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Probing for Affective Side Effects of Drugs Used in Geriatric Practice: Use of Daily Diaries to Test for Effects of Metoclopramide and Naproxen

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The aim of this study was to develop the use of daily diaries of affects and events as measures of pharmacological effects on affective processes and to apply them to evaluate the possible affective toxicity of metoclopramide and naproxen, two medications commonly used in geriatric practice. In all, 105 adults aged 65 years or older were randomized to receive metoclopramide (up to 40 mg/day), naproxen (up to 1000 mg/day), or placebo under double-blind conditions for a period of 5 weeks. Patients were seen weekly for evaluations of affective and cognitive outcomes as well as safety. In addition, patients kept diaries with daily records of positive and negative affect and reports of significant daily events. Findings included mixed model analyses of drug assignment, time, events, and interactions for both positive affect and days with significant negative affect. Subjects exhibited high levels of adherence in completing daily diaries. Neither the pattern of dropouts nor the weekly assessments demonstrated significant drug effects on mood or affect. However, diary data demonstrated that metoclopramide increased the apparent impact of negative events on both positive and negative affect relative to placebo, and that naproxen increased the apparent impact of positive events on positive affect and, possibly, of negative events on negative affect relative to placebo. The findings confirm the utility of diary methods for studying drug effects on affective processes in normal elderly subjects. They suggest that both metoclopramide and naproxen can affect the associations between daily events and affects. If replicated, they would demonstrate that drug effects can extend beyond the intensity of affect and/or the emergence of full-fledged psychiatric disorders to include moderation of the interactions between daily events and affect.
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INTRODUCTION

Affective symptoms and related behaviors are often listed in FDA-approved labeling as adverse reactions to drugs (PDR, 2004). The frequent listing of these side effects and their diversity support the idea that affective toxicity is a significant clinical problem. However, there must be questions about the methods used for identifying these symptoms, and the clinical and statistical significance of the findings. Clinical and experimental approaches to the identification of cognitive toxicity have advanced as a result of general models about anticholinergic side effects, the development of methods for screening for delirium, and the availability of brief cognitive assessment instruments. In contrast, less is known about affective toxicity. Much of the hypothesis-testing research in this area has focused on questions about whether or not medications can cause well-defined psychiatric syndromes such as major depression. However, drugs can, in principle, cause subsyndromal conditions or atypical clusters of symptoms, and, therefore, such studies may lack sensitivity for the detection of adverse effects that may be of clinical and public health significance, especially for older adults and those taking medications for the treatment of chronic disease.

To begin to address the problem of affective toxicity in a systematic manner, we conducted a randomized, placebo-controlled, double-blind trial to evaluate the effects of two medications often used by older adults. Metoclopramide, an agent used to treat decreased gastric motility and related symptoms, was chosen for investigation to test the hypothesis that dopamine antagonists could cause anhedonia and to follow-up on case reports that it can lead to

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depression and other psychiatric symptoms (Anfinson, 2002; Friend and Young, 1997; Masters and O'Grady M, 1995; Weddington and Banner, 1986). Naproxen, a non-steroidal anti-inflammatory agent, was chosen to allow systematic follow-up of case reports of depressive symptoms as side effects (Browning, 1996; Jiang and Chang, 1999). The two medications were studied in parallel to decrease the possibility that the blind could be broken as a result of gastrointestinal symptoms. The study was conducted with normal volunteers, rather than individuals with clinical indications for the medications to avoid confounding between residual target symptoms, therapeutic responses, and side effects.

To advance this line of investigation, we evaluated the feasibility and utility of paper and pencil daily diaries for studying drug side effects. Potential benefits of diary methods include their decreased dependence on subjects' recall of their affective states during the time between scheduled assessments, and the increased statistical power that can result from the availability of multiple repeated measures. Self-reports of symptoms using daily diaries and related methods have been used for the assessment of treatment outcomes for conditions such as asthma (Santanello *et al*, 1997), headaches (Carpay *et al*, 2004), and panic disorder (Lepola *et al*, 2003), where symptoms are known to vary over time. Although they have been utilized in studies of premenstrual symptoms (Freeman *et al*, 1996) and bipolar disorder (Scharer *et al*, 2002), they have been used less frequently in studies of other depressive disorders, possibly as a reflection of assumptions that depressive symptoms are significant only when they are persistent or of a quality and severity that makes them easily recalled. The methods for affective assessment in this study were derived from those of Lawton and colleagues (Winter *et al*, 2000; Lawton *et al*, 1992a, b, 1993, 1995a, b, 1996; Kleban *et al*, 1992), and were designed to avoid biases due to these assumptions. As previously applied by Furlan and coworkers to characterize drug responses (Furlan *et al*, 2004), mixed-method analyses using diary data can be used to characterize mean levels of positive and negative affect, changes over time, and the impact of both positive and negative events on positive and negative affects.

In evaluation of the feasibility and reliability of dairy methods, this study evaluated completion of diaries, concurrent validity of paper and pencil diary records relative to 'real-time' telephone assessments of affect, and internal consistency in reports of events and affects. In applying the diary methods to drug effects, it tested the hypotheses that metoclopramide would lead to anhedonia, manifest by drug-related decreases in positive affect or in the affective responses to positive events, and that naproxen would lead to dysphoria, manifest by drug-related increases in the proportion of days during which significant levels of negative affect were reported.

METHODS

Volunteers

The study sample consisted of 105 healthy volunteers over the age of 64 years who responded to newspaper advertisements, talks at senior centers, and other forms of outreach. Prior to study entry, consenting volunteers received a screening evaluation consisting of a physical examination, a semistructured psychiatric interview developed for use in older subjects (Parmelee *et al*, 1989), and an evaluation of cognitive capacity. The exclusion criteria included erythrocyte sedimentation rate greater than 60, creatinine level greater than 1.8, current regular use of anti-inflammatory medication, hospitalizations or significant medication changes within the past month, <8 years of education, Minimental State Examination (MMSE) scores <24, CES-D scores >12, significant laboratory abnormalities, CNS disease, alcohol or substance abuse within the past 5 years, history of mental retardation, history of a psychotic disorder, history of major depression or bipolar disorder, active liver or kidney disease evidenced from a review of systems or screening laboratory evaluations, insulin-dependent diabetes, taking medication capable of causing cognitive impairment (eg benzodiazepines or agents with significant anticholinergic activity), taking concomitant medications with significant interaction with study medications, and performance outside the range of normal on practice tasks conducted during the baseline evaluation. Written informed consent was obtained prior to any study procedures. Protocols were approved by the Institutional Review Board of the University of Pennsylvania.

Study Procedures

The study was a randomized double-blind, placebo-controlled clinical trial. The process for obtaining informed consent occurred during their first visit to the Geriatric Behavioral Psychopharmacology Laboratory of the University of Pennsylvania. The session included instructions on how to complete the daily affect diary, and practice in test procedures. Subjects were asked to return the following week (with their diaries) for baseline testing. Subsequently, patients were started on study medication or placebo under double-blind conditions. They were seen weekly for cognitive and affective assessments, safety monitoring, and collection of diaries. The volunteers were seen at various times of the day with individual volunteers reporting to the laboratory at the same time each test session.

Medication Administration

Subjects received metoclopramide in divided doses up to a total of 40 mg/day, naproxen in divided doses up to a total of 1000 mg/day, or placebo for 5 weeks. To maintain the double blind, all medication was prepared in opaque identical-appearing red-and-blue gelatin capsules, which were sealed in blister cards with each individual dose identified on the packaging by day and time it was to be taken.

Assessments

Each study visit included evaluations of mood and depressive symptoms using the Center for Epidemiological Studies-Depression scale (CES-D; Radloff, 1977), the Apathy Evaluation Scale (Marin *et al*, 1991), and probes for DSM-IV symptoms of major depression. Safety evaluations

conducted at each study visit included structured probes for known side effects of metoclopramide and naproxen, the Unified Parkinson's Disease Rating Scale (Fahn *et al*, 1987), screening tests for occult blood in stool, and open-ended questions. In addition, a battery of cognitive tests was administered; findings on cognitive outcomes will be reported separately. These assessments of safety and outcomes were supplemented by weekly telephone calls during which subjects were asked to report on their current affect using the Lawton Positive and Negative Affect Scales (Lawton *et al*, 1992a) and about side effects.

Daily Diaries

At every visit, volunteers were given booklets that included forms for completing daily records of affects and events. They were asked to complete the Lawton Positive Affect and Negative Affect Rating Scales at the end of each day for the length of the study (Lawton *et al*, 1992a). These scales consist of five positive affect terms and five negative affects terms on which the volunteer rated his or her affective state at the end of each study day on five-point scales. The positive affect scale is comprised of the average ratings for affective states of energetic, warmth towards others, interested, happy, and content; and the negative affect scale, of the average ratings for the affective states of annoyed, irritated, depressed, worried, and sad/blue. In addition, subjects were asked to record daily events that were outside of their usual routine. The valances of the events were scored by independent raters using a 'reasonable person' standard. Thus, a visit from an adult child was considered positive, even though it is, in principle, possible that the child abused or exploited the subject. Events were rated as positive (eg 'I went to dinner and a movie with friends'), negative (eg 'I got in a fender-bender on the way home'), or neutral (eg 'I picked up the dry-cleaning'). Two judges independently assigned valences and attained an agreement $>97\%$.

Statistical Methods

Baseline sample characteristics between treatment groups were compared using *t*-tests for continuous measures and χ^2 tests for categorical measures. The analyses for weekly measures included testing and estimating effects across time for the entire sample and within and between each treatment group using mixed model analyses with SAS Proc Mixed. Statistical significance was based on whether two-sided *p*-values were less than 0.05 and 0.01. *P*-values are unadjusted to allow readers to apply the multiple comparison adjustment of choice.

For the analyses on diary data, positive affect scores, defined by the Lawton Daily Affect Scale, were modeled as a continuous outcome. Highly skewed negative affect scores were dichotomized using two different cut points ($\geqslant 1.8$ and $\geqslant 2.2$) to form two binary variables corresponding to one 'dysphoric' day approximately every 2 weeks, and one approximately every month in normal subjects; we report on findings for these two categorical variables because choice of either one could be viewed as somewhat arbitrary. Linear and logistic mixed effects regression models were used depending on the type of outcome, continuous, or binary, respectively. Models for estimating lag effects were calculated by recoding the day number associated with events. For calculations of drug effects, there was a preliminary test of the significance of group effects (metoclopramide *vs* naproxen *vs* placebo) and two- and three-way interactions that identified significant group-event and group $\times$ event $\times$ time interactions. As the studies were conducted to evaluate drug effects *vs* placebo rather than differences between active medications, subsequent analyses considered each drug group *vs* the common placebo group separately. Findings for the two drugs are presented in separate tables (for metoclopramide and for naproxen). Each model included main effects for baseline positive and negative affect scores, baseline positive and negative events, time (days), time-varying events (positive events were scored as 1 if one or more positive events were reported for the day, and 0 if there were none; negative events were scored in an analogous manner), and treatment group (placebo or medication). In addition, the models included two- and three-way interactions among day, time-varying events (positive and negative separately), and treatment group. The models also included random intercepts and slopes for time to account for longitudinal within-subject correlations. To account for residual correlations beyond those addressed with the random effects structure, the models included an additional covariance structure based on first-order autocorrelated errors. In case there was any further residual correlation, we used robust standard errors (Diggle *et al*, 1994). These models were fit using Proc Mixed for the linear mixed regression model and the Glimmix macro for the logistic mixed regression model. Both procedures were used within SAS V8 (SAS Institute Inc., Cary, NC). For the linear mixed effects regression model with positive affect as the outcome, slope main effects are reported in terms of the change in positive affect with respect to a unit change in a covariate. Estimates of these main effects are presented with 95% confidence intervals. Main effects from the logistic mixed regression models for dichotomous negative affect are the change in log odds of moderate or high *vs* low negative affect with a one-unit change in a covariate such as the occurrence of a negative event. Odds ratios and 95% confidence intervals are reported for these covariate effects. For both positive and negative affect outcomes, slopes and odds ratios, respectively, are presented for positive and negative event covariates separately by treatment group.

The specific hypotheses to be tested were as follows: (1) in models with positive affect as the dependent variable, there would be significant main effects of drug or drug $\times$ time interactions, and/or drug $\times$ positive event or drug $\times$ positive event $\times$ time interactions for metoclopramide; and (2) in models with days with clinically significant negative affect as the dependent variable, there would be significant effects of drug or drug $\times$ time interactions for naproxen. Other contrasts and findings must be viewed as exploratory.

RESULTS

Study Sample

The participants in this study included 105 individuals: 36 randomized to metoclopramide; 35 to naproxen; and 34 to

placebo (Table 1). The subjects were of average age 70.9 (SD 4.9) with 14.6 (SD 2.9) years of schooling, and 3.7 (SD 2.1) self-reported chronic health conditions. They were cognitively intact with average MMSE scores of 29.2 (SD 1.1), and euthymic with average CES-D scores of 4.1 (SD 3.9). There were no significant differences between groups in baseline variables. In all, 20.0% of subjects had serum creatinine concentrations greater than 1.0, and 20.2% had erythrocyte sedimentation rates greater than 20. There were no differences between groups in these proportions, and the findings were not affected by excluding these individuals from the analyses.

Subjects reported an average of 29.6 (SD 26.1) events while receiving study medications; 17.7 (SD 18.4) positive events, 6.6 (SD 6.2) negative events, and 5.2 (SD 7.2) neutral events (Table 1). A total of 40% of subjects had days with more than one event, 21% with more than two, 9% with more than three, and 1% with more than 5. There were no significant differences between study groups in any event-related parameters.

Table 1 Subject Characteristics and Disposition

		Metoclopramide (*N* = 36)			
	Placebo (*N* = 34)	**Mean (SD) or %**	**Naproxen (*N* = 35)**	**F**	***p*-value**
Age (years)	71.2 (5.2)	70.2 (5.8)	71.4 (4.7)	0.446	0.641
Years of schooling	14.4 (3.4)	14.5 (2.7)	14.8 (2.7)	0.203	0.817
Health conditions	3.68 (2.06)	3.37 (1.90)	4.01 (2.36)	0.823	0.442
MMSE	29.2 (0.76)	29.0 (0.84)	29.4 (0.75)	2.42	0.089
CES-D	4.50 (3.71)	4.56 (3.37)	5.18 (3.03)	0.431	0.651
Days on medication	30.4 (8.0)	31.6 (6.9)	30.5 (8.3)	0.256	0.775
Pill adherence (%)	97.3 (5.9)	96.5 (10.3)	97.4 (14.5)	0.082	0.921
Missing diary days (%)	2.6 (5.7)	2.4 (3.2)	2.9 (4.9)	0.583	0.560
Missing items (% days)	1.6 (2.8)	1.7 (4.8)	2.8 (4.3)	0.891	0.414
Total events	28.5 (25.5)	28.4 (23.6)	31.7 (29.6)	0.161	0.852
Positive events	15.6 (16.9)	17.8 (16.0)	19.6 (22.0)	0.357	0.701
Negative events	6.2 (4.0)	6.2 (6.5)	7.5 (7.7)	0.423	0.657
Neutral events	6.6 (9.1)	4.5 (6.6)	4.6 (5.5)	0.852	0.430
				χ^2	***p*-value**
Sex					
% Female	52.9	41.7	48.6	0.91	0.634
Ethnicity					
% African-American	17.6	16.7	11.4	0.603	0.704
Marital status					
%Currently married	50.5	58.3	51.4	4.287	0.74
Country of birth					
%US	91.2	100	100	6.449	0.634
Native language					
% English	100	100	100	—	—
Creatinine					
% > 1.0	21.9	17.1	21.2	0.279	0.87
Sedimentation rate					
% > 20	15.6	26.5	18.2	1.328	0.515
Disposition					
% Early termination	26.5	19.4	25	0.581	0.748

Pill compliance during the course of the study was 97.1% (SD 10.7) and was similar across groups (Table 1). In all, 23.6% of the subjects dropped out during the course of the study: 19.4% from the group randomized to metoclopramide (for increased blood pressure (1); decreased MMSE score (1); tremor (2); and withdrawal of consent (3)); 25.0%, from naproxen (for bruising (1); rash (1); heme-positive stool (2); intercurrent illness (1); and withdrawal of consent (4)) and 26.5% from placebo (for CES-D >16 (1); heme-positive stool (2); neck pain (1); itching (1); and withdrawal of consent (4)). Only one subject, an individual randomized to placebo, was discontinued due to the emergence of depressive symptoms manifest by a high CES-D score. The causes of early termination for the other subjects reflect either general medical side effects of the medications, intercurrent medical illnesses, or withdrawal of consent due to logistic or personal reasons. None of the other dropouts could be attributed to affective side effects of study medications. Subjects who dropped out during the course of the study did not differ from completers in baseline measures of affect. Findings on affective processes in completer analyses were similar to those for the intention-to-treat analyses reported here.

Feasibility and reliability of diary measures. The average rate for completion of the diaries during the subjects' participation in the study was 95.1% (SD 6.0), and was similar across groups (Table 1). In all, 85% of subjects recorded complete data on the Positive and Negative Affect Scales on 90% or more of their study days, and 95% on 85% or more. The 4.9% missing data on the Positive and Negative Affect Scales included 2.9% (SD 4.0) with no diary data for the date, and 2.0% (SD 4.1) with one or more missing items.

Evidence for the concurrent validity of diary measures comes from evaluations of their associations with periodic telephone assessments of affect. During the course of the study, the research staff placed calls, usually during business hours, to subjects at least weekly to inquire about potential side effects and to utilize the Positive and Negative Affect Scales to inquire about current ('right now') affect; in all, 399 telephone assessments to study subjects were completed. For positive affect, the Pearson correlation of telephone assessments with the same day's diary record of positive affect was 0.587, 0.438 for yesterday's, and 0.410 for the day before yesterday's; for comparison, the correlation of today's diary measure with yesterday's was 0.679, and 0.604 with the day before yesterday's. For negative affect, the Spearman rank-order correlation of telephone assessments with the same day's diary record of negative affect was 0.528, 0.401 for yesterday's, and 0.238 for the day before yesterday's; for comparison, the correlation of today's diary measure with yesterday's was 0.586, and 0.446 for the day before yesterday's.

Evidence on the internal consistency of diary measures comes from associations between daily affects and events pooling all randomization arms (Table 2). On days when positive events were reported, there were significant increases in positive affect and decreases in negative affect. On days when negative events were reported, there were significant increases in negative affect and decreases in positive affect. All of these effects were attenuated in analyses that tested for one- and two-day lag effects, that is, for the changes in positive and negative affect associated with events reported 1 or 2 days previously. For negative, but not for positive affect, a number of the lag affects were statistically significant. In general, the findings on the relationship between events and affect, and the attenuated lag effects support the potential utility of diary data for studies of both affect and the contingency of affect on events.

Table 2 Diary Data: Associations between Events and Affects

	Estimate	95% CI	*T*
Positive affect			
Day	−0.0042	−0.01763 to 0.009231	−0.62
Positive events			
Same day	***0.193***	0.1381 to 0.2478	6.9
One-day lag	0.03021	−0.02481 to 0.08522	1.08
Two-day lag	−0.02367	−0.06925 to 0.02190	−1.02
Negative events			
Same day	***−0.1964***	−0.2813 to 0.1115	−4.53
One-day lag	−0.05842	−0.1334 to 0.01658	−1.53
Two-day lag	−0.03362	−0.09076 to 0.02353	−1.15
Negative affect > 1.8			
Day	***−0.02748***	−0.04053 to −0.01444	−4.18
Positive events			
Same day	***−0.5989***	−0.8228 to −0.375	−5.24
One-day lag	***−0.2646***	−0.4855 to −0.04367	−2.35
Two-day lag	***−0.2338***	−0.4491 to −0.01845	−2.13
Negative events			
Same day	**2.0624**	1.8254 to 2.2994	17.06
One-day lag	0.193	−0.03320 to 0.4191	1.67
Two-day lag	0.2278	0.002281–0.4533	1.98
Negative affect > 2.2			
Day	−0.02483	−0.05355 to 0.003883	−1.72
Positive events			
Same day	***−0.5389***	−0.885 to −0.1928	−3.05
One-day lag	−0.1714	−0.5044 to 0.1616	−1.01
Two-day lag	0.1314	−0.1873 to 0.4502	0.81
Negative events			
Same day	***2.519***	2.2433 to 2.7947	17.91
One-day lag	***0.6937***	0.4125 to 0.9749	4.84
Two-day lag	***−0.331***	−0.636 to −0.02607	−2.13

Notes: Bolded, italicized and underlined estimates; $p<0.05$.
Model also included intercept, baseline positive affect, baseline negative affect, baseline positive events, baseline negative events, and drug assignment.

Use of diaries to study drug effects. There were no significant main effects of drug or drug by week interactions on weekly measures of MMSE or CES-D scores, apathy, positive or negative affect, or extrapyramidal symptoms. Although one subject dropped out with a decreased MMSE score, and two with tremor, cognitive and extrapyramidal side effects did not emerge as statistically significant.

Initial analyses of diary data evaluated group assignment (to metoclopramide, naproxen, or placebo), and found significant group by event and group by event by time interactions at the 0.01 level. Thus, subsequent analyses considered each drug separately *vs* placebo. Tables 3 and 4 present findings from mixed effects analyses evaluating positive affect, and the probability of days with at least moderate levels of negative affects (scores $\geqslant 1.8$) and days with high levels of negative affects (scores $\geqslant 2.2$) for models that evaluated the effects of drug, time, positive events, negative events, and interactions. Findings are presented in terms of parameters for each medication and placebo for day, positive events, negative events, and the 2 day by event interactions. There were no effects of either of the medications on levels of positive affect or on the probability of days with moderate or high levels of negative affect. However, there were a number of significant drug by event and drug by event by day interactions demonstrating an impact of medications on the contingency of affects on events. First, analyses of metoclopramide *vs* placebo demonstrated a significantly greater decrease in positive affect on days with negative events for those randomized to active medication. There was also a significantly greater increase in the probability of days with at least moderate levels of negative affect for days with negative events, and a greater increase over time in the probability of days with high levels of negative affect on days with negative events for those on metoclopramide. Thus, metoclopramide appears to amplify the impact of negative events on both positive and negative affect. Second, analyses of naproxen *vs* placebo demonstrated a significantly greater increase in positive affect on days with positive events for those randomized to active medication. There was also a significantly greater increase in the probability of days with high levels of negative affect on days with negative events for those on naproxen, but there was no comparable effect for days with moderate levels of negative affect. Thus, naproxen appears to amplify the impact of positive events on positive affect, and, possibly, the impact of negative events on negative affect.

DISCUSSION

The findings reported here demonstrate that older volunteers can complete diaries of daily events and affects in a consistent manner, that the data have concurrent validity when compared with telephone assessments, and that they are internally consistent in terms of the association of same day affects with events and the attenuation of these relationships over time. Thus, they confirm the feasibility of using daily diaries of events and affects as probes for the outcomes of clinical trials, at least for cognitively intact individuals without psychiatric illness. In addition, they demonstrate the sensitivity of diary methods for the detection of drug effects that are not readily detectable with standard measures.

In these studies, neither the pattern of dropouts nor the findings from weekly assessments provided any indication

Table 3 Diary Data: Metoclopramide Effects

	Positive affect		Moderate negative affect (threshold >1.8)		High negative affect (threshold >2.2)	
	Estimate	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Drug						
Intercept	−0.03579	−1.8252 to 1.7536	**−7.282**	−10.3072 to −4.2568	**−11.3417**	−17.512 to −5.1714
Day	−0.0074	−0.03285 to 0.01805	**−0.04242**	−0.0705 to −0.01435	**−0.09783**	−0.1879 to −0.00781
Positive events	**0.1227**	0.003862 to 0.2416	−0.2469	−0.7337 to 0.2398	−0.1962	−1.0973 to 0.7050
Day × positive events	0.00302	−0.00524 to 0.01128	−0.01836	−0.05083 to 0.01411	−0.06	−0.1293 to 0.009319
Negative events	**−0.2434***	−0.3565 to −0.1304	**2.6373****	2.0176 to 3.2570	**1.3796**	0.5288 to 2.2304
Day × negative events	0.001809	−0.00896 to 0.01258	−0.01533	−0.05191 to 0.02125	**0.1164****	0.05393 to 0.1789
Placebo						
Intercept	−0.06108	−1.8965 to 1.7743	**−7.2678**	−10.2205 to −4.3151	**−10.7295**	−16.7693 to −4.6897
Day	−0.00488	−0.02252 to 0.01276	−0.00831	−0.03352 to 0.01690	−0.04582	−0.1204 to 0.02878
Positive events	0.09688	−0.04098 to 0.2347	−0.4289	−0.9573 to 0.09949	−0.3488	−1.0885 to 0.3909
Day × positive events	0.005713	−0.00297 to 0.01439	−0.02067	−0.05253 to 0.01119	−0.01985	−0.07271 to 0.03301
Negative events	**−0.1164***	−0.2291 to −0.00365	**1.3258****	0.7147–1.9370	**1.6989**	1.1512 to 2.2467
Day × negative events	−0.00448	−0.01155 to 0.002590	0.02568	−0.01128 to 0.06264	0.004622**	−0.03071 to 0.03995

Notes: For positive affect outcomes, estimates are terms in mixed-model, linear models; for negative affect, estimates are natural logs of the odds ratios.
Bolded, italicized and underlined estimates: differ from 0, $p < 0.05$
For drug placebo interactions: *$p<0.05$; **$p<0.01$.
Models also included baseline positive affect, baseline negative affect, baseline positive events, and baseline negative events.

Table 4 Diary Data: Naproxen Effects

	Positive affect		Moderate negative affect (threshold ⩾1.8)		High negative affect (threshold ⩾2.2)	
	Estimate	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Drug						
Intercept	0.01564	−1.8257 to 1.8570	***−6.1954***	−8.7875 to −3.6034	***−8.6222***	−12.8941 to −4.3503
Day	−0.00296	−0.02417 to 0.01825	−0.02247	−0.04903 to 0.004089	−0.02753	−0.07630 to 0.02123
Positive events	***0.21****	0.06764 to 0.3523	***−0.5834***	−1.0833 to −0.0834	−0.2296	−0.8761 to 0.4168
Day × positive events	0.00037	−0.01074 to 0.01148	0.01881	−0.01252 to 0.05015	0.006347	−0.03581 to 0.04851
Negative events	***−0.2048***	−0.3125 to −0.09703	***1.6896***	1.1523 to 2.2270	***2.8254****	2.1999 to 3.4509
Day × negative events	0.003265	−0.00487 to 0.01140	0.03062	−0.00307 to 0.06431	0.005269	−0.03221 to 0.04275
Placebo						
Intercept	0.03251	−1.7678 to 1.8328	***−6.1975***	−8.7553 to −3.6397	***−8.2266***	−12.4265 to −4.0267
Day	−0.00481	−0.01985 to 0.01023	−0.00832	−0.03412 to 0.01748	−0.03802	−0.09010 to 0.01406
Positive events	0.09845*	−0.06572 to 0.2626	−0.4219	−0.9467 to 0.1028	−0.3869	−1.2323 to 0.4584
Day × positive events	0.005641	−0.00372 to 0.01500	−0.02128	−0.05320 to 0.01063	−0.01083	−0.07031 to 0.04865
Negative events	−0.1142	−0.2397 to 0.01125	***1.3097***	0.7022 to 1.9171	***1.5546****	0.9309 to 2.1782
Day × negative events	−0.00463	−0.01216 to 0.002893	0.02622	−0.01064 to 0.06309	0.01293	−0.02782 to 0.05367

Notes: For positive affect outcomes, estimates are terms in mixed-model, linear models; for negative affect, estimates are natural logs of the odds ratios.
Bolded, italicized and underlined estimates: differ from 0, $p<0.05$
For drug placebo interactions: *$p<0.05$; **$p<0.01$.
Models also included baseline positive affect, baseline negative affect, baseline positive events, and baseline negative events.

of an effect of the study medications on affective processes. Analyses of diary data did not demonstrate any drug effects on levels of positive and negative affect in the absence of events. However, analyses of the relationships between events and affects suggested that both medications had effects on affective processes. The findings did not confirm the hypothesis that administration of the dopamine antagonist metoclopramide was associated with decreased positive affect or anhedonia. Instead, metoclopramide was associated with an apparent increased impact of negative events on both negative and positive affect. These effects occurred in the absence of any statistically significant effect of metoclopramide on UPDRS ratings of extrapyramidal symptoms. Thus, they are likely to reflect direct effects on affective processes, rather than indirect effects mediated through extrapyramidal side effects.

The findings with naproxen did not confirm an increased risk of depression. However, they demonstrated that naproxen administration increased the impact of positive events on positive affect and, possibly, the impact of negative events on negative affect. Although the findings could not be attributed to selective effects in subjects with marked increases in erythrocyte sedimentation rate, mechanisms mediated by anti-inflammatory activity cannot be excluded. Alternatively, it is possible that the observed effects could follow from drug effects on prostaglandin-mediated mechanisms regulating affective responses (Sublette *et al*, 2004).

In spite of the potential value of the methods reported here, it is important to recognize their possible limitations. First, some investigators have suggested that the validity of diary data is limited by subjects' nonadherence regarding the timing of entries (Schwartz and Stone, 1998; Stone, 2000; Stone *et al*, 2003). We addressed this possibility through a number of safeguards, including collection of diaries every week, and validation of diary entries through periodic telephone inquiries. Further evidence for the validity of diary data in the elderly subjects who participated in this research within our program came from the analysis of lag effects as reported previously (Furlan *et al*, 2004) and confirmed here. Second, while it is reasonable to interpret the association between diary entries of affects and events as a reflection of affective reactions to events, it is important to recognize that this interpretation could be challenged. An alternative explanation is that recollections of events could be biased by the subjects' states at the time that entries were recorded. However, given that there were no significant drug effects on affect, such a mechanism could not explain drug effects on the association of events with affects. Third, the analyses and findings reported here focus on demonstrations of group-level effects. In principle, they cannot address questions about the frequency with which clinically significant effects are observed in individual subjects. Further analyses are in progress to identify individual patients or subgroups in whom the effects demonstrated here are clinically significant.

The findings reported here are significant at several levels. From a methodological perspective, they confirm the feasibility and value of using diary methods as systematic probes for pharmacological effects on affective processes in normal subjects. From a substantive perspective, they suggest the processes that determine affective responses to daily events are separable from those that determine 'baseline' levels of affect. More specifically, they suggest

that increased sensitivity to negative events can be a side effect of metoclopramide, and that increased affective responses to positive events and, possibly, negative events may occur with naproxen. More generally, provided that these results are replicated, they would demonstrate that diaries allow for greater sensitivity to side effects of medications that may extend to more subtle and complex interactions between life events and affect, beyond the intensity of reported affect and/or the emergence of full-fledged psychiatric disorders such as depression.

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