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ORIGINAL ARTICLE

Tricyclic Antidepressants for Chronic Vomiting in Diabetic Patients

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Abstract Chronic vomiting in diabetic patients often is unresponsive to prokinetic agents and poorly explained by delayed gastric emptying or neuropathy. This retrospective study examines clinical response to tricyclic antidepressants, a treatment of reported benefit in nondiabetic patients with unexplained vomiting syndromes. Outcomes were studied in 24 diabetic outpatients who had been treated with tricyclic antidepressants specifically for nausea and vomiting after an unsatisfactory response to prokinetic therapy. Symptom patterns and treatment response were determined from chart review and telephone interview. Ten patients (42%) had recurrent, stereotypical vomiting episodes with symptom-free intervals suggesting cyclic vomiting syndrome; 14 (58%) had persistent symptoms. By chart review, at least moderate symptom response to tricyclic antidepressant treatment (median dosage, 50 mg/day) occurred in 88% of subjects, with complete or nearly complete resolution of symptoms in one-third. At follow-up interview, 77% self-reported at least moderate symptom improvement during therapy and 68% rated tricyclic antidepressants the most effective treatment received. Duration of diabetes, presence of neuropathy, and psychiatric status were not predictive of treatment outcome in multivariate analysis, but a cyclical symptom pattern attenuated antidepressant response ($P < 0.05$). In this retrospective review, the majority of diabetic patients with chronic vomiting and incomplete response to prokinetic therapy benefited from tricyclic antidepressants in low-dose, open-label regimens and rated them the most effective treatment received. This therapeutic option should be further studied in diabetic patients considering the morbidity of chronic vomiting in this population.

Keywords Diabetes · Nausea · Vomiting · Antidepressants · Gastroparesis

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Introduction

Nausea and vomiting are problematic for diabetic patients, commonly escalating the need for medical attention and precipitating hospitalization. Annual hospitalization costs for persistent vomiting in diabetic subjects exceed $34 million [1], a number that represents but a fraction of the total healthcare resource burden associated with this condition. Management approaches primarily are directed at gastroparesis but often are unsatisfactory [2, 3]. This, in part, relates to the fact that a direct explanation for vomiting in the diabetic patient typically is unavailable, even when delayed gastric emptying is evident [4].

Antidepressants, particularly the tricyclic antidepressants (TCAs), have been used to manage a variety of unexplained symptoms and syndromes in nondiabetic patients [5]. They

are effective in functional gastrointestinal (GI) disorders that lack pathological explanation [6, 7] and have been successful in managing chronic, unexplained vomiting in nondiabetic subjects [8]. Because the persistent or recurrent vomiting that occurs in diabetic patients shares some features with the functional vomiting syndromes described in nondiabetic patients, we began using TCAs in diabetic patients with chronic vomiting unresponsive to prokinetic agents. The present report describes the outcome of this open-label approach in a group of outpatients with type 1 or type 2 diabetes.

Materials and methods

Subjects

All subjects in this study were patients with type 1 or type 2 diabetes who had been evaluated in the outpatient gastroenterology office of one of the authors (R.E.C.). Subjects were identified by reviewing the patient database over a 4-year period for compatible diagnoses and from subsequent chart review. Each met the following eligibility requirements: (1) the principal complaint leading to initial outpatient referral was persistent or recurrent nausea and vomiting, (2) no structural or metabolic explanation for the symptoms other than diabetes was detected during evaluation (nonobstructive delayed gastric emptying was not an exclusion), (3) the symptoms had been present in a continuous or relapsing manner for a minimum of 3 months, (4) the patient was prescribed a TCA specifically for the management of the vomiting syndrome, and (5) the patient used the TCA for a minimum of 3 months and returned for at least one follow-up visit. Although most of the study data were extracted from chart review, subjects also were contacted for a direct follow-up interview. This investigative protocol was approved by the Human Studies Committee of Washington University School of Medicine prior to its inception.

Chart review and telephone interview

Outpatient records were systematically reviewed by one of the authors (M.S.S.) who had not participated in the care of the subjects, and data were extracted using a structured form. Recorded information included patient demographics, symptom pattern and duration, diabetes history (type, duration, and complications), GI investigation, and additional medical and psychiatric history. Complications of diabetes were assessed by a combination of current symptoms, physical examination, objective test results obtained from review of clinical records, and the patient's self-report of prior diagnoses. Patients were categorized as having delayed gastric emptying if they showed delayed solid-food emptying at 4 h on a radionuclide gastric emptying study or if food residue was detected in the stomach at upper endoscopy following an overnight fast and there was no evidence of obstruction. Each patient could be identified as having one of two patterns of vomiting. A *cyclical symptom pattern*, matching the features of cyclic vomiting syndrome in nondiabetic patients, described patients with a history of three or more stereotypic episodes of nausea and vomiting, each lasting from hours to days, that was associated with complete resolution of symptoms between episodes [9, 10]. A *continuous symptom pattern* described patients with a more persistent pattern of symptoms who did not meet the above criteria.

Baseline symptom severity at the time of TCA initiation was graded from the transcribed 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 telephone interaction and 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. The reproducibility of this rating method was demonstrated by separate, blinded grading by two observers of 80 outpatient chart notes from randomly selected patients from the outpatient office over this same period of time wherein the interobserver agreement was very high ($\kappa = 0.89$).

The TCA prescribed, daily dosage, and adverse effects of treatment were chronologically sequenced from review of each chart note. Reason for treatment change was categorized as insufficient response or adverse effect. The adverse effects were further categorized as sedation, agitation, other central nervous system side effects, anticholinergic effects, cardiovascular side effects, and others. For stratifying treatment outcome, a Likert-type scale was employed that incorporated health-care resource use as well as symptom response [11]: 0 = no improvement or worse; 1 = slight improvement, but requiring more tests or treatment change; 2 = moderate improvement, stable regimen but not completely resolved, <3 months follow-up contact recommended; 3 = complete or nearly complete resolution of symptoms, follow-up contact ≥3 months. A rating of ≥2 was required for treatment response [11]. As for baseline symptom severity, reproducibility of the treatment outcome rating method was determined by comparing separately rated, blinded scores from two raters on 80 outpatient chart notes from patients receiving treatment for GI disorders; inter-observer agreement again was very high ($\kappa = 0.86$).

Each subject also was contacted for a telephone interview. Data were gathered using a scripted questionnaire designed specifically for this purpose that included total duration of TCA use, reason for discontinuation, and estimated initial improvement in nausea and vomiting while on the antidepressant using a self-reported four-part Likert scale similar

to that used for chart review (0 = no improvement or worse, 1 = slight improvement, 2 = moderate improvement, 3 = complete or nearly complete resolution of symptoms). Subjects also were asked to complete the following statement with the choice that best reflected their experience with TCA treatment: "When compared to other medications you have used for symptom control, the antidepressant. . ." (a) did not improve symptoms or made symptoms worse, (b) improved symptoms but was not as effective as other medications, (c) improved symptoms and was as effective as other medications, or (d) improved symptoms and was the most effective drug used.

Statistical methods

Data are reported as mean ± SE throughout. Grouped data were compared using two-tailed Student's *t* test and Fisher's exact test, as appropriate. A *P* value of <0.05 was required for statistical significance. Linear regression analysis with backward elimination was used to determine independent predictors of treatment response; $P < 0.1$ was required for retention of the predictor in the model, and $P < 0.05$ was required for significance as an independent predictor. Backward elimination was chosen because of the potentially large number of relevant clinical predictors relative to the number of subjects.

Results

Twenty-four subjects met eligibility criteria and formed the study sample. The average age was 44 ± 2 years (range, 21–74 years), and 15 subjects (62%) were female. The majority had type 1 diabetes, and the mean duration of diabetes at the time of index evaluation was 16 years. Demographic and other clinical characteristics of the study subjects are detailed in Table 1. Fourteen subjects (58%) had chronic persistent symptoms, while the remaining 10 subjects (42%) had a cyclical pattern. In addition to nausea and vomiting, 11 subjects (46%) complained of abdominal pain and/or bloating as a part of their symptom complex. Each subject had undergone routine laboratory testing, upper endoscopy, and an abdominal ultrasound or CT scan; most had undergone a more extensive evaluation. Delayed gastric emptying was identified in 5 of 14 subjects who had undergone radionuclide gastric emptying studies and in another 2 subjects with food residue at endoscopy. At least moderately severe baseline symptom ratings (≥2 on symptom severity scale) were determined for all subjects, the median rating being 3, and all subjects had received conventional antiemetic and prokinetic trials before referral.

Amitriptyline, nortriptyline, and desipramine were the most commonly used medications (1 patient received imipramine), the median final dose at maintenance being 50 mg/day across the group (range, 10–75 mg/day). Starting dosages ranged from 10 to 25 mg/day. At least moderate symptom improvement was rated through chart review in 21 subjects (88%), while complete or nearly complete resolution of symptoms was recorded in 8 (33%) (Fig. 1). Outcomes were similar for the subset with delayed gastric emptying, wherein 6 of 7 (86%) described at least moderate symptom improvement and 1 (14%) had complete or nearly complete resolution. In early follow-up, 11 subjects (46% of the total)

Table 1 Clinical characteristics of the subject group

Clinical characteristic	
Age[a]	44 ± 2 yr
Sex	15 F/9 M
Diabetes mellitus	
Type 1	17 (71%)
Type 2	7 (29%)
Duration of diabetes mellitus[a]	16 ± 2 yr
Peripheral neuropathy	9 (38%)
Symptom pattern	
Continuous	14 (58%)
Cyclical[b]	10 (42%)
Duration of symptoms[a]	2 ± 1 yr
Concurrent psychiatric disorder[c]	9 (38%)

[a] Averaged data reported as mean ± SE.

[b] History of three or more stereotypic attacks of nausea and vomiting with complete resolution of symptoms between attacks.

[c] Chart notation of currently active anxiety state or affective disorder.

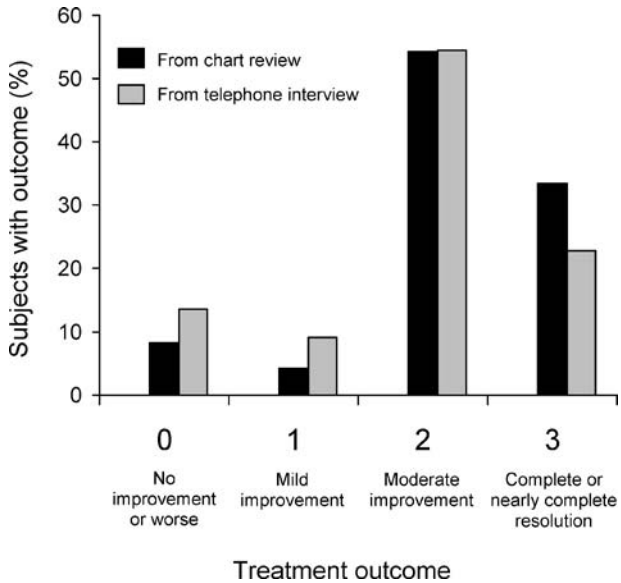

Fig. 1 Symptomatic outcome from TCA therapy as extracted from clinician ratings (chart review; $n = 24$) and as subject-rated during the telephone interview ($n = 22$). There was no difference between the distributions of responses ($P = 0.8$)

reported side effects from TCA therapy necessitating either change to a different TCA, dose reduction, or discontinuation (1 patient because of tachycardia; Table 2). The average duration of treatment at Washington University School of Medicine was 13 ± 3 months, after which follow-up was provided by referring physicians.

Twenty-two of the 24 subjects (92%) could be contacted for a telephone interview 52 ± 8 months after initiation of TCA therapy. One patient had died in the interim and another could not be located. Self-reported response to TCA therapy on interview closely matched the response extracted from chart review (Fig. 1); 17 (77%) rated at least moderate improvement. Of these 17, 7 were continuing to use TCA therapy for symptom control, whereas 10 had discontinued the medications either because of symptom resolution or late side effects (Fig. 2). Overall, only 3 (14%) of the 22 patients available for telephone interview had discontinued TCA therapy because of medication intolerance. Delayed side effects included hypertension and weight gain. On direct questioning, 15 of the 22 subjects (68%) rated TCAs the most effective treatment they had received for these symptoms, and another 2 (9%) stated they were as effective as any other medication. All of the 7 subjects with delayed gastric emptying were available for telephone interview. Six (86%) rated at least moderate improvement during TCA therapy, and all 7 (100%) stated that TCAs were the most effective treatment they had received for these symptoms.

Predictors of response to TCAs were first examined using univariate comparisons of outcome ratings extracted from chart review. Of the clinical characteristics listed in Table 1, only symptom pattern was related to outcome, the cyclical symptom pattern being associated with poorer response to TCA therapy ($P = 0.03$). This finding persisted in the regression analysis using the same clinical characteristics as initially entered independent variables (Table 1). Symptom pattern remained a significant independent predictor of response, the cyclical symptom pattern interfering with outcome ($P = 0.025$). Peripheral neuropathy showed an independent trend toward reducing TCA response ($P = 0.074$). Chart notation of a currently active anxiety and/or affective disorder was not an important indicator of response in either univariate or regression analyses.

Table 2 Early side effects from tricyclic antidepressant therapy and required interventions

Side effect and required intervention	Number of subjects (%), $n = 24$
Side effect	
Sedation	6 (25)
Agitation	3 (12)
Anticholinergic effects	3 (12)
Cardiovascular effects	1 (4)
Any side effect	11 (46)[a]
Required intervention	
Change to different TCA	7 (29)
Decrease in dose	3 (12)
Discontinuation	1 (4)

[a]Two of the 11 subjects had more than one side effect.

Discussion

In this study of 24 diabetic patients with chronic vomiting, we found that more than three-fourths reported at least moderate response to a course of TCAs. The responses determined from retrospective chart review were corroborated by subsequent telephone interview, wherein 68% described TCAs as the most effective medications they had received for nausea and vomiting. Similar outcomes were observed in the subset with known delayed gastric emptying. Chronic use of TCAs was common. Side effects requiring dose modification or change in TCA occurred in a large minority of patients soon after TCA initiation, but early or late side effects resulted in TCA discontinuation in <20% of patients. The multivariate analysis used in this report demonstrated that a cyclical pattern of symptoms resembling cyclic vomiting syndrome in nondiabetic subjects predicted a poorer outcome from TCA therapy compared to a more continuous pattern of symptoms resembling functional nausea and vomiting.

Vomiting in diabetic patients can be a source of high morbidity and health-care resource utilization [1]. The problem typically is ascribed to delayed gastric emptying despite the fact that much scientific information speaks against gastric motor abnormalities as being directly responsible for symptoms in many patients. For example, nausea and vomiting are sporadic in diabetic patients and correlate poorly with the degree of gastric emptying delay in short- and long-term follow-up [12–14]. Indeed, many patients with severe delays are asymptomatic, while patients presenting with symptoms often have normal emptying [14, 15]. The poor correlation is emphasized further by outcomes from prokinetic medications, such as metoclopramide and domperidone [16, 17]. These medications may have nonsustained effects on emptying but prolonged effects on symptoms through central nervous system actions. Short-term treatment trials also demonstrate the dissociation between degree of gastric emptying and symptoms [17, 18]. Most recently, studies using gastric electrical stimulation also demonstrate the ability of an intervention to affect symptoms independently of an improvement in gastric emptying [19]. Thus, the bulk of information supports searching for agents that can suppress symptoms without overt concern for their potential to improve gastric motor physiology, at least in the short term.

The pathophysiology behind nausea and vomiting in many diabetic patients, once delayed gastric emptying is given limited credence, remains unknown. In nondiabetic patients, the

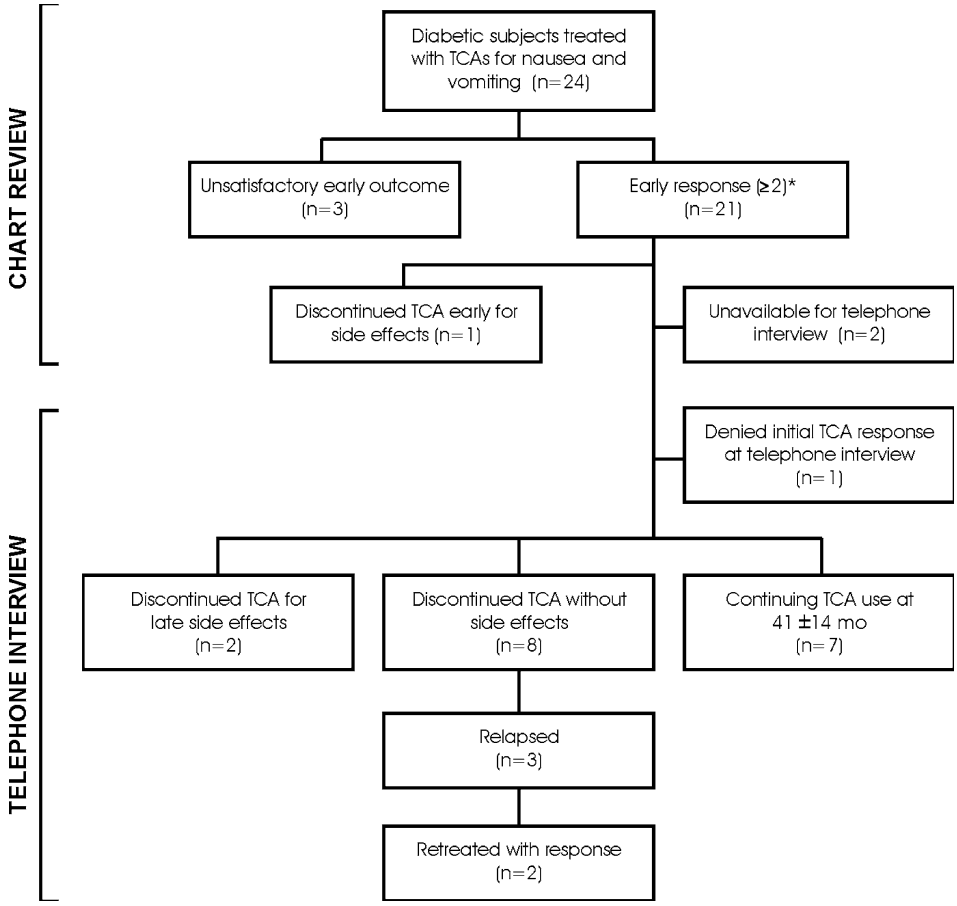

Fig. 2 Schematic representation of outcomes from TCA therapy in diabetic patients with nausea and vomiting. *Rated ≥2 on the Likert response scale

symptoms would be considered functional, and treatments oriented toward functional symptoms would be employed. Even in nondiabetic patients with functional dyspepsia or functional nausea and vomiting, delayed gastric emptying is found in up to 40% of subjects [20], is not predicted by presenting symptoms [including nausea or vomiting] [21], and is given little weight in management algorithms [22]. Antidepressants, and more specifically the TCAs, commonly are used in managing functional symptoms, particularly those that are of moderate to severe intensity and unresponsive to less morbid interventions (e.g., prokinetic antiemetics) with simpler adverse effect profiles [23]. TCAs improved symptoms to at least a moderate degree in 84% of 37 nondiabetic patients with functional nausea and vomiting who were managed with open-label therapy [8]. As in the current study, outcome was less robust when a group of 17 adult subjects with cyclic vomiting syndrome was treated with open-label TCAs, although again 76% reported at least moderate improvement [11]. TCAs now are considered acceptable alternative interventions for subjects with protracted, unexplained nausea and vomiting who fail other approaches and are the most regularly used maintenance medications in adult patients with cyclic vomiting syndrome [24].

Is there evidence that diabetic patients have a distinct mechanism for nausea and vomiting that is unique from the pathophysiology behind functional symptoms? Epidemiological data from a large population survey demonstrated a slightly increased prevalence of nausea and vomiting in the diabetic cohort (94.8% type 2 diabetes) compared with nondiabetic subjects (for vomiting: 1.7% vs 1.1%), the prevalence of nausea and vomiting being associated with poorer glycemic control when controlling only for age and sex [25]. In an Olmstead County community survey, however, no differences in the rates for nausea or vomiting could be detected in either type 1 or type 2 diabetic patients compared to the nondiabetic residents [26]-raising questions regarding the pathogenetic significance of diabetes toward the symptoms. A recent study of nearly 400 type 1 diabetic patients did find a mild increase in upper GI symptoms in the diabetic group compared with nondiabetic subjects, especially symptoms of higher intensity [27]. Symptoms were not predicted by degree of glycemic control nor presence of peripheral neuropathy in these type 1 subjects who have more difficulty with diabetes management and more neuropathic complications than type 2 patients. Evidence for an autonomic neuropathic pathogenesis is limited [25]. Thus, if the increase in symptom

prevalence is linked directly to diabetes, the explanation is unclear.

Anxiety and depression are more prevalent in both types of diabetes [28, 29], are associated with poorer glycemic control [30, 31], and are linked with functional symptoms in nondiabetic subjects, primarily as markers of an indirect central mechanism [23]. Depression accelerates the appearance of diabetes complications [32] and its treatment improves glycemic control independently of adherence to diabetes management [33, 34]-possibly through reversal of depression-associated insulin resistance [35]. A multivariate analysis of symptom predictors in a mixed group of type 1 and type 2 diabetic patients found that the presence of psychiatric disorder was a strong predictor of upper GI symptoms, whereas neuropathy (peripheral or autonomic) was not, suggesting that this marker may be indicating the presence of functional symptoms in the diabetic group [36]. Epidemiological surveys have not addressed this issue directly with regard to nausea and vomiting, but for other GI symptoms, the level of psychological symptoms importantly correlates with their appearance and disappearance in longitudinal observation [37]. These findings support trials of medications oriented toward management of functional symptoms in diabetic patients when other explanations for symptoms are inconspicuous.

The mechanism of action of TCAs for managing nausea and vomiting also is presently unknown. Although the agents have broad neurotransmitter effects that might influence pathways involved in the vomiting process (e.g., antihistaminic, anticholinergic, serotonergic effects), the action may be more related to a generalized dampening of symptom amplification mechanisms that have presumed relevance in the functional disorders [23]. The agents are not considered prokinetic and actually delay intestinal transit [38]. The fact that outcome from TCA therapy was not influenced by gastric emptying in our study further supports an effect that is independent of a prokinetic mechanism. Presence of psychiatric disorder was not required for response, an observation also made when nondiabetic patients with functional GI disorders are managed with TCAs. If anything, active psychiatric disorder, particularly depression, can reduce responsiveness to low-dose TCA regimens largely because of side effect intolerance [39]. Side effects also were reported commonly by our patients, but discontinuation was limited by dose adjustments and changes in specific agents, as has been recommended when TCAs are used in nondiabetic patients with functional GI disorders [23, 40].

In summary, this retrospective review of open-label treatment indicates that TCAs may have an important role in managing diabetic patients with chronic vomiting disorders that are refractory to conventional medical treatments. The strength of our conclusions is restricted by the limitations imposed by chart review, although we also employed a prospective telephone interview with subject-rated outcomes to corroborate the principal findings. Some clinical variables used in the regression analysis may not have been recorded systematically in chart notations (e.g., psychiatric diagnoses), and further prospective investigation with larger samples and better validated outcome measures will be required to best define patients that might respond to this type of medical intervention. Additionally, the relationship of outcome to gastric emptying should be more accurately defined. Nevertheless, these findings provide a novel alternative for patients in whom vomiting not only produces significant symptomatic burden but also interferes with diabetes management and results in increased medical morbidity. TCAs have anticholinergic and hyperglycemic effects that may be counterproductive for some patients [33], and other side effects were common in our subjects. Whether other antidepressants with side effect profiles better suited to the diabetic patient would have similar benefits on these GI symptoms merits investigation [41].

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