Improving Medication Tolerance

A Pilot Study in Disorders of Gut-brain Interaction Treated With Tricyclic Antidepressants

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Objectives: Tricyclic antidepressants (TCAs) are commonly used to treat disorders of gut-brain interaction (DGBI). However, these medications are often associated with side effects that lead to early treatment discontinuation. Research in other chronic medical conditions suggests that many TCA side effects may be caused by nocebo (negative placebo) effects. The current study tests a brief, verbal intervention aimed at improving tolerance of TCAs in DGBI by providing education about nocebo effects.

Materials and Methods: This pilot randomized controlled trial was performed in a tertiary care gastroenterology clinic. Participants with DGBI were randomized "standard information," describing the benefits and risks of TCAs, or "augmented information," which included an additional < 30-second education about nocebo effects. Two weeks after their visit, participants were emailed a survey evaluating the number and bothersomeness of side effects, adequate relief, global improvement, and treatment satisfaction.

Results: Thirty-one patients were randomized and 22 responded to the survey. The average age was 40% and 59% were women. Although not statistically significant, the augmented group attributed nominally fewer symptoms to TCAs than the standard group, with a medium effect size (1.5 vs. 4.2, effect size $d = 0.56$, $P = 0.212$) and reported being significantly less bothered by those symptoms (13.4 vs. 38.1, $P = 0.037$). A nominally larger percentage of the augmented group reported adequate relief of symptoms after 2 weeks of treatment compared with the standard group (55% vs. 27%, respectively).

Conclusions: This pilot study demonstrates that a brief (≈30 s) clinical intervention addressing nocebo effects may improve tolerance of TCAs. These findings provide support for future, fully powered studies to evaluate the impact of framing on clinical outcomes, especially in chronic conditions.

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One significant barrier to care of patients with chronic medical conditions, especially those with waxing and waning symptoms, is poor tolerance of medications and early discontinuation of treatment, both of which have been linked to "nocebo effects" (eg, adverse reactions due to anticipation or worry about possible side effects).[1] This is especially true among patients with disorders of gut-brain interaction (DGBI), which affect up to 40% of the world population and account for significant health care costs.[2,3] A significant proportion of patients with these conditions do not report satisfactory relief of symptoms with medical management alone, and early discontinuation of medications is common.[4]

Early discontinuation of medications is an important consideration for tricyclic antidepressants (TCAs), which are prescribed to target visceral hypersensitivity and dysfunction in the brain-gut axis in DGBI.[5] Unfortunately, TCAs are frequently associated with unpleasant side effects (eg, fatigue, dry mouth, sleep disturbance, headache, dizziness) occurring within the first few weeks of starting the medication. In randomized controlled trials (RCTs) of TCAs for other chronic medical conditions (eg, migraine, chronic pain, depression) the occurrence of many of these side effects is often not significantly different between treatment and placebo groups and participants in placebo groups withdraw from the study due to side effects at least as often as those in the treatment groups.[6–8] This raises the question of whether some of these common side effects might be better explained as nocebo effects.[9] Although this has not been formally studied in DGBI, data from an RCT of a TCA in irritable bowel syndrome (IBS) revealed that side effects known to be associated with the pharmacology of TCAs (eg, dry mouth, sleep disturbance, constipation) were commonly reported in the placebo arm. Furthermore, several nonspecific side effects commonly attributed to TCAs (eg, dizziness, fatigue, headache) were reported at least as often in the placebo group compared with the TCA group.[10]

There is a growing body of literature to suggest that how information is presented can affect patient reporting of side effects and tolerance of treatment. For example, presenting positively framed (% of patients who tolerate a treatment) versus negatively framed (% who did not tolerate

the treatment) can impact tolerance of the influenza vaccine, with those receiving positively framed information reporting fewer side effects in the days following inoculation.[11] This has been replicated with other, one-time treatments (eg, epidural placement)[12] as well as in experimental studies using healthy participants.[13–16] However, such an intervention has not been tested regarding tolerance of daily medications prescribed in clinical practice. The existing research suggests that there might be a simple and ethical way to present information about side effects when prescribing a new medication to reduce nocebo effects, like TCAs, with high side effect profiles.[17]

The aim of this pilot study was to test whether adding a very brief verbal intervention during a routine clinic visit could affect tolerance of TCAs. In this study, we evaluated 2 versions of the standard of care when prescribing TCAs to patients with DGBI: (1) providing a list of potential benefits and common side effects associated with TCAs; and (2) providing an identical list of potential benefits and side effects, augmented with a very brief description (≈30 s duration) of nocebo effects based on data from TCA RCTs. Similar patient-centered approaches have been proposed in the literature, albeit never so brief[17–19]; and the approach has never been empirically tested in a clinical setting.

MATERIALS AND METHODS

Participants

Patients presenting for a routine clinical appointment at a tertiary care gastroenterology clinic from August 2017 to December 2019 were eligible for this study if they were diagnosed with a DGBI and if their physician decided to prescribe a TCA at the time of their visit.

Physicians

To avoid any prescribing bias by the physician, verbal consent was obtained by a research assistant in the waiting room before their appointment and the study physicians (J.N., J.I., V.R., and A.L.) were not informed as to whether the patient had agreed to participate until after deciding to prescribe a TCA. At that time, the physician randomized the patients to 1 of 2 different descriptions of possible side effects (described below). Randomization assignments were kept in opaque, sealed, sequentially numbered envelopes that were opened only after deciding to prescribe a TCA for consented patients. Patients were blind to assignment and physicians were blind until after making the decision to prescribe a TCA. Participants were debriefed about the full details of the study and could withdraw their data after completing the follow-up survey.

Ethics

The institutional review board ethics committee determined that this study was not an interventional RCT but rather a "quality assurance" project, testing 2 versions of legitimate informed consent (ClinicalTrials.Gov Identifier: NCT03475550).

Interventions

Standard Information

The physician provided information (verbal and written) about common benefits and side effects associated with TCAs. Written information was printed from *uptodate.com*, an evidence-based clinical decision support resource. The following reassurance was provided:

(1) Most patients do not have these side effects/most people tolerate this well.
(2) If you do have a side effect, it will likely go away over time if you continue to take the medication.

Augmented Information

In addition to receiving identical information described above, patients also received the following information:

(I) One thing that many people don't know is that when this drug was tested in trials against placebo, the patients taking placebo (eg, sugar pills) who thought they were getting the real drug also experienced many of these same side effects (optional: This is called the Nocebo effect—it's like the Placebo effect's "evil twin"). It's possible that worry or anticipation about side effects can produce these symptoms.

The augmented information was deliberately brief (< 30 s) to make it feasible in a busy medical practice. Furthermore, we hypothesized that providing brief, straightforward framing would be more effective than encouragement to ignore side effects or formal education on nocebo effects.

Outcomes

A follow-up survey was emailed to participants 2 weeks after randomization. This survey first evaluated whether the patient had started and/or discontinued the medication. For those who had started the medication, the survey asked whether the participant had experienced any of 37 symptoms since starting the medication. These symptoms were derived from previously published literature on nonspecific side effects commonly reported in clinical trials,[20] as well as common side effects reported in RCTs of TCAs. The complete list is included in Appendix 1 (Supplemental Digital Content 1, http://links.lww.com/JCG/A752). For each reported symptom, participants indicated if they attributed the symptom to the medication (yes/no) and how bothersome the symptom was in the last week (0 to 100 Visual Analogue Scale).

Finally, the survey included 2 global clinical improvement measures: (1) adequate relief (AR, a validated global questionnaire used in DGBI research) "in the last week, have you experienced adequate relief of your symptoms?" (yes/no); and (2) a validated Global Improvement Scale (GIS) "Compared to the way you felt before starting the medication, how have your symptoms been over the past week?" with a 7-point response scale ranging from "substantially improved" to "substantially worse." We also included a measure of satisfaction with the medication, and a measure of satisfaction with treatment overall, each using 100-point Visual Analogue Scale.

Statistical Analyses

Given that this was a small pilot study with low power, we have chosen to report effect sizes that are substantial in size, even when not statistically significant, to serve as suggestions for potential research targets in future adequately powered studies. Another reason for reporting effect sizes from this pilot study is to provide future researchers with the information they need to conduct power analyses.

Data were analyzed using IBM SPSS, version 26. Categorical data are reported as percentages and analyzed with χ^2 tests, and continuous data are reported as mean (SD) and analyzed with *t* tests. For continuous measures, we

also computed effect sizes in the form of Cohen *d*, which is the standardized difference between the 2 groups. By convention, $d=0.2$ is considered a small effect, $d=0.5$ is medium, and $d=0.8$ is large.[21] Although this pilot study necessarily had low statistical power, we provide *P*-values as an aid to interpretation. Nevertheless, any significant findings (or lack thereof) should be interpreted with caution.

RESULTS

Demographics

Thirty-one patients were prescribed TCAs and randomized into the study. Of those, 22 (71%) responded to the emailed survey. At the time of the survey, 2 had discontinued the medication due to side effects (1 from each intervention group); data from these 2 participants were included in our analyses. A higher percentage of participants in the augmented group (85%, n = 11) responded to the survey compared with 61% (n = 11) in the standard information group who responded to the survey, however, this was not a statistically significant difference ($P=0.155$). The mean age was 40 (SD = 15.5) and 59% were women. Although all patients with DGBI were eligible for this study, TCAs were only prescribed to patients with IBS and/or functional dyspepsia (FD) during the study period. Of the 22 participants included in the study, 10 (45%) had IBS, 9 (41%) had FD, and 3 (14%) had both.

Outcomes

Number and Bothersomeness of Side Effects

Although not statistically significant, patients in the *Augmented* group reported about half as many symptoms (whether or not they attributed them to the medication) as the *Standard* group [5.1 (4.5) vs. 9.6 (7.2), $P=0.089$] with a large effect size ($d=0.75$). Similarly, and again not significant statistically, *Augmented* patients also attributed less than half as many symptoms to the medication as did the *Standard* group [1.5 (2.6) vs. 4.2 (6.3), $P=0.212$] with a medium effect size ($d=0.56$). Of the symptoms reported, the *Augmented* group reported being substantially less bothered by symptoms in general [29.8 (27.0) vs. 49.4 (25.4), $P=0.095$] with a large effect size ($d=0.75$) and a trend towards statistical significance ($P=0.095$). They also reported being substantially less bothered by symptoms attributed to the medication [13.4 (14.7) vs. 38.1 (33.4)]. This difference was statistically significant ($P=0.037$) with a large effect size ($d=0.96$).

GIS and AR

On the basis of the GIS, a substantially, but not statistically significant, a larger proportion of the *Augmented* group reported feeling better since starting the medication compared with the *Standard* group (73% vs. 46%, $P=0.242$). Similarly, but again not significantly, a substantially larger percentage of the *Augmented* group reported AR of symptoms after 2 weeks of TCA treatment as compared with the *Standard* group (55% vs. 27%, $P=0.193$) (Fig. 1).

Satisfaction With Treatment

Although not significant statistically, participants in the *Augmented* group, compared with the *Standard* group, reported being more satisfied with treatment overall [63.5 (22.3) vs. 46.4 (22.3), $P=0.087$] as well as more satisfied with the medication [51.1 (25.9) vs. 36.5 (24.9), $P=0.19$]. Effect sizes were large for overall satisfaction ($d=0.77$) and medium for satisfaction with medication ($d=0.59$).

DISCUSSION

This pilot study presents preliminary data suggesting that a brief (≈30 s) clinical intervention addressing nocebo effects and patient expectations may improve tolerance of TCAs in DGBI. TCAs are known to be associated with

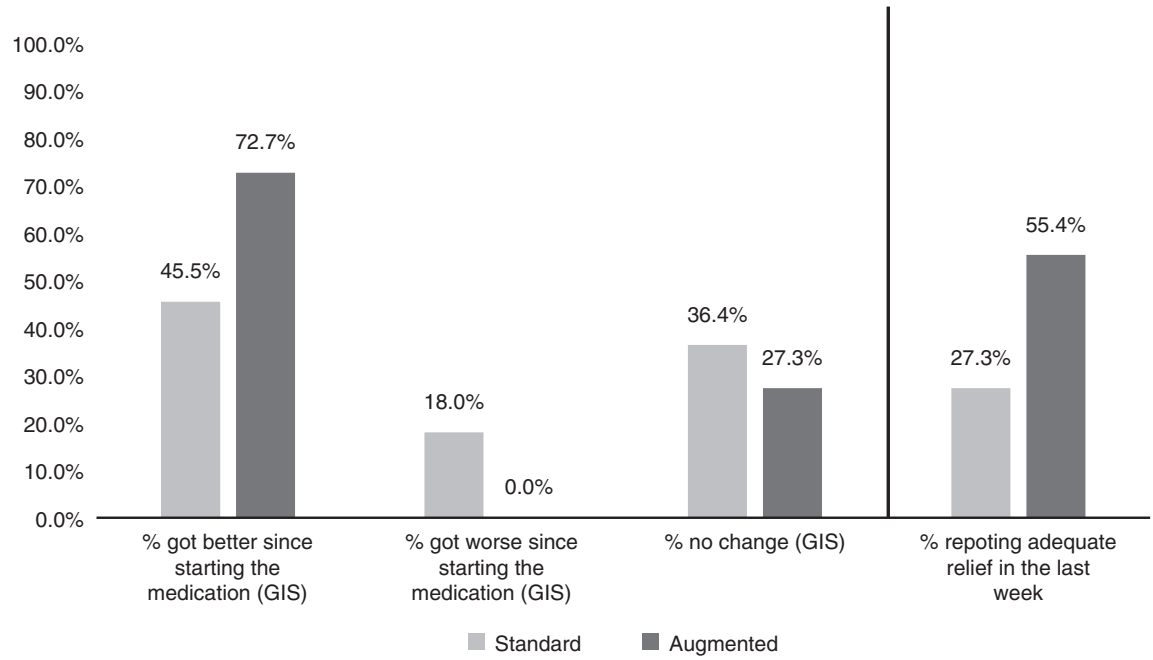

FIGURE 1. Percentage of the patient in each group reporting improvement, worsening, no change, and adequate relief after starting the medication. GIS indicates Global Improvement Scale.

unpleasant side effects and high rates of treatment discontinuation that often occur before any clinical benefit can accrue. Therefore, a brief, verbal intervention that could improve tolerance of these medications among patients with DGBI could have meaningful clinical implications.

Although most effects were not statistically significant, our observed data indicate that patients who received "augmented" information (ie, information about common side effects plus an explanation of nocebo effects) reported fewer side effects, and reported being less bothered by those side effects in the first 2 weeks after starting medication as compared with the group who received only the standard list of side effects. The observed effect sizes for those differences were large, ranging from 0.75 to 0.96. The observed data also show that patients who received this augmented version of the standard of care were also more likely to report AR and symptom improvement compared with patients who received only information about the possible side effects of the medication. Furthermore, those in the augmented group reported more satisfaction with their treatment overall and higher satisfaction with the medication, with medium to large effect sizes. We hasten to add, however, that given the small sample size of the current study and the lack of statistical significance for most outcomes, these results should be treated as hypothesis-generating, and they need to be confirmed in a larger adequately powered study.

The scientific literature suggests that how information is presented can affect reporting of side effects. For example, in one study evaluating side effects of the influenza vaccine, 292 patients were randomized to be informed of either the percentage of patients who reported side effects (negative framing), or the percentage who did not report side effects (positive framing). Although the 2 groups, objectively, received the same information, the positive framing group reported significantly fewer side effects 3 days after the vaccine as compared with the negative framing group ($P < 0.05$).[11] Another study comparing different word choices before administering an epidural to women in labor (n = 140) ("we are going to give you a local anesthetic so you will be comfortable during the procedure" vs. "you are going to feel a big bee sting and this is the worst part of the procedure") revealed that women who received positive expectations reported significantly less pain during the epidural placement than those who were told to expect pain ($P < 0.001$).[12] Multiple other studies have evaluated the influence of different valences of framing of possible side effects among clinical populations and healthy volunteers receiving placebo and, similarly, have found that positive and personalized framing resulted in improved outcomes.[13–16] Our findings add to this literature by testing a similar intervention among DGBI patients in the clinic at the time that a TCA was prescribed. This study marks the first time that such an intervention has been tested in a gastroenterology population.

There is strong evidence to suggest that many commonly reported side effects to TCAs (eg, dizziness, fatigue, headache) may be better attributed to nocebo effects.[6–8,10] Although most of this research has not been done in gastroenterology, one study of desipramine in IBS found that most reported side effects to the drug were present at baseline and that side effects were significantly associated with psychological distress but not with drug blood levels.[22] As a result, it is important to develop and study clinical interventions, such as the one presented here, aimed at mitigating nocebo effects to TCAs in DGBI. However, when developing and testing such interventions, it is vital that researchers and clinicians consider the role of perceived stigma in this patient population,[23] especially in the context of being prescribed a neuromodulator.[24] Establishing a strong patient-provider relationship can help to reduce both perceived stigmatization[25] as well as the risk of nocebo effects[26] and the role of patient-provider communication should be further evaluated in future studies aimed at reducing nocebo responses to TCAs in this patient population.

There were several limitations of this study, primarily associated with a small sample size and inadequate power for statistical tests. A second limitation, as mentioned earlier, includes a lack of baseline assessment to control for clinical characteristics, psychological factors, or the doctor-patient relationship that may have influenced tolerance of TCAs. Third, although all patients with DGBI were eligible for the study, TCAs were only prescribed to those with IBS and FD during the study period, which may limit generalizability to these 2 diagnoses. Fourth, at the time of the survey, only 2 participants had discontinued treatment (1 in each study group). Longer follow-up is necessary to evaluate treatment discontinuation rates. Nonetheless, the findings of this pilot study provide support for future, fully powered studies to evaluate whether positive framing can reduce side effects and improve clinical outcomes, especially in chronic gastrointestinal conditions.

In conclusion, this study provides preliminary data to support the use of a brief, < 30-second verbal intervention aimed at improving tolerance of TCAs among patients with DGBI. Although most of the results were not statistically significant, the observed data indicate that the intervention tested resulted in fewer reported side effects, lower Bothersomeness of side effects, and higher rates of reported AR and global improvement when compared with the control group. Although underpowered for tests of clinical significance, all comparisons of the 2 study groups produced medium to large effect sizes.

REFERENCES

1. Barsky AJ, Saintfort R, Rogers MP, et al. Nonspecific medication side effects and the nocebo phenomenon. *JAMA*. 2002;287:622–627.
2. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders: results of Rome Foundation Global Study. *Gastroenterology*. 2020;160:99.e3–114.e3.
3. Canavan C, West J, Card T. Review article: the economic impact of the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2014;40:1023–1034.
4. Whitehead WE, Levy RL, Von Korff M, et al. The usual medical care for irritable bowel syndrome. *Aliment Pharmacol Ther*. 2004;20:1305–1315.
5. Lembo A. Irritable bowel syndrome medications side effects survey. *J Clin Gastroenterol*. 2004;38:776–781.
6. Rief W, Nestoriuc Y, von Lilienfeld-Toal A, et al. Differences in adverse effect reporting in placebo groups in SSRI and tricyclic antidepressant trials: a systematic review and meta-analysis. *Drug Saf*. 2009;32:1041–1056.
7. Amanzio M, Corazzini LL, Vase L, et al. A systematic review of adverse events in placebo groups of anti-migraine clinical trials. *Pain*. 2009;146:261–269.
8. Häuser W, Bartram C, Bartram-Wunn E, et al. Adverse events attributable to nocebo in randomized controlled drug trials in fibromyalgia syndrome and painful diabetic peripheral neuropathy: systematic review. *Clin J Pain*. 2012;28:437–451.
9. Rief W, Avorn J, Barsky AJ. Medication-attributed adverse effects in placebo groups: implications for assessment of adverse effects. *Arch Intern Med*. 2006;166:155–160.

10. Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. *Gastroenterology*. 2003;125:19–31.
11. O'Connor AM, Pennie RA, Dales RE. Framing effects on expectations, decisions, and side effects experienced: the case of influenza immunization. *J Clin Epidemiol*. 1996;49:1271–1276.
12. Varelmann D, Pancaro C, Cappiello EC, et al. Nocebo-induced hyperalgesia during local anesthetic injection. *Anesth Analg*. 2010;110:868–870.
13. Heisig SR, Shedden-Mora MC, Hidalgo P, et al. Framing and personalizing informed consent to prevent negative expectations: an experimental pilot study. *Health Psychol*. 2015;34:1033–1037.
14. Faasse K, Huynh A, Pearson S, et al. The influence of side effect information framing on nocebo effects. *Ann Behav Med*. 2019;53:621–629.
15. Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side effects. *Clin Pharmacol Ther*. 1987;42:250–253.
16. Lang EV, Hatsiopoulou O, Koch T, et al. Can words hurt? Patient-provider interactions during invasive procedures. *Pain*. 2005;114:303–309.
17. Wells RE, Kaptchuk TJ. To tell the truth, the whole truth, may do patients harm: the problem of the nocebo effect for informed consent. *Am J Bioeth*. 2012;12:22–29.
18. Häuser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Dtsch Arztebl Int*. 2012;109:459–465.
19. Bingel U. Placebo Competence Team. Avoiding nocebo effects to optimize treatment outcome. *JAMA*. 2014;312:693–694.
20. Rief W, Barsky AJ, Glombiewski JA, et al. Assessing general side effects in clinical trials: reference data from the general population. *Pharmacoepidemiol Drug Saf*. 2011;20:405–415.
21. Cohen J. A power primer. *Psychol Bull*. 1992;112:155–159.
22. Thiwan S, Drossman DA, Morris CB, et al. Not all side effects associated with tricyclic antidepressant therapy are true side effects. *Clin Gastroenterol Hepatol*. 2009;7:446–451.
23. Taft TH, Keefer L, Artz C, et al. Perceptions of illness stigma in patients with inflammatory bowel disease and irritable bowel syndrome. *Qual Life Res*. 2011;20:1391–1399.
24. Yan X-J, Luo Q-Q, Qiu H-Y, et al. The impact of stigma on medication adherence in patients with functional dyspepsia. *Neurogastroenterol Motil*. 2021;33:e13956.
25. Feingold JH, Drossman DA. Deconstructing stigma as a barrier to treating DGBI: lessons for clinicians. *Neurogastroenterol Motil*. 2021;33:e14080.
26. Olshansky B. Placebo and nocebo in cardiovascular health: implications for healthcare, research, and the doctor-patient relationship. *J Am Coll Cardiol*. 2007;49:415–421.