramine and its dose, and the time frame in assessment of side effects.

As noted above, neither the mean number of symptoms nor the individual symptoms except for *dizziness* correlated with the desipramine blood level in our study. In the Nelson study [14] only three out of 24 symptoms were positively correlated with drug level, namely tremors, lightheadedness and dry mouth, and in another study, most of the side effect symptoms decreased significantly by the end of treatment despite lack of significant reduction in plasma levels[15]. This is not surprising, as we have shown that the therapeutic response to TCA in functional GI disorders does not correlate with the drug level[7]. In contrast, the reporting of symptoms is strongly associated with psychological distress, including anxiety and depression more than being related to the effect of the medication. We can conclude that the more symptoms patients' report, the less likely it is related to the medication.

Our clinical observation is that many patients are reluctant to start antidepressants. They are concerned about developing side effects since many do develop symptoms after starting. We have observed clinically that the symptoms patients report are not necessarily temporally related to the medication but are associated with the patient's verbalized anxiety about the medication effect. In fact, many patients will discontinue the medication without consultation. Similarly, the majority of patients in our NIH treatment trial who discontinued desipramine reported side effects as the main concern. From our clinical experience we find that if we address the symptoms through reassurance and negotiate a treatment adjustment and/or provide an anxiety reducing medication, these "side effects" resolve concurrent with clinical improvement [19]. The data from this study support our clinical observations and highlight the importance of the value of effective communication between physician and patient to optimize the patient's ability to take this type of medication.

Our study has some limitations. First, among 81 desipramine arm patients, 24 were not included in the analysis because of lack of week 2 data or dropouts. However, the relatively low number (n=5) of dropouts due to side effects should not compromise our findings. Second, there may be a selection bias as our patient population was comprised of only females recruited from a tertiary clinic and advertisements and who had moderate to severe symptoms. This may limit the generalizability of these findings to males or the majority of patients with milder symptoms

who do not have high levels of psychological distress; in general somatic symptoms reporting relates to severity [10]

To conclude, this study shows that those symptoms that are potentially related to the anticholinergic side effects of desipramine tend to worsen after treatment is initiated. Furthermore, most of the symptoms reported by patients with functional GI disorders who are on antidepressant while presumed to be medication related are not in fact related to it. These symptoms appear related to anxiety, worries about taking the medication, or other psychosocial factors that may increase the tendency to report symptoms. Physicians who treat patients with functional GI disorders need to be aware of the possibility of their patient's pre-existing somatic symptoms before starting antidepressant therapy. Some of these symptoms will relate to the potential anti-cholinergic effects as side effects of the medication and many will not. This knowledge will permit proper monitoring of the patient so as, to avoid premature discontinuation. The data from this study highlights the importance of effective communication between physician and patient to optimize their ability to take this class of medications.

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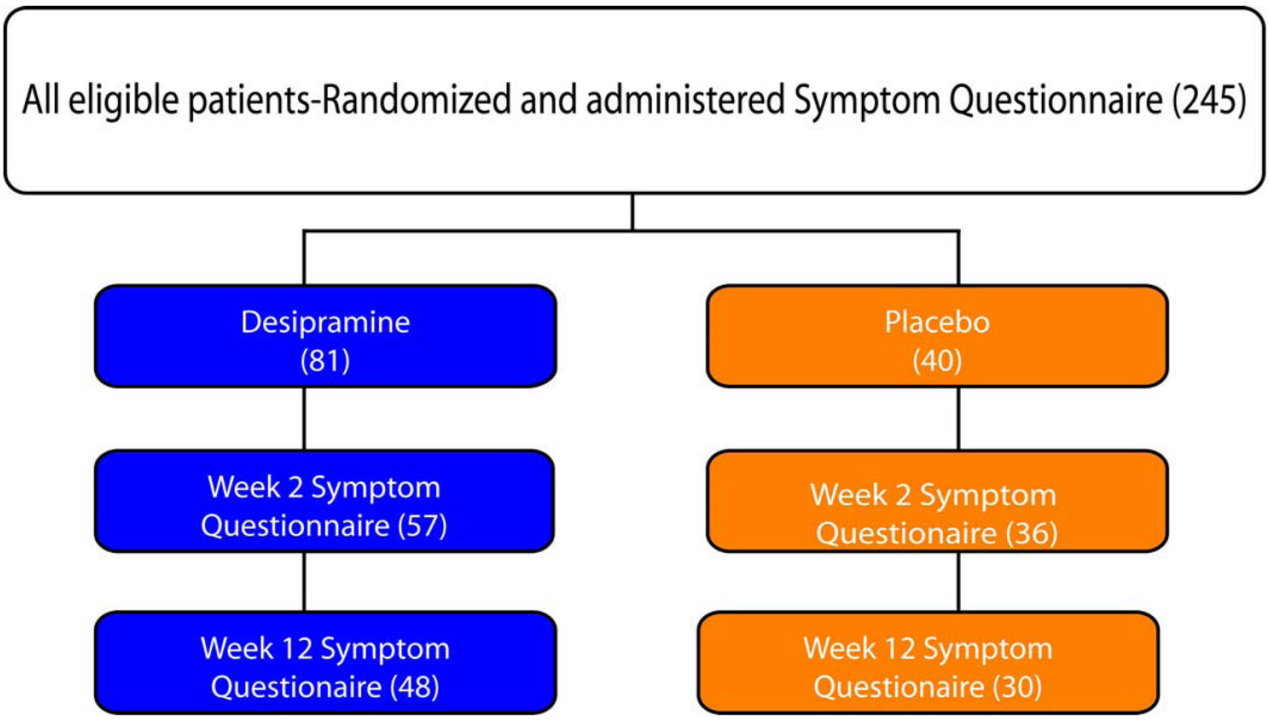

Figure 1.
Flow chart of study and questionnaire distribution.

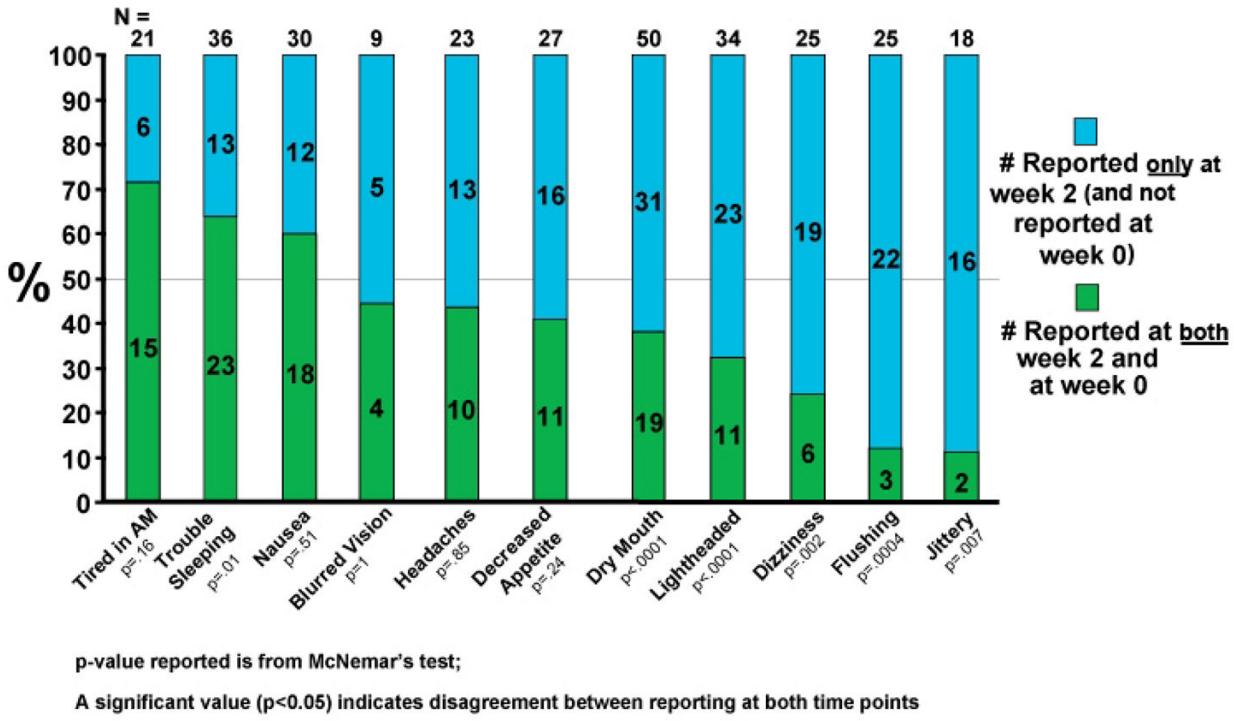

Figure 2.

Shows the symptoms reported only at week 2 and not at week 0 (top bars) to symptoms reported at both week 0 and week 2 (bottom bars). N=the proportion of patients reporting symptoms 2 weeks after taking desipramine. P value is reported from McNemar's test. A significant difference ($p < 0.05$) indicates disagreement between the symptoms reported at both time points.

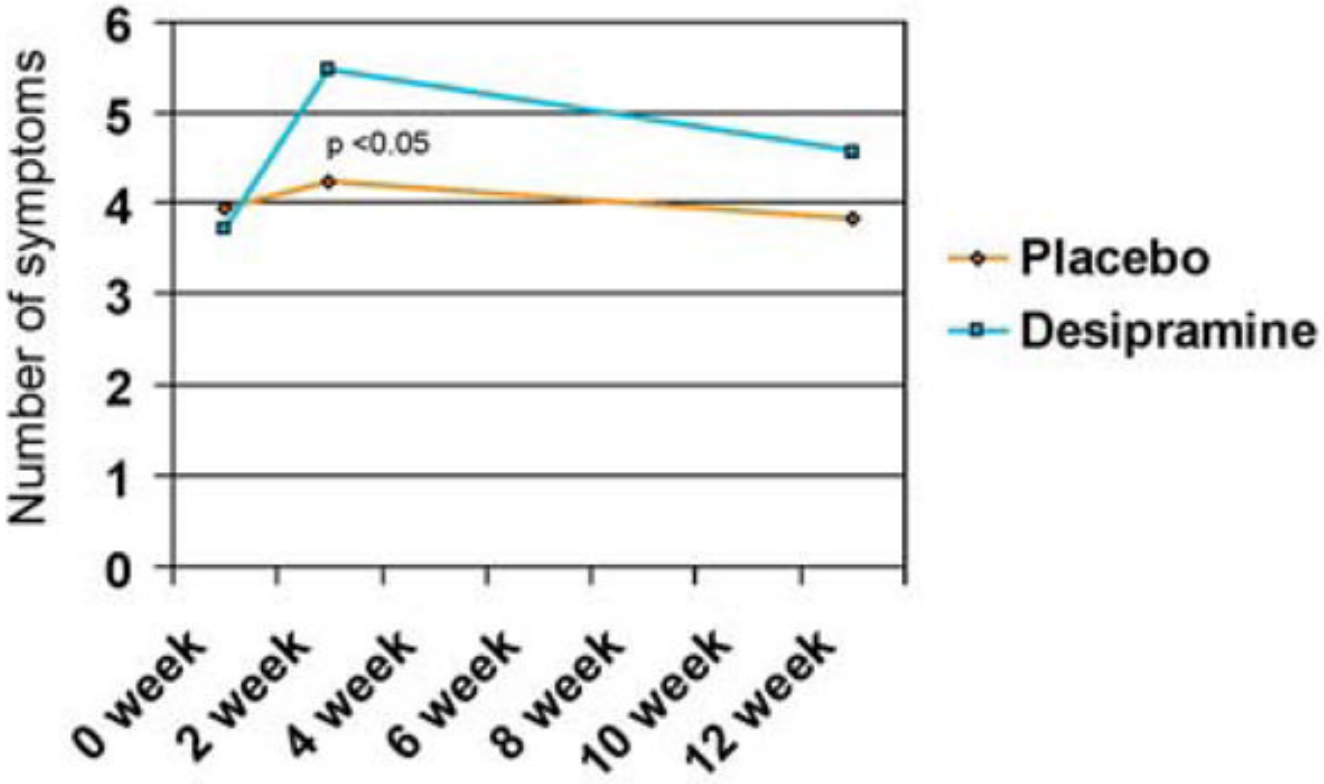

Figure 3.
No of patients for desipramine and placebo at week 0, 2 and 12 were 81, 59, 60 and 41, 38, 33 respectively. P <0.05 indicates a significant difference between desipramine and placebo at week 2 only.

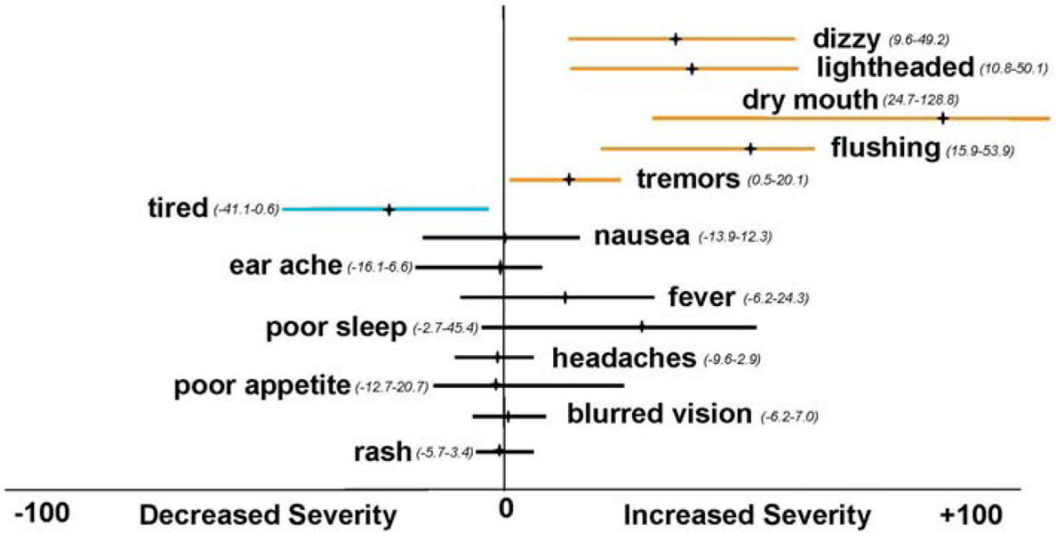

Figure 4.

is a forest plot showing the mean difference in the total severity scores between week 2 and week 0 with 95% CI. Bars to right of midline indicate worsening symptoms, left of the midline indicate improvement in symptoms. Bars crossing the midline did not change significantly.

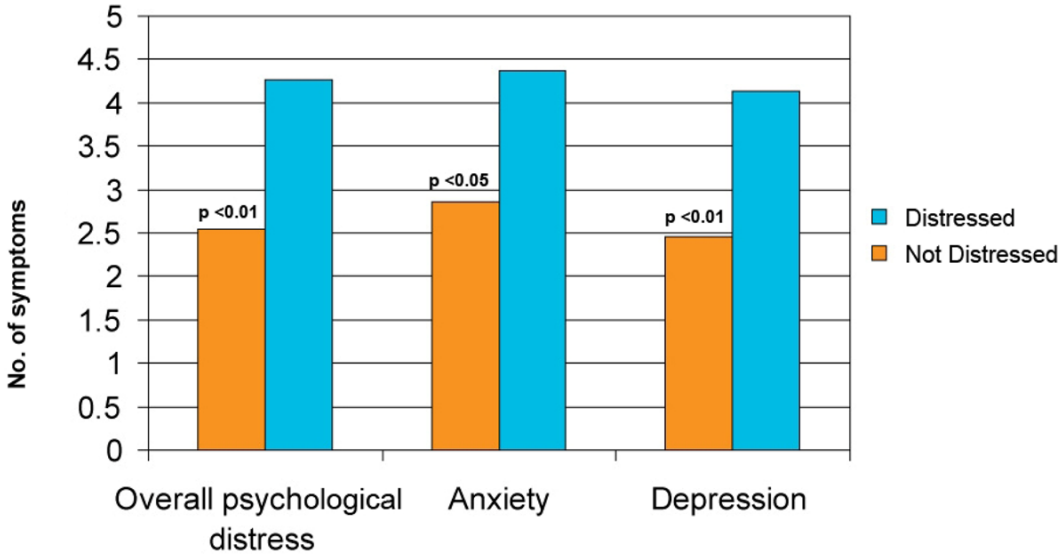

Figure 5.

Comparison of number of symptoms reported between subjects clinically distressed vs. those not clinically distressed. Clinically distressed indicates a SCL-90 GSI subscale score of >0.36 for GSI, a SCL-90 anxiety subscale score of >0.37 for anxiety subscale and a SCL-90 depression subscale score of >0.46 for depression.

Table 1

Demographics

		Desipramine			Placebo		
		N	**Mean**	**SD**	**N**	**Mean**	**SD**
Age		57	39	12	36	40	12
Education: Years in school		57	15	3	36	16	3
		N	%		N	%	
Race	White	48	84		30	83	
Married		33	58		18	50	
Site	US	39	68		21	58	
	CAN	18	32		15	42	