OBJECTIVE PSYCHOLOGICAL MEASUREMENT AND CLINICAL ASSESSMENT OF ANXIETY IN ADVERSE DRUG REACTIONS

Debra Ong, M.Sc.[1], Alpa Popat, M.Sc.[1], Sandra R. Knowles, B.Sc.Phm.[2,3], John S. Arrowood, Ph.D.[4], Neil H. Shear, M.D.[1,2,3,6], Karen E. Binkley, M.D.[3,5,6]
[1] Department of Pharmacology, University of Toronto, [2]Division of Clinical Pharmacology, Sunnybrook & Women's College Health Sciences Centre, [3]Drug Safety Clinic, Sunnybrook & Women's College Health Sciences Centre, [4]Law and Mental Health Program, Centre for Addiction and Mental Health, [5]Division of Clinical Immunology and Allergy, University of Toronto, [6]Department of Medicine, University of Toronto

ABSTRACT

Background
A confounding factor in the diagnosis of adverse drug reactions (ADRs) is the psychological state of the patient. Patients with underlying anxiety and related disorders may present with psychogenic reactions, which involve physiologic responses originating from psychological, rather than organic factors.

Objective
To examine the contribution of anxiety and related disorders to adverse drug events.

Methods
Participants from an adverse drug reaction clinic completed the Trauma Symptom Checklist-40 (TSC-40), a 40-item questionnaire consisting of six subscales: anxiety, depression, dissociation, sexual abuse trauma index (SATI), sexual problems, and sleep disturbance. Physicians assessed the likelihood that adverse events were due to anxiety or drug(s) by providing an anxiety score (0 to 10) and an ADR score (0 to 10), respectively, for each participant.

Results
Patients clinically assessed as having "high anxiety" (anxiety score 7-10 and ADR score 0-3; n = 11) scored higher than patients clinically assessed as having a "true ADR" (anxiety score 0-3 and ADR score 7-10; n = 19) on the TSC-40 total (P = 0.006) as well as anxiety (P = 0.012), depression (P = 0.007), and SATI subscales (P = 0.016).

Conclusion
This study is the first to use a validated psychological measurement to indicate that a substantial percentage of reported adverse drug events may in fact be a manifestation of underlying anxiety and/or related disorders. We suggest that mechanisms of symptom generation may be analogous to those operative in idiopathic environmental intolerance.

Keywords: adverse drug reaction, anxiety, idiopathic environmental intolerance, psychogenic reactions, trauma symptom checklist-40

Abbreviations and Acronyms: Adverse drug reaction (ADR), idiopathic environmental intolerance (IEI), multiple chemical sensitivity (MCS), posttraumatic stress disorder (PTSD), sexual abuse trauma index (SATI), trauma symptom checklist-40 (TSC-40)

An adverse drug reaction (ADR) is any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy.[1] ADRs represent an important issue in clinical practice. Epidemiologic studies have shown that ADRs occur in approximately 10-20% of all hospitalized patients[2] and that 3-6% of all hospital admissions are the result of ADRs.[3]

ADRs can be classified based broadly on predictability. Predictable ADRs, also known as Type A reactions, are related to the pharmacologic action of the drug and are usually dose-dependent. Predictable reactions include overdose or toxicity, side effects occurring at therapeutic doses, and drug interactions. Unpredictable ADRs or Type B reactions are not related to the pharmacologic action of the drug and are usually dose-independent.[4] Unpredictable reactions include intolerance or lower threshold for side effects, idiosyncratic reactions, allergic reactions, pseudoallergic reactions, and psychogenic reactions. Psychogenic reactions, which involve physiologic responses originating from psychological, rather than organic factors, are significant because drugs are inappropriately implicated in the adverse event, leading to unnecessary drug avoidance and suboptimal therapy.

Although many patients report an allergic reaction to local anesthetics, most of these reactions are not immune-mediated but are toxic, idiosyncratic or unrelated to the local anesthetic (e.g., operative trauma, epinephrine-related).[5] In fact, psychogenic reactions are commonly seen with the administration of local anaesthetics.[6] Many patients erroneously attribute anxiety-related symptoms to local anaesthetic allergy, and in avoiding these agents, are denied adequate pain control. Symptoms suggestive of an immunoglobulin-E (IgE)-mediated phenomenon (i.e., redness, swelling, itching) are absent and allergy skin tests to local anaesthetics are negative in these patients, supporting a psychogenic mechanism of symptom generation.

At our multidisciplinary Drug Safety Clinic, we frequently see patients who attribute symptoms to drug allergy that are likely anxiety-related. Patients with multiple chemical sensitivity syndrome (MCS), now called idiopathic environmental intolerance (IEI), are particularly likely to report anxiety-like symptoms after drug administration, which they attribute to their purported chemical intolerance.[7]

IEI has been extensively studied. While proponents of toxicogenic theories of IEI purport that symptoms such as lightheadedness, disorientation, breathlessness, and nausea are due to exposure to harmful environmental triggers, scientific evidence to support these claims is lacking.[7-9] Available evidence suggests that IEI represents a psychophysiologic response to otherwise non-noxious environmental stimuli.[7, 9-18.] Panic attacks, triggered by psychologically conditioned non-noxious stimuli, can explain many of the symptoms reported by IEI patients, though the clinical picture is modified by other factors such as somatizaton, cognitive processes (i.e., learning, suggestion, over-valued belief systems) and concurrent psychiatric and medical conditions.

Multiple studies have suggested that IEI is a manifestation of psychiatric or personality disorder.[19-22] High rates of childhood trauma and abuse have been reported among IEI patients,[23] which is thought to contribute to the development of anxiety-related symptomatology via neurobiologic mechanisms, analogous to that seen in posttraumatic stress disorder (PTSD).[7] Anxiety is associated with decreased tolerance of physically unpleasant sensations, and anxious persons are more self-aware and likely to notice trivial somatic symptoms.[7] Anxious persons tend to interpret such sensations as being alarming in nature (so-called "catastrophic thinking"), a tendency that has been demonstrated in IEI patients.[16] It is possible that such increased awareness and concern over minor side effects of medications contribute to poor tolerance of drugs by IEI and other anxious patients.

The Trauma Symptom Checklist-40 (TSC-40) is a research measure that evaluates symptomatology in adults arising from childhood or adult traumatic experiences.[24] It measures not only post-traumatic stress, but also other symptom clusters found in traumatized individuals. The TSC-40 has predictive validity with reference to a wide variety of traumatic experiences.[25-29]

We hypothesized that mechanisms of symptom generation, similar to those in IEI patients, including previous trauma leading to anxiety-related disorders and somatic hypervigilance, might be operative in some patients reporting anxiety-related symptoms after drug administration. To address this question, we assessed trauma-related symptoms using the TSC-40 in patients presenting to our clinic. TSC-40 scores of patients reporting symptoms consistent with anxiety were compared with scores of patients reporting symptoms consistent with "true" ADRs.

METHODS

Materials

Trauma Symptom Checklist-40 (TSC-40)

The TSC-40 is a self-reported research tool that evaluates symptomatology in adults associated with childhood or adult traumatic experiences.[24] The 40-item questionnaire uses a four-point rating scale to obtain a TSC-40 total score ranging from 0 to 120. The TSC-40 is comprised of six scored subscales: anxiety, depression, dissociation, sexual abuse trauma index (SATI), sexual problems, and sleep disturbance. Each symptom item is rated according to its frequency of occurrence over the prior two months, using a four point scale ranging from 0 ("never") to 3 ("often"). The TSC-40 requires approximately 10-15 minutes to complete, and can be scored in approximately 5-10 minutes. Studies using the TSC-40 indicate that it is a relatively reliable measure (subscale alphas typically range from 0.66 to 0.77, with alphas for the full scale averaging between 0.89 and 0.91). The TSC-40 and its predecessor, the TSC-33, have predictive validity with reference to a wide variety of traumatic experiences.[25, 30]

Anxiety Score

The anxiety score was a subjective physician assessment (i.e., based on clinical judgment) of the likelihood that the adverse drug event was due to anxiety. Scores, using a Likert scale, ranged from 0 (definitely not) to 10 (definitely).

ADR Score

The ADR score was a subjective physician assessment (i.e., based on clinical judgment) of the likelihood that the adverse drug event was due to a drug(s). Scores, using a Likert scale, ranged from 0 (definitely not) to 10 (definitely).

Procedures

Patients were randomly recruited from the Drug Safety Clinic at Sunnybrook & Women's College Health Sciences Centre (Toronto, Canada) from April 1999 to March 2000. A study investigator explained the nature and purpose of the research project to all subjects. Participants provided written informed consent and completed the TSC-40. Patients were then assessed as usual in consultation with a clinic physician, who specialized in Internal Medicine, Allergy and Immunology, Dermatology and/or Clinical Pharmacology. No clinical or structured interview for past or current history of anxiety or trauma was completed. Afterwards, treating physicians were asked to provide both an anxiety score and an ADR score for each adverse drug event in the participant's medical history. Eight clinic physicians partook in the study and all were blinded to the results of the TSC-40. This research protocol was approved by the Research Ethics Board at Sunnybrook & Women's College Health Sciences Centre.

Data Analysis

Data limited to patients aged 18-70 who experienced an adverse drug event within six months of their consultation were analyzed. A time limitation was placed with respect to the adverse drug event in order to maximize the correlation between the patient's state of mind at the time of the event and at the time of the TSC-40 completion.

Comparisons Between Groups

Patients were grouped based on physician assessments of anxiety and ADR. TSC-40 results were compared between patients with "high anxiety" (anxiety score 7-10 and ADR score 0-3) and patients with a "true ADR" (anxiety score 0-3 and ADR score 7-10), between males and females, and between "single reactors" (history of 1 adverse drug event) and "multiple reactors" (history of ≥2 adverse drug events) using the Mann-Whitney test.

Correlation Analyses
Physician assessments of anxiety and ADR were tested for correlation with the TSC-40 results using the Spearman test.

Inter-Rater Reliability
The inter-rater reliability for physician assessments of anxiety and ADR was calculated by the following method. Twenty study patients were randomly chosen and their adverse drug event history was written in a standardized case format. The eight participating physicians were asked to provide a subjective score for anxiety and ADR, in accordance with the definition used throughout the study. Kappa statistics were calculated as measures of agreement between physicians.

RESULTS

Patients
Of 162 patients recruited, 115 provided informed consent. Of these patients, 62 patients aged 18-70 who experienced an adverse drug event within six months of their consultation were enrolled in the study and completed all 40-items of the questionnaire. Demographics of the 62 patients are summarized in **Table 1**. Drugs that were implicated in the ADRs are shown in **Table 2**.

TSC-40 Scores
Descriptive statistics of the TSC-40 results, including total and subscale scores, are found in **Table 3.**

Physician Assessments
Patients were grouped based on anxiety and ADR scores: low (0-3), medium (4-6), and high (7-10). The numbers and percentages of patients in each group are shown in **Table 4**.

Comparisons Between Groups
Patients with "high anxiety" (n = 11) scored higher on the TSC-40 total (P = 0.006), anxiety subscale (P = 0.012), depression subscale (P = 0.007) and SATI subscale (P = 0.016) than patients with a "true ADR" (n = 19). No significant differences in scoring were found for the subscales measuring dissociation, sexual problems, and sleep disturbance. These comparisons are depicted in **Figure 1**. No differences in TSC-40 results were found between males (n = 17) and females (n = 45). Similarly, there were no differences between "single reactors" (n = 36) and "multiple reactors (n = 26) with respect to TSC-40 scores.

Correlation Analyses
Physician assessments of anxiety were positively correlated with TSC-40 total and subscale scores. A significant correlation was found between physician anxiety score and the depression subscale score (P = 0.043).

Between ADR scores and TSC-40 scores, a negative correlation was found. TSC-40 total (P = 0.014), anxiety subscale (P = 0.029), depression subscale (P = 0.007), and sleep disturbance subscale (P = 0.041) were significantly correlated with physician assessments of ADRs.

Inter-Rater Reliability
The level of agreement between physicians for ADR scores was moderate (k = 0.33). A slightly higher agreement between physicians was found for anxiety scores (k = 0.46).

TABLE 1
Relevant patient characteristics (n = 62).

GENDER		
Male	17	27.4%
Female	45	72.6%
AGE		
18-24	6	9.7%
25-29	6	9.7%
30-39	16	25.8%
40-49	17	27.4%
50-59	13	21.0%
60-65	1	1.6%
66-70	3	4.8%
DRUG REACTION		
Single Reactor		58%
Multiple Reactor		42%

Single reactor: history of 1 adverse drug event
Multiple reactor: history of two or more adverse drug events.

TABLE 2
Drugs Implicated in ADRs for 62 patients

Antibacterials		19
Penicillins	10	
Cephalosporins	3	
Macrolides	2	
Antibiotic Cream	1	
Fluoroquinolones	1	
Tetracyclines	1	
Sulfonamides	1	
NSAIDs		5
ASA		3
Lipid Lowering Agents		3
Local Anaesthetics		3
Anticonvulsants		2
Antiretroviral Agents		2
Antihypertensives		1
Corticosteroids		1
General Anaesthetics		1
Combination		13
Other		9

TABLE 3 Summary of TSC-40 scores (n = 62)

Subscale	**Mean (±SD)**	**Median**	**Range**	**Maximum Possible Score**
TSC-40† Total	26.5 ± 18.6	21.5	3 – 86	120
Anxiety	5.1 ± 3.9	4	0 – 18	24
Depression	6.7 ± 5.5	6	0 – 20	27
Dissociation	3.9 ± 3.4	3	0 – 14	18
SATI‡	3.5 ±3.4	2.5	0 – 16	21
Sexual Problems	3.1 ± 4.0	2	0 – 19	24
Sleep Disturbance	8.0 ± 4.5	8	0 – 18	18

† trauma symptom checklist-40 ‡ sexual abuse trauma index

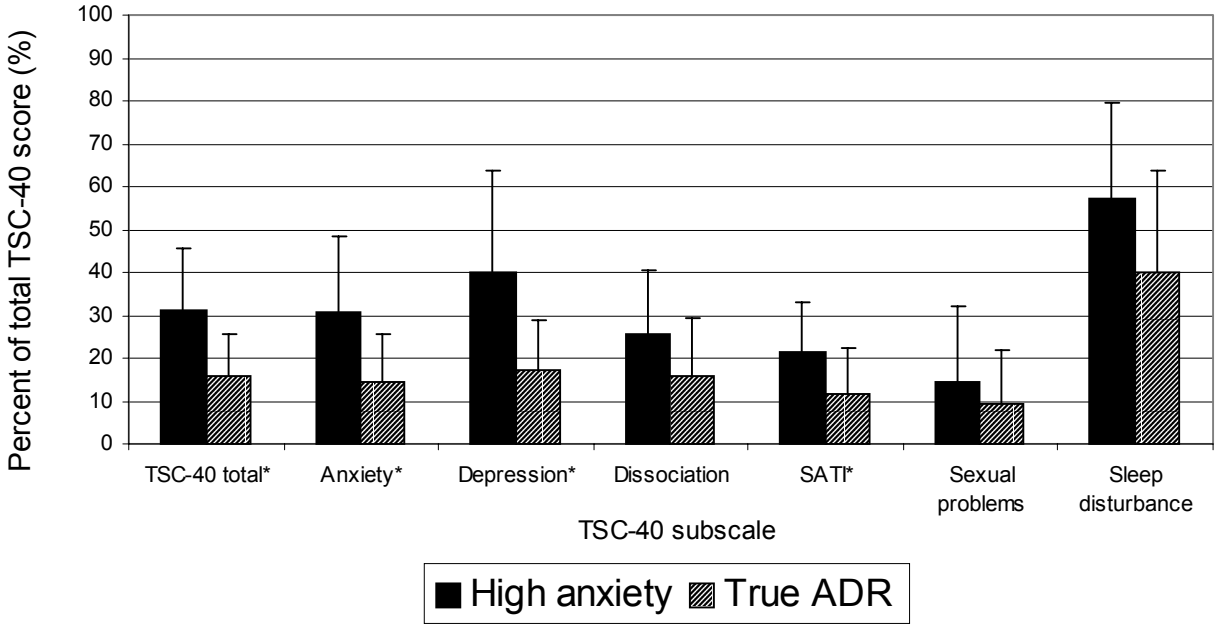
Can J Clin Pharmacol Vol11(1) Spring 2004:e8-e16; April 1, 2004

TABLE 4 Summary of physician scores for most recent adverse drug event (< 6 months).

	Anxiety Score		ADR† Score	
Group	**Number**	**Percentage**	**Number**	**Percentage**
Low (0-3)	36	58.1 %	27	43.5 %
Medium (4-6)	11	17.7 %	7	11.3 %
High (7-10)	15	24.2 %	28	45.2 %
Total	62	100.0%	62	100.0%

† adverse drug reaction

Figure 1 TSC-40 results among "high anxiety" (n = 11) and "true ADR" (n = 19) groups.



SATI: sexual abuse trauma index
* significant difference (P<0.05)

DISCUSSION

In this study, we found that trauma-related symptoms, as measured by a standardized questionnaire (the TSC-40), were more prevalent in patients suspected as having anxiety-related symptoms after drug administration, than in a control group of patients with "true", non-anxiety-related ADRs. Our data revealed significant differences between "high anxiety" and "true ADR" groups for the TSC-40 total as well as anxiety, depression, and SATI subscales. These results support the clinical impression that psychogenic reactions are not uncommon among patients referred for evaluation of ADRs and that these reactions complicate the diagnosis of true reactions to drugs.

The TSC-40 was used to assess anxiety and trauma-related symptoms because it is easily administered, enables quantification of subscales such as anxiety and depression, evaluates symptomatology arising from childhood or adult traumatic experiences, and measures post-traumatic stress and other symptom clusters found in traumatized individuals. The TSC-40 is a research measure only. While other, more detailed measures are available, we chose the TSC-40 for its brevity so as not to deter patient participation.

Objective scales measuring causality of ADRs are available,[31] however, we did not feel that they were appropriate for our purposes. It was reasoned that the use of instruments such as the Naranjo adverse reaction probability scale would have inappropriately placed the majority of anxiety-related cases in the "possible" or "probable" category of causation, due to the temporal correlation of anxiety symptoms with drug administration. We therefore designed a novel method for physicians to provide subjective assessments for anxiety and ADR. Goals in our analysis were to correlate the objective measurements and subjective assessments utilized in the study and to assess the inter-rater reliability of the physician assessments.

Our findings indicated that the physician assessments of anxiety and drug(s) as causal factors for adverse drug events were consistent with the psychological states of patients as measured by the TSC-40. Inter-rater reliability was found to be moderate to low, which may reflect true disagreements in physician scoring or result from a less than ideal method of calculation. Although we would have preferred to use actual cases in the clinic for assessing rater agreement, this was not logistically possible, and thus standardized written cases were deemed sufficient for our purposes.

Our study was prompted by the similarity of suspected psychogenic reactions after drug administration to "reactions" reported in IEI, as well as the coexistence of the two conditions in some patients. Psychogenic mechanisms best explain symptom generation in IEI.[7, 9-15, 17, 18]

In several studies, a high prevalence of psychiatric and/or psychological conditions, particularly anxiety, depression, and somatoform disorders have been reported in patients with IEI.[19-22] Childhood trauma, also common in this group, is thought to predispose individuals to anxiety and related disorders via neurobiologic mechanisms, analogous to those operative in PSTD, including activation of the stress response and deleterious effects on the limbic system.[7.23]

Our results, showing that patients with anxiety-related symptoms after drug administration have higher trauma-related symptoms, are consistent with the concept that mechanisms of symptom generation may be similar to those in IEI. Increased somatic vigilance, with a tendency to catastrophically interpret minor physical sensations, seen in anxious and IEI patients,[16] may contribute to symptom reporting and poor tolerance of medications in these groups. Female gender is associated with individual self-reports of being "allergic or unusually sensitive to everyday chemicals."[32] Consistent with this finding is the fact that close to 75% of patients seen at the Drug Safety Clinic are female.[33] Thus, it would be expected that females would score higher than males on the TSC-40; however, our analysis revealed no difference based on gender.

In IEI, patients describe symptoms after multiple triggers, and therefore, it might be expected that patients presenting with a history of multiple adverse drug events would score higher on the TSC-40 than those presenting with only a single adverse drug event. Indeed, in our patient sample, mean TSC-40 scores were higher for

"multiple reactors" than "single reactors", with the exception of the sleep disturbance subscale; however these differences were not found to be statistically significant.

In summary, this study was designed to better recognize and understand that adverse drug events may be influenced by anxiety and related disorders. Our results suggest that psychogenic reactions after drug administration are common. Among our patient population, there was a distinct group of patients who were highly anxious and presented with adverse events unlikely to be drug-related. Moreover, this group could be distinguished from the group of patients who presented with low anxiety and a convincing history of an ADR. It is possible that symptom generation in anxious patients occurs by mechanisms analogous to those operative in IEI.

This is the first study, to our knowledge, to use a validated questionnaire to suggest that some reported adverse drug events may in fact be a manifestation of underlying anxiety and/or related psychological disorders. These findings have significant implications for the diagnosis and management of adverse drug events.

ACKNOWLEDGEMENTS

The authors would like to thank Scott Walker for his assistance with statistical methods and the physicians at the Drug Safety Clinic for their participation and support in the study.

REFERENCES

1. Karch F, Lasagna L. Adverse drug reactions. JAMA 1975;234:1236-41.
2. Miller R. Drug surveillance utilizing epidemiologic methods. A report form the Boston Collaborative Drug Surveillance Program. Am J Hosp Pharm 1973;30:584-92.
3. Lakshmanan M, Hershey C, Breslau D. Hospital admissions caused by iatrogenic disease. Arch Intern Med 1986;146:1931-4.
4. Edwards I, Aronson J. Adverse drug reactions: definitions, diagnosis and management. Lancet 2000;356:1255-9.
5. Haber J, Knowles S, Knight A. Allergy to local anaesthetics. Allergy Asthma 2000;12:27-34.
6. Fiset L, Milgrom P, Weinstein P, Getz T, Glassman P. Psychophysiological responses to dental injections. J Am Dent Assoc 1985;111:578-83.
7. Staudenmayer H. Environmental illness: myth and reality. Boca Raton: Lewis Publishers; 1999.
8. American Academy of Allergy Asthma and Immunology. Idiopathic, enironmental intolerances (position statement). J Allergy Clin Immunol 1999;103:36-40.
9. Sparks P. Idiopathic environmental intolerances: overview. In: Sparks P, editor. Multiple Chemical Sensitivity/Idiopathic Environmental Intolerance. Philadelphia: Hanley & Belfus; 2000. p. 497-510.
10. Binkley K, King N, Poonai N, Seeman P, Ulpian C, Kennedy J. Idiopathic environmental intolerance: increased prevalence of panic disorder-associated cholecystokinin B receptor allele seven. J Allergy Clin Immunol 2001;107:887-90.
11. Giardino N, Lehrer P. Behavioral conditioning and idiopathic environmental intolerance. In: Sparks P, editor. Multiple Chemical Sensitivity/Idiopathic Environmental Intolerance. Philadelphia: Hanley & Belfus; 2000. p. 519-28.
12. Leznoff A, Binkley K. Idiopathic environmental intolerances: results of challenge studies. In: Sparks P, editor. Multiple Chemical Sensitivity/Idiopathic Environmental Intolerance. Philadelphia: Hanley & Belfus; 2000. p. 529-37.
13. Dalton P, Hummel T. Chemosensor function and response in idiopathic environmental intolerance. In: Sparks P, editor. Multiple Chemical Sensitivity/Idiopathic ENvironmental Intolerance. Philadelphia: Hanley & Belfus; 2000. p. 539-56.
14. Black D. The relationship of mental disorders and idiopathic environmental intolerance. In: Sparks P, editor. Multiple Chemical Sensitivity/Idiopathic environmental Intolerance. Philadelphia: Hanley & Belfus; 2000. p. 557-70.
15. Staudenmayer H. Psychological treatmnet of psychogenic idiopathic environmental intolerance. In: Sparks P, editor. Multiple Chemical Sensitivity/Idiopathic Environmental Intolerance. Philadelphia: Hanley & Belfus; 2000. p. 627-46.
16. Poonai N, Antony M, Binkley K, et al. Carbon dioxide inhalation challenges in idiopathic environmental intolerance. J Allergy Clin Immunol 2000;105:358-63.
17. Leznoff A. Provocative challenges in patients with multiple chemical sensitivity. J Allergy Clin Immunol 1997;99:438-42.
18. Binkley K, Kutcher S. Panic response to sodium lactate infusion in patients with multiple chemical sensitivity syndrome. J Allergy Clin Immunol 1997;99:570-4.
19. Staudenmayer H, Camazine M. Sensing type personality, projection and universal allergic reactivity. J Psychol Type 1989;18:59-62.
20. Black D, Rathe A, Goldstein R. Environmental illness: a controlled study of 26 subjects with "20th

century disease". JAMA 1990;264:3166-70.

21. Rosenberg S, Freedman M, Schmaling K, Rose C. Personality styles of patients asserting environmental illness. J Occup Med 1990;32:678-81.
22. Selner J, Staudenmayer H. Neuropsychophysiologic observations in patients presenting with environmental illness. Toxicol In Health 1992;8:145-55.
23. Staudenmayer H, Selner M, Selner J. Adult sequelae of childhood abuse presenting as environmental illness. Ann Allergy 1993;711:538-46.
24. Briere J, Runtz M. The trauma symptom checklist (TSC-33): early data on a new scale. J Interpersonal Violence 1989;4:151-63.
25. Elliott D, Briere J. Sexual abuse trauma among professional women: validating the Trauma Symptom Checklist-40 (TSC-40). Child Abuse Negl 1992;16:391-8.
26. Gold S, Milan L, Mayall A, Johnson A. A cross-validation study of the Trauma Symptom Checklist: the role of mediating variables. J Interpersonal Violence 1994;9:12-16.
27. Zlotnick C, Shear M, Begin A, Pearlstein T, SImpson E, Costello E. The validation of the Trauma Symtpom Checklist-40 (TSC-40) in a sample of inpatinets. Child Abuse Negl 1996;20:503-10.
28. Whiffen V, Benazon N, Bradshaw C. Discriminant validity of the TSC-40 in an outpatient setting. Child Abuse Negl 1997;21:107-15.
29. Gold J, Cardena E. Convergent validity of three posttraumatic symptoms inventories among adult sexual abuse survivors. J Trauma Stress 1998;11:173-80.
30. Briere J. Psychometric review of the Trauma Symptom Checklist-40. In: Stamm B, editor. Measurement of stress, trauma, and adaptation. Lutherville: Sidran Press; 1996.
31. Naranjo C, U, Sellers E, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
32. Kreutzer R, Neutra R, Lashuay N. Prevalence of people reporting sensitivities to chemicals in a population-based survey. Am J Epidemiol 1999;150:1-12.
33. Tran C, Knowles S, Liu B, NH. Gender differences in adverse drug reactions. J Clin Pharmacol 1998;38:1003-9.