Adverse effects of medications that occur at low frequency or low severity are often not detected in the current framework of drug approval and monitoring. Of particular concern are potential behavioral consequences such as depression or cognitive dysfunction that may occur from commonly prescribed medications. This study explores the use of measuring daily affect, both positive and negative, as a method for detecting clinically relevant affective toxicity from medications commonly prescribed to older adults. Findings from this study suggest that metoclopramide may have the potential for causing significant changes in affect among healthy elderly adults. This may suggest that more vulnerable or disabled adults may be at even greater risk for affective changes related to this medication.

The Institute of Medicine has recently called for a greater emphasis on postmarketing research in order to improve the detection of adverse effects of medications that occur at a low incidence or occur when medications are used for a longer duration or at a higher dose than intended. Morrison and Katz have previously suggested that the current procedures for recognizing adverse effects of new drugs are designed to identify effects that are serious and common. However, these procedures are conducted predominantly in young and middle-aged populations of adult subjects and may not be adequate to detect side effects that are significant in the elderly. Of particular concern are central nervous system effects, such as cognitive changes or affective disturbances, which, unless explicitly examined, often go unnoticed or ignored. As highlighted by a recent report from the US General Accounting Office (GAO), the growing elderly population may be particularly vulnerable to adverse drug reactions and is an issue that is important to national health care policy as well as clinical practice. Moreover, the GAO report emphasizes that, even in the absence of serious injury, less severe or persistent adverse reactions can decrease the general quality of life of patients. In this context, it is important to ask whether medications prescribed commonly for older patients regularly cause impairments in affect and/or cognitive functioning. Previous research by Katz and colleagues has established methodologies for the systematic examination of the cognitive effects of medications in healthy noncognitively impaired elderly adults. This line of investigation has demonstrated reproducible cognitive impairment from medications such as oxybutynin and has failed to demonstrate effects of other medications such as cimetidine. We have now begun to extend this methodology to include the systematic evaluation of affective or mood disturbances related to commonly

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prescribed medications in nondepressed elderly adults. The dopamine antagonist metoclopramide has been reported in several case reports to cause or exacerbate depressive symptoms. Although the magnitude of this effect is not well known, the general impression that dopamine antagonists cause affective toxicity suggests that this agent may be particularly well suited to examine the sensitivity of the methods for detecting affective toxicity. The hypothesis for this research is that measures of daily positive and negative affect are useful in detecting clinically significant affective toxicity in nondepressed elderly adults.

**Methods**

Strategies for recruitment and the inclusion/exclusion criteria of this study were similar to those for an earlier study involving repeated measures of cognitive performance on normal volunteers. Briefly, inclusion criteria for subjects included: age 55 years or older, medically stable (no hospitalizations or significant medication changes within the previous month), cognitively intact (no hospitalizations or significant medication changes within the previous month), cognitively intact (Brief orientation-Memory-Concentration Test score <3 and Mini-Mental State Examination score >26), and euthymic (a 20-item Center for Epidemiologic Studies Depression Scale score <12). Subjects were also required to have completed at least 8 years of school, learned English by age 6, and to have vision/hearing adequate to complete the assessments. Exclusion criteria included a history of central nervous system disease, alcohol or substance abuse within the past 5 years, mental retardation, schizophrenia, or bipolar or psychotic disorders. Subjects were also excluded if they were taking centrally acting medication(s) or medications capable of causing drug-related cognitive impairment, such as benzodiazepines, antihistamines, antidepressants, antipsychotics, antispasitics, lithium, opioid analgesics, seizure medications, and digoxin.

**Design**

The study was conducted as two double-blind, placebo-controlled randomized trials of metoclopramide (40 mg/day) administered daily for up to 5 weeks. Results from an initial study (n=10) comparing placebo and metoclopramide were pooled with results from a second study (n=12) that randomized subjects to placebo, metoclopramide, or sertraline. Subjects randomized to the sertraline arm were not included in this report. The experimental protocols were otherwise identical. After an initial screening examination and assessment for eligibility, each subject completed a daily affect diary for 1 week prior to randomization. At the time of randomization, subjects were started on either 10 mg/day of metoclopramide or placebo. The dose of metoclopramide was increased by 10 mg per week until the final dose of 40 mg/day was reached. Positive and negative affective state was measured during the placebo lead-in week and then daily for 5 weeks. Lawton’s positive and negative daily affective scale was used as the principal assessment instrument. This scale has discriminate validity for both minor and major depression among the elderly.

Subjects were seen weekly for safety and to monitor medication compliance. In addition to pill counts, riboflavin was added to the study medication to probe for medication adherence. Riboflavin is a nonpsychoactive vitamin that has been used in other investigations as a check on medication compliance and is visually detected in the subject’s urine by the presence of fluorescence under ultraviolet illumination.

**Statistical analyses**

For the analysis of drug effects, the random slope for positive and negative affect were compared between the placebo group and the metoclopramide group using a linear mixed-model analysis. The average baseline affective measure was controlled in the analysis. Baseline characteristics were compared using standard t-tests and chi-square analysis.

**Results**

The sample for the study consisted of 14 men and 8 women. There were few significant demographic differences between subjects in the metoclopramide (n=12) and placebo (n=10) groups. The mean age [SD] of subjects was 70.7 [5.2] (range 57 to 79) years (t=2.18, 20 df, P=0.030). The mean number of years of education [SD] was 14.7 [2.8] (range 10 to 20) (t=3.72, 20 df, P=0.001) and 59.1% of the subjects were married (χ²=0.006, 1 df, P=0.937). Subjects were cognitively intact: mean score [SD] on the Mini-Mental Status Examination was 28.9 [1.1]; (range 26 to 30) (t=2.21, 20 df, P=0.040), and were without significant depression: mean score [SD] on the (20-item) Center for Epidemiologic Studies - Depres-
sion Scale 4.2 [2.0]; (range 0 to 10) \((t=1.08, 20 \text{ df, } P=0.294)\). Compliance with recording of daily affect was 100% during trial participation and greater than 90% for pill compliance. Riboflavin results were consistent with pill counts in all but one subject (placebo) who tested negative for riboflavin on 3 of 5 occasions. Five subjects did not complete the protocol. Four subjects complained of lethargy/depression (3 on metoclopramide and 1 on placebo) and one subject had scheduling difficulties (placebo) \((\chi^2=0.078, 1 \text{ df, } P=0.781)\). All subjects completed an average of 28.6 (SD: 6.8) days on study medication with no difference between the two groups \((t=0.803, 20 \text{ df, } P=0.432)\).

The primary outcome measures were the change over time in measures of positive and negative daily affect. As shown in Table I, there were no significant differences in the slopes for the 2 groups for positive or negative affect. One subject (metoclopramide) experienced an 18% decrease in positive affect averaged over the last week of medication compared with baseline. No subjects experienced a significant increase in negative affect. Combining subjects who dropped out for psychiatric symptoms with the subjects who experienced at least a 15% decrease in positive affect resulted in 4 of 12 subjects in the metoclopramide versus 1 of 10 subjects in the placebo group experiencing significant affective toxicity \((\chi^2=1.691, 1 \text{ df, } P=0.193)\). Change in positive affect from baseline to the final week of study medication in the remaining subjects ranged from an increase of 14.7% to a decrease of 13.6% \((t=0.675, 16 \text{ df, } P=0.509)\).

**Discussion**

As the goal of this investigation is to provide the most sensitive methodology for detecting affective toxicity, it is reasonable to explore both toxicity in the broader sense that may affect all subjects who are exposed to a given medication, and also whether particular patients or patient groups are vulnerable to a given medication. In order to explore the more global toxicity issues, we were able to examine the aggregate slopes representing the effect of metoclopramide. The results from this analysis demonstrate that metoclopramide does not cause significant reproducible decrements in positive or negative affect in healthy older adults.

In order to enhance the sensitivity of detecting effects for individuals, one must consider combining effects that lead to study withdrawal with significant changes in individuals who are able to tolerate study completion. In this study, the finding that 4 subjects in the metoclopramide group and 1 in the placebo group withdrew from the study due to lethargy/depressive symptoms or experienced significant affective toxicity (33% of those on metoclopramide versus 10% on placebo), suggests that metoclopramide may cause significant affective toxicity in individual subjects. Indeed, though the small sample size of this study does not allow detection of a statistically significant effect, this difference is potentially very significant clinically. Using methods developed by Cohen, a study with 96 subjects would be predicted to reproduce this finding with a power of 80% (128 subjects for 90% power).16

In addition to the limitations apparent by the small sample size of each study group, there is the possibility that the measures employed were insensitive to measuring affective toxicity. Given that these data are highly suggestive of an effect, concern for this is dampened. In addition, combining study noncompletion information with results from patients who do complete the study, but have significant effects, introduces the need to develop methods for selecting appropriate parameters for defining the effect. Clearly, the choice of at least a 15% decrement in positive affect from baseline to completion is arbitrary and will need further exploration.

In summary, studies on admittedly small samples of older adults strongly suggest that certain healthy individuals may be particularly vulnerable to affective toxicity from metoclopramide. This supports the findings from the several published case reports and empha-

### Table I.

|                        | Slope       | Standard error | P-value for group differences |
|------------------------|-------------|----------------|------------------------------|
| **Positive affect**    | Metoclopramide | -0.0167        | 0.0173                       |
|                        | Placebo     | -0.0223        | 0.0198                       |
| **Negative affect**    | Metoclopramide | -0.0116        | 0.0129                       |
|                        | Placebo     | -0.0389        | 0.0149                       |

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sizes the need to consider affective changes in healthy as well as more debilitated adults. The findings reported also support the further development of this methodology for exploring behavioral consequences of other commonly prescribed medications.

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Exploracion de la toxicidad a nivel afectivo de medicamentos de prescripcion frecuente en sujetos de edad avanzada

Hay medicamentos que pueden tener efectos secundarios poco frecuentes y de poca gravedad, los que generalmente no son detectados a traves de la formacovigilancia. Los fármacos comúnmente prescritos en sujetos de edad avanzada pueden provocar potenciales consecuencias a nivel conductual como la depresión o la disfunción cognitiva. Este estudio unide los afectos diariamente, tanto los positivos como los negativos, como un método para detectar la “toxicidad afectiva”, clinicamente relevante, de medicamentos comúnmente prescritos en sujetos de edad avanzada. Los hallazgos de este estudio sugieren que la metoclopramida puede tener la potencialidad de causar cambios significativos en el afecto de sujetos de edad avanzada sanos. Esto puede sugerir que los adultos más vulnerables o más debilitados pueden tener un mayor riesgo de cambios en los afectos relacionados con este fármaco.

Exploration de la toxicité affective des médicaments couramment prescrits chez le sujet âgé

Les effets secondaires des médicaments qui sont peu fréquents ou peu sévères ne sont pas souvent détectés dans le cadre des procédures habituelles d’autorisation de mise sur le marché et de surveillance. Les effets comportementaux potentiels, tels la dépression ou les dysfonctionnements cognitifs, imputables aux médicaments couramment prescrits s’avèrent particulièrement intéressants. Dans cette étude, la mesure quotidienne de l’affect, tant positif que négatif, est évaluée en tant que méthode susceptible de déterminer la toxicité affective des médicaments couramment utilisés chez le sujet âgé, dès lors qu’elle est cliniquement significative. Les résultats obtenus suggèrent que le métoclopramide peut provoquer des modifications affectives significatives chez le sujet âgé en bonne santé. De ce fait, le risque d’un tel effet iatrogène pourrait être nettement plus élevé chez des malades, plus vulnérables ou à fortiori handicapés.