Published in final edited form as:

Postgrad Med J. 2013 March ; 89(1049): 131–136. doi:10.1136/postgradmedj-2012-131284.

Sensory neuromodulators in functional nausea and vomiting: predictors of response

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Abstract

Background—Tricyclic antidepressants (TCAs) are known to benefit subjects with functional nausea and vomiting (FNV), but it is not known if alternate neuromodulators are also beneficial. We retrospectively evaluated outcomes and clinical predictors of response in FNV subjects treated with any neuromodulator, including TCAs.

Methods—We identified 94 subjects (43.8 ± 1.4 year, 79 F) with FNV (Rome III criteria) over a 12 year period, treated with neuromodulators and followed up for 8.5 ± 1.1 months. Clinical presentation, demographics and gastric emptying study (GES) findings (when available) were extracted. Likert scales determined symptom severity at baseline and symptom response or remission at follow-up. Outcomes and predictors of response were evaluated using univariate and multivariate analyses.

Results—At least moderate symptom improvement was reported by 72.3%, and 22.3% had symptom remission. Proportions achieving moderate improvement and remission, and mean outcome Likert scores were similar regardless of neuromodulator agent used or GES status. On univariate and multivariate logistic regression analysis, baseline symptom severity affected symptom response, and pain negatively impacted symptom remission to treatment ($p = 0.04$ for each); GES status failed to predict treatment response or remission.

Conclusions—Symptom improvement with neuromodulators may be seen in over two-thirds of subjects with FNV regardless of the specific agent administered. Response may be suboptimal in pain predominant presentations.

INTRODUCTION

Chronic functional nausea and vomiting (FNV) includes both chronic idiopathic nausea (CIN) and functional vomiting, as defined by the Rome III criteria for functional gastrointestinal (GI) disorders.¹ CIN refers to bothersome nausea occurring at least several times weekly, not necessarily associated with vomiting, with the absence of abnormalities at upper endoscopy or any metabolic disease that explains the nausea. Functional vomiting, likewise, refers to an average of one or more episodes of vomiting weekly in the absence of any eating disorder, rumination, major psychiatric disease, self-induced vomiting, chronic

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Presented in preliminary form at the Annual Meeting of the American College of Gastroenterology, San Antonio, October 2010.

Contributors AP: study design, data collection and analysis, manuscript preparation; GSS: study design, data analysis, critical revision of manuscript; VK: data analysis, critical revision of manuscript; CPG: study concept and design, data analysis and interpretation, manuscript preparation for intellectual content and critical revision.

Competing interests None.

Ethics approval Human Research Protection Office, Washington University School of Medicine, St. Louis.

Provenance and peer review Not commissioned; externally peer reviewed.

cannabinoid use, central nervous system abnormalities or metabolic disease that explains the vomiting. In each of these disorders, criteria need to be fulfilled for the previous 3 months, with symptom onset at least 6 months prior to diagnosis.²

Published literature suggests that there is considerable overlap between functional foregut disorders and gastric neuromuscular dysfunction resulting in gastroparesis, and even the category of gastroparesis itself is heterogeneous with varying underlying mechanisms.³ Consequently, patients presenting with chronic nausea and vomiting in the absence of structural and metabolic aetiology (as determined by upper endoscopy, upper gut radiological studies and metabolic blood work) often undergo gastric emptying studies (GES) during symptom work-up.^{4, 5} An abnormal GES with delayed emptying can be seen in 30–50% of functional foregut syndromes,^{6–8} but specific presenting symptoms may not necessarily predict delayed gastric emptying.⁹ Some of these patients with delayed gastric emptying on GES therefore may have FNV rather than clinically significant abnormal gastric emptying.

Neuromodulators, particularly tricyclic antidepressants (TCAs), other antidepressants and antiepileptic agents, often are successfully employed in the management of functional foregut disorders.^{10–14} Data so far has focused on TCAs, and there are no systematic reports addressing multiple antidepressant and antiepileptic medications in a ‘real world’ clinical setting involving FNV.

The aims of the current study were to determine symptomatic outcomes in a cohort of subjects with FNV fulfilling Rome III criteria for CIN and functional vomiting treated with neuromodulator therapy, and to determine if outcomes varied depending on the specific agent administered. A secondary aim was to identify clinical predictors of FNV response to neuromodulator therapy.

MATERIALS AND METHODS

Subjects

This retrospective review was performed at a 1400 bed tertiary medical centre in the USA, catering to referrals from internists and subspecialists, including gastroenterologists and foregut surgeons. Subjects were identified by searching the outpatient databases of two of the authors (CPG and GSS) for the terms ‘gastric emptying’, ‘functional dyspepsia’, ‘functional nausea’ and ‘functional vomiting’ over a 12-year period, from 1 January 1998 to 1 May 2010. Outpatient charts were scrutinised to determine if other eligibility requirements were satisfied.

Identified adult subjects (>18 years old) were considered further if the following eligibility criteria were satisfied: (a) a principal complaint of chronic persistent nausea and vomiting, a clinical diagnosis of FNV fulfilling retrospectively applied Rome III criteria for CIN and/or functional vomiting, (b) no structural or metabolic explanation for symptoms detected during investigation, other than well controlled diabetes mellitus on oral hypoglycaemic agents alone, (c) initial prescription and use of neuromodulator specifically for the management of their functional disorder, and (d) at least one follow-up interaction after initiation of neuromodulator therapy. Evaluation of the upper gastrointestinal tract by endoscopy or upper gastrointestinal x-ray series were minimum requirements, though most patients had more exhaustive evaluations, including small bowel follow-through, oesophageal manometry, abdominal CT scanning, and abdominal ultrasound examination. Subjects with cyclic vomiting syndrome, gastroparesis requiring nutritional support, foregut surgery or significant systemic comorbidities (advanced or uncontrolled diabetes mellitus, collagen vascular diseases) were excluded. Records were scrutinised to determine if nuclear

medicine GES was performed as part of the evaluation; subjects were designated 'no GES' group if this test had not been performed. Solid phase GES results were dichotomised into 'normal' and 'delayed'; when possible, $t_{1/2}$ was calculated and used in supplementary analysis. When multiple neuromodulators were tried, the agent which resulted in symptomatic benefit (in the opinion of the treating gastroenterologist) was recorded. Formal psychiatric analysis was not performed as part of routine clinical evaluations, but self-reported psychiatric diagnoses (depression, anxiety) were recorded; subjects with active psychiatric disease on antidepressants or needing ongoing psychiatric intervention were not included in this study.

Chart review and data collection

Outpatient records were systematically reviewed by one of the authors (AP) who had not participated in the care of the subjects. Data were extracted using a structured recording template created a priori for this purpose, and included patient demographics, clinical and laboratory data leading up to the time of treatment, GES details, medication history, comorbid medical and psychiatric disorders, type and dose of neuromodulator used, and treatment response to the neuromodulator.

Baseline symptom severity at the time of neuromodulator initiation was assessed on a 4-point Likert-type scale (figure 1) from chart notations of severity, activity interference and degree of needed intervention: 0=no symptoms; 1=mild symptoms that required no treatment or were well controlled on current therapy; 2=moderate, bothersome symptoms that prompted at least treatment change and/or interfered to a limited degree with daily activities; 3=severe, disabling symptoms that markedly interfered with daily activities and/or resulted in urgent outpatient or emergency room visits.^{10, 11} This Likert scale has been applied in prior published reports assessing foregut symptoms,^{10–13} wherein reproducibility and high interobserver agreement between two clinicians ($\kappa=0.89$) was documented using blinded grading methodologies comparing the Likert scales.¹¹

Treatment response at follow-up was graded *post hoc* using chart descriptors extracted from the clinical record following a 4-point Likert-type response scale: 0=no improvement or worse; 1=slight improvement, but requiring more tests or treatment change; 2=moderate improvement, stable regimen but not completely resolved, no further evaluation; 3=clinical remission, near-complete resolution of symptoms, complete satisfaction with treatment.^{10, 11} 'Responders' were characterised as patients with a treatment response score of 2 or 3 on the Likert-type scale, and 'remitters' were defined as those patients with a score of 3 (figure 1). Similar to the baseline symptom severity scale, the treatment response Likert scale also previously has demonstrated reproducibility and high inter-observer agreement ($\kappa=0.86$) upon comparison of separately rated, blinded scores.¹¹

Data analysis

Data are reported as mean $\pm$ SE of mean unless stated otherwise. Categorical data were compared using χ^2 test or Fisher's exact test as appropriate. Grouped data were compared using two-tailed Student's *t* test. Analysis of variance was used to determine if differences across the three groups were statistically significant. Univariate analysis initially was used to assess differences in demographic, clinical and GES parameters between groups, and between subjects with and without symptom response and symptom remission. Logistic regression analyses were then performed to determine the independent significance of demographic data and clinical parameters in predicting symptom response and remission from antidepressant therapy. Only parameters that demonstrated trends toward significance ($p<0.1$) on univariate analysis were included in the multivariate regression models. Exponentiated β values were calculated as approximations of independent variable OR. In

all cases, $p < 0.05$ was required for statistical significance. All statistical analyses were performed using PASW Statistics V.17.0 (SPSS Inc., Chicago, Illinois, USA).

The review of records for research proposed in this study was approved by the Human Research Protection Office of Washington University School of Medicine, with a waiver of patient consent reflecting the retrospective nature of this study.

RESULTS

Subjects

A total of 94 subjects (mean age 43.8 ± 1.4 year, range 19.3–74.3 years, 84% women) met eligibility criteria and formed the study group (table 1). All subjects had nausea and/or vomiting as their dominant symptoms; secondary symptoms included abdominal pain, bloating, early satiety, weight fluctuations and constipation (table 1). There were 10 subjects with well-controlled diabetes mellitus and without neuropathy in the study cohort, with similar proportions across the three study groups; mean glycosylated haemoglobin (HbA1c) was $6.8 \pm 0.4\%$. Within the study cohort, 42 subjects (44.7%) had GES performed as part of their evaluation, and the remaining 55.3% had no GES performed despite similar presentation (table 1). There were no significant differences in age, gender, symptom presentation, psychiatric co-morbidities, or diabetes mellitus between subjects with delayed GES, normal GES, and those without GES performed (table 1, $p = \text{ns}$ across groups for each comparison).

Baseline symptoms

Using the Likert scale described in figure 1, mean baseline symptom severity was 2.14 ± 0.04 , and was similar across the three groups (figure 2, $p = \text{ns}$ across groups). Severe disabling symptoms interfering with daily activities was reported by 13 subjects (13.8%), and moderate baseline symptoms by 81 (86.2%); none of the subjects had mild symptoms at presentation. Investigation for excluding structural and metabolic aetiologies for symptoms included routine laboratory testing and upper endoscopy examination in 100% of subjects; most subjects (89.4%) had undergone additional testing as determined by chart review. Abdominal cross sectional imaging (CT and MRI/MRCP) and colonoscopy were the most frequent additional tests performed (54.3% and 52.1% of subjects, respectively); other tests included abdominal ultrasound (27.7%), radiological luminal contrast studies evaluating the oesophagus, stomach and small bowel (27.7%), oesophageal physiological tests including manometry and ambulatory pH monitoring (14.9%), nuclear medicine hepatobiliary scans (13.8%) and endoscopic ultrasound and endoscopic retrograde cholangiopancreatography (5.3%).

Treatment response

All subjects were treated with neuromodulators (table 2) and had at least one subsequent interaction with treating faculty over a cumulative mean of 8.5 ± 1.1 months of follow up. Of the 94 total study subjects, 21 subjects (22.3%) had complete remission of symptoms. At least moderate symptom response (score of 2 or 3, figure 1) was seen in 68 subjects (72.3%). A range of neuromodulators were offered to the subjects (table 2). Sixty-five subjects (69.1%) were treated with TCAs, and the remaining 29 (30.9%) were treated with alternate neuromodulators (table 2). As many as 75.9% reported symptom response to neuromodulators other than TCA, no different from the response to TCA (72.3%). Proportions of subjects attaining treatment response and mean treatment response scores were similar regardless of medication regimen used, TCA or other ($p = 0.68$).

When assessed by severity of baseline symptoms, 46.2% with severe symptoms and 75.3% with moderate symptoms had at least moderate symptom response ($p=0.046$). Proportions of subjects achieving remission and response were evaluated according to GES status; no difference was noted across groups ($p=ns$ for each comparison, figure 3). Further, mean treatment response scores on the outcome Likert scale were similar regardless of GES status (1.7 ± 0.2 with delayed GES, 1.9 ± 0.3 with normal GES, and 1.8 ± 0.1 when no GES was performed, $p=ns$ across groups).

Univariate analysis

Univariate analysis was performed to determine if demographic or clinical parameters were different between subjects achieving response and remission. Comparing responders (score of at least 2 on the outcome Likert scale, figure 1) with non-responders, younger age, symptom severity at baseline and pain predominance were significantly associated with non-response ($p=0.03$ for each). When subjects with symptom remission were compared with the remainder of the cohort, female gender and pain predominance were associated with a poor outcome ($p=0.02$ for each), while symptom duration ($p=0.1$) and weight loss ($p=0.06$) trended in the same direction. GES status failed to predict treatment response or remission in univariate analysis.

Of the 42 subjects with GES performed, 27 (64.3%) had delayed emptying according to individual test centre cut-offs. Within this cohort, no demographic or clinical parameter was significantly associated with delayed GES, but female gender ($p=0.09$), presence of affective psychiatric comorbidity ($p=0.08$), pain predominance ($p=0.1$) and bloating ($p=0.08$) favoured delayed GES. Mean $t_{1/2}$ (when available) was not different statistically between responders and non-responders (208.6 ± 64.5 min vs 151.8 ± 40.2 min, $p=0.53$). When per cent emptying at 120 min was available (13 studies), mean per cent emptying was similarly equivalent between responders and non-responders ($33.6\pm8.4\%$ vs $23.9\pm10.5\%$, $p=0.52$). Proportions of studies with percent emptying reported for other time frames were either small or overlapped with studies compared above, hence meaningful comparisons could not be performed further.

Multivariate logistic regression

In order to determine independent contributions of response predictors, a multivariate logistic regression analysis was performed in a model that included each parameter that returned a p value of <0.1 on univariate analysis as dependent variables (table 3), using symptom response (scores of 2 or 3 on the outcome Likert scale, figure 1) and remission (score of 3) as outcome variables. The presence of pain as a presenting symptom negatively impacted symptom remission but not symptom response, and severe baseline symptoms negatively impacted symptom response (table 3).

DISCUSSION

In this report, we demonstrate that over two-thirds of FNV subjects demonstrate at least moderate improvement with neuromodulator therapy. Further, we report that neuromodulator response is independent of the actual agent prescribed, and non-TCA antidepressants provided comparable relief as TCAs. Symptom severity at baseline and pain predominance predicted less favourable outcomes from neuromodulator therapy, but only pain dominance interfered with symptom remission on regression analysis. Finally, our results support the conclusion that FNV and gastroparesis are heterogeneous disorders, and gastric emptying status does not necessarily predict symptom improvement with neuromodulator therapy. These findings support the initial management of FNV with

neuromodulators regardless of GES status, with best expected response in patients without pain or severe symptoms.

Moderate symptom response with TCAs has been reported in 71–88% of FNV,^{10, 11, 15} including a small subgroup of seven patients with gastric emptying delay, where response was noted in 86%;¹¹ however, these were all either open label or retrospective observations. Better quality evidence exists for other functional gastrointestinal diseases; the OR for global improvement of irritable bowel syndrome has been reported at 2.6 (95% CI 1.9 to 3.5) in meta-analysis.¹⁶ The numbers needed to treat for efficacy have been calculated at 3.2–4.3.^{12, 17–19} Cumulative benefit is rated at 80% by treating physicians with this approach in open label studies.^{12, 17–19} Based on these data and our results, a trial of antidepressant medications appears to have merit in the initial management of FNV.^{9, 14, 20} There is limited data on the efficacy of alternate agents in functional syndromes, but most studies have focused on either irritable bowel syndrome, or atypical chest pain or other pain syndromes.^{21–24} A single report documents the benefit of mirtazapine in suppressing symptoms in the setting of severe gastroparesis in a one patient.²⁵ We report, albeit in a retrospective open label experience, the benefit of considering alternate antidepressant and antiepileptic medications in settings wherein TCAs may not be desirable or tolerated. There is robust literature on the use of TCAs in cyclic vomiting syndrome, a disorder thought to be associated with migraine-like tendencies and putative differences in underlying pathophysiology compared with chronic FNV.^{26–28} We carefully excluded subjects with cyclic vomiting syndrome, as we wanted this report to reflect the management of FNV.

Pain interfered with symptom improvement in our study cohort—we postulate that pain may be a surrogate indicator of a more significant symptomatic state, in the realm of a somatisation disorder or fibromyalgia, conditions both known to commonly overlap with functional gastrointestinal disorders.²⁹ The concept of somatisation postulates that a central neurophysiological process, separate from anxiety and depression, drives distorted afferent signal processing and the reporting of various distinct functional syndromes.³⁰ These central processes, associated with functional gastrointestinal disorders, appear to be only modestly responsive to psychopharmacological treatment.³¹ When a response was seen, the effective dosages of antidepressants used for functional gastrointestinal disorders are often lower compared with those dosages used for primary psychiatric disorders.³² This point also held true with our results (table 2). While the exact mechanisms of benefit are unclear, a combination of central and peripheral effects at the neurotransmitter and receptor level have been postulated.³³ Central mechanisms, such as depression remission, anxiolysis, ‘anti-somatisation’, sleep restoration, analgesia, interference with input to the nausea/vomiting centre, or modulation of visceral pain perception, may contribute to the efficacy of neuromodulators in FNV patients.^{34–36} These points suggest that antidepressants address symptom mechanisms other than attenuation of visceral hypersensitivity, and may impact central mechanisms associated with global distress more so than gut physiological abnormalities or specific gastrointestinal complaints.^{10, 17} Our study findings are consistent with experimental evidence that the observed benefit from antidepressants in symptomatic foregut disorders does not derive from an impact on gastric emptying.^{37–39} Functional foregut disorders, including those with diabetes, may have delayed gastric emptying inherent to the functional disorder rather than a mechanism for symptoms,^{40–42} and this could potentially explain symptomatic response from neuromodulator therapy. Our findings also suggest that metabolic disorders such as diabetes mellitus have heterogeneous mechanisms for foregut symptoms including an idiopathic functional mechanism akin to patients without metabolic disorders; these subjects may fulfil ‘soft’ Rome III criteria for CIN and functional vomiting in that the metabolic disorder does not necessarily explain their symptom pattern. We have indeed used such an expanded interpretation of the Rome III criteria, partly based

on our prior experience with treating functional foregut symptoms in diabetics with neuromodulators.¹¹

Our conclusions are tempered by a few limitations, especially those intrinsic to any retrospective analysis which employs chart review and uncontrolled medication use. Our retrospective chart review design meant that no objective measures (including systematic questionnaires to address concurrent psychiatric disorders) were available to corroborate the recorded clinical impressions; we relied on the Likert-type scales scored by chart notations. Although we have previously demonstrated reliability, reproducibility and high inter-observer and inter-rater agreement using these Likert scales in previous reports,¹¹ systematic prospective evaluations using validated outcome measures would provide a greater level of scientific support of our conclusions. While we attributed response to neuromodulators, other measures inherent to tertiary referral could have played a role in symptom improvement, including use of ancillary symptomatic therapy (eg, proton pump inhibitors, other concurrent medications) and dietary adjustments; further, placebo response could also have influenced outcomes. From a retrospective study of this sort, benefit from other concurrent approaches cannot be teased out, and we acknowledge that the absence of a control group not treated with neuromodulators weakens our conclusion. However, our success rates with neuromodulators matches that reported in the literature for other functional syndromes, and we believe that this likely represents a true neuromodulator effect. Finally, our cohort was over-represented by subjects at the moderate-to-severe end of the symptomatic spectrum, as would be expected in a tertiary care centre. Therefore, while our study may not have addressed mild FNV, we can safely say that higher symptomatic states within FNV may benefit from neuromodulator therapy.

In summary, symptom improvement with neuromodulator treatment was seen independent of gastric emptying status in a tertiary care population of FNV patients. Over two-thirds of patients can expect at least moderate benefit with this approach regardless of the neuromodulator regimen used, especially in the absence of pain as a major symptom. Prospective controlled studies are needed to further address the role of neuromodulators in FNV.

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Main messages

- Neuromodulators led to at least moderate symptomatic improvement in 72% of functional nausea and vomiting (FNV) patients
- Non-tricyclic antidepressants (TCA) offered comparable symptom improvement to TCA in FNV
- Pain on presentation predicted less symptom improvement with neuromodulator therapy
- Gastric emptying status failed to predict symptom response or remission with neuromodulator therapy in FNV

Current research questions/further areas of research

- What are the exact mechanisms of benefit of neuromodulator therapy in FNV?
- In a population of mild FNV, how effective is neuromodulator treatment?
- When should non-TCA neuromodulators be used in place of TCA in FNV?
- What role, if any, do gastric emptying studies have in the management of FNV?

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Baseline	Score	Outcome	Response	Remission
Severe, disabling symptoms that markedly interfered with daily activities and/or resulted in urgent outpatient or emergency room visits	3	Clinical remission, complete satisfaction with treatment		☐
Moderate, bothersome symptoms that prompted at least treatment change and/or interfered to a limited degree with daily activities	2	Moderate improvement, stable regimen but not completely resolved, no further evaluation		
Mild symptoms that required no treatment	1	Slight improvement, but requiring more tests or treatment change		
No symptoms	0	No significant improvement or worse		

Figure 1.

Likert-like scales used for extracting baseline symptom severity and treatment outcome from chart review. The scales have documented reproducibility and high interobserver agreement ($\kappa = 0.86\text{--}0.89$) (Sawhney). In the outcome scale, scores of 2 or 3 represented treatment response, while a score of 3 was required for symptom remission.

Figure 2.

Comparison of baseline symptoms and treatment response to neuromodulators relative to gastric emptying study (GES) status. No difference in baseline symptom severity was evident using the baseline Likert scale ($p=0.31$ across groups). Mean treatment response scores using the outcome Likert scale were also similar across the three groups ($p=0.74$).

Figure 3.

Proportions of subjects achieving moderate improvement and remission, according to gastric emptying study (GES) status. A mean of 72.3% of subjects had symptom response (includes both moderate improvement and remission, corresponding to scores of 2 and 3 on the outcome Likert scale, respectively); proportions of subjects with moderate improvement and remission were similar across the three groups ($p>0.54$).

Table 1

Demographics and clinical characteristics of the subject groups

N	All subjects n=94	Delayed GES n=27	Normal GES n=15	No GES n=52
Age (years)	43.8±1.4	42.7±2.3	40.9±3.5	45.1±1.9
Female gender	79 (84%)	24 (89%)	10 (67%)	45 (87%)
Duration of symptoms (years)	4.0±0.7	2.5±0.5	3.9±1.9	4.8±1.0
Additional symptoms*				
Pain	73 (78%)	22 (81%)	9 (60%)	42 (81%)
Bloating	35 (37%)	13 (48%)	3 (20%)	19 (37%)
Early satiety	11 (12%)	6 (22%)	2 (13%)	3 (6%)
Weight loss	41 (44%)	12 (44%)	9 (60%)	20 (38%)
Weight gain	22 (23%)	9 (33%)	3 (20%)	10 (19.2%)
Constipation	38 (40%)	8 (30%)	7 (47%)	23 (44%)
Concurrent psychiatric disorder	48 (51%)	12 (44%)	11 (73%)	25 (48%)
Diabetes mellitus	10 (11%)	2 (7%)	2 (13%)	6 (12%)
Duration of follow up (months)	8.5±1.1	5.8±1.1	12.9±5.7	8.6±1.0

* Nausea and/or vomiting was an criterion for study inclusion, and was reported by 100% of study subjects.

No statistical differences were noted across the three study groups ($p>0.09$ for each comparison), or between subjects with normal and delayed GES ($p>0.10$ for each comparison).

GES, gastric emptying study.

Table 2

Neuromodulators used for functional nausea and vomiting

Category	N	Responders	Dose range
Tricyclic Antidepressants	65	47 (72%)	20–100 mg
Amitriptyline			
Nortriptyline			
Imipramine			
Desipramine			
Selective Serotonin Reuptake Inhibitor (SSRI)	5	5 (100%)	20–50 mg
Paroxetine			
Sertraline			
Citalopram			
Escitalopram			
Norepinephrine-Dopamine Reuptake Inhibitor	10	7 (70%)	150–450 mg
Bupropion			
Serotonin-Norepinephrine Reuptake Inhibitor	5	2 (40%)	30–60 mg
Duloxetine			
Antiepileptic agents	3	3 (100%)	150–400 mg
Zonisamide			
Tetracyclic antidepressants	1	1 (100%)	22.5 mg
Mirtazapine			
Other			
Buspirone	4	3 (75%)	10–20 mg
Doxepin	1	1 (100%)	50 mg

Response was not statistically different when TCA therapy was compared to other agents used ($p=0.68$); numbers were too small to perform meaningful comparisons between individual agents.

Table 3

Predictors of symptom response and remission on multivariate analysis

Predictor	Symptom response			Symptom remission		
	OR	95% CI	p Value	OR	95% CI	p Value
Age *	1.04	0.99 to 1.08	0.08	1.01	0.97 to 1.06	0.59
Female gender	1.61	0.32 to 7.87	0.55	2.94	0.67 to 9.27	0.17
Baseline symptom severity *	0.18	0.05 to 0.73	0.01	0.52	0.08 to 3.45	0.50
Symptom duration *	1.001	0.99 to 1.01	0.79	0.99	0.97 to 1.01	0.23
Pain	0.18	0.02 to 1.60	0.13	0.25	0.07 to 0.91	0.04
Weight loss	1.3	0.48 to 3.75	0.57	2.3	0.76 to 6.93	0.14

* Included as continuous ordinal variables in the regression model; remaining predictors were dichotomised.

Symptom response: scores of 2 or 3 on the outcome Likert scale (figure 1).

Symptom remission: score of 3 on the outcome Likert scale.