

Depressive Symptoms Attributable to Medication Exposure in a Medical Inpatient Population

Scott B Patten, MD, PhD¹, Jeanne VA Williams, BA², Edgar J Love, MD, PhD³

Objective: Exposure to certain drugs—angiotensin-converting enzyme inhibitors, β -blockers, calcium channel blockers, corticosteroids, H₂ blockers, and sedative hypnotics—may be associated with an increased risk of depression. These drugs are commonly used in inpatient medical therapeutics. Since population attributable risk (PAR) is generally related both to strength of association and to the frequency of exposure to a risk factor, the PAR of depressive symptoms associated with these drug exposures is potentially high. The objective of this study was to estimate the depressive symptoms population attributable risk percent (PAR%) in a medical inpatient population.

Methods: A prospective cohort design was used in this study. Nondepressed, nondrug-exposed subjects (N = 178) were selected from a series of 369 newly admitted medical inpatients at the Calgary General Hospital. Eighty-six of these 178 subjects were prescribed one of the drugs in question, forming an exposed cohort. The remaining subjects formed a nonexposed cohort. Depressive symptoms and associated psychosocial variables were measured in both subgroups during the hospital stay.

Results: Seventeen of the 86 exposed subjects and 5 of the 92 nonexposed subjects developed incident depressive symptoms during their stay in hospital. The PAR% associated with drug exposure (56.0%) exceeded that associated with poverty (17.9%) or unemployment (21.7%).

Conclusions: Drug exposures may have a sizeable impact on the incidence of depressive symptoms in medical inpatient populations.

(Can J Psychiatry 1996;41:651–654)

Key Words: depressive symptoms, substance-induced depression, population attributable risk percent, adverse drug reactions

Numerous medications have been implicated in causing depression as a side effect, although literature documenting these purported associations is poorly developed (1). Depressive symptoms and depressive disorders are common among medical inpatients (2–4). Medical inpatients are frequently exposed to many of the medications that have been

implicated in causing depression. It is plausible that medication exposures are an important determinant of depressive symptoms in this population.

In epidemiology, parameters have been developed specifically to estimate the impact of a risk factor in a population. These measures of *impact* differ from the measures of *association*, which are more frequently utilized in epidemiological research. The latter set of measures includes the prevalence ratio, odds ratio, and risk ratio. These measures reflect the degree of elevation in risk associated with exposure to a risk factor. Measures of impact, by contrast, tend to be based on differences between crude or adjusted incidence and prevalence rates, thereby comparing risks on an additive, rather than multiplicative scale. Attributable risk is one such parameter: it reflects the amount of disease or other health-related outcome that is attributable to the risk factor exposure. A related measure is the PAR%, which estimates the impact of a risk factor on a population by describing the proportion

Manuscript received February 1996, revised June 1996.

¹Population Health Investigator, Alberta Heritage Foundation for Medical Research; Assistant Professor, Departments of Community Health Sciences and Psychiatry, Faculty of Medicine, The University of Calgary, Calgary, Alberta.

²Research Assistant, Department of Psychiatry, Calgary Regional Health Association, Bow Valley Site (Calgary General Hospital), Calgary, Alberta.

³Professor, Department of Community Health Sciences, Faculty of Medicine, The University of Calgary, Calgary, Alberta.

Address reprint requests to: Dr SB Patten, Faculty of Medicine, The University of Calgary, 3330 Hospital Drive NW, Calgary, AB T2N 4N1

Table 1
PAR for Incident Depressive Symptoms Associated with Medication Exposure, Poverty, and Unemployment

Exposure	n/N (%)			PAR%
	Total Incidence in Exposed and Nonexposed Cohorts	Incidence in the Exposed Cohort	Incidence in the Nonexposed Cohort	
Drug exposure (n = 86)	22/178 (12.4)	17/86 (19.8)	5/92 (5.4)	56.0
Poverty (n = 20)	22/175 ^a (12.6)	6/20 (30.0)	16/155 (10.3)	17.9
Unemployment (n = 23)	22/178 (12.4)	7/23 (30.4)	15/155 (9.7)	21.7

^aMissing data on income for 3 subjects.

(expressed as a percentage) of cases in the population attributable to risk factor exposure.

We have recently conducted a prospective cohort study in which we determined the incidence of depressive symptoms in 2 cohorts of nondepressed medical inpatients. In this paper, we use the incidence data to estimate the PAR for medication exposures in the medical inpatient population.

Methods

Data collection procedures have been described in detail in a previous publication (5). The study subjects were selected from a series of 369 newly admitted medical inpatients. Of these, 178 patients who were not already depressed, not severely cognitively impaired, and not exposed to the drugs of interest were identified as potential subjects. These subjects were subsequently divided into exposed and nonexposed cohorts, depending on whether or not they were prescribed one of the drugs of interest while they were in hospital. The exposed cohort consisted of 86 patients newly exposed to one or more of 6 drugs or drug classes that have been implicated in the literature as possible risk factors for depression: angiotensin-converting enzyme inhibitors, β -blockers, calcium channel blockers, corticosteroids, H₂ blockers, and sedative hypnotics. Although many drugs have been implicated as risk factors for depression, some of these drugs are very rarely used either because they have been replaced by other drugs (as in the case of reserpine and, to a lesser extent, digoxin), or because indications for their use are uncommon (as, for example, interferon- α). The 6 drug classes mentioned were selected, therefore, based on a literature review evaluating epidemiological evidence of an association (1) and on an expectation that these drugs would be utilized fairly frequently in the study setting.

The nonexposed cohort consisted of 92 subjects who were not exposed to any of these medications. All subjects were consenting inpatients newly admitted to one of the medical inpatient units at the Bow Valley Centre of the Calgary General Hospital. All subjects were nondepressed, as confirmed by a score of less than 16 on a modified version of the Center for Epidemiological Studies Depression rating scale

(CES-D), and were not exposed to the medications of interest at the time of admission to hospital. A number of psychosocial risk factors for depressive symptoms were also measured. Income below the poverty line was determined using Statistics Canada definitions (total family income adjusted for family size and place of residence). The subjects' highest grade attained at school and employment status were determined by questionnaire. Respondents were able to classify their employment status into 5 categories: employed, unemployed, retired, full-time homemaker, or student. Incident depressive symptoms were identified by repeat administration of the modified CES-D every fifth day for as long as the subject was in hospital. If the subject was in hospital for less than 5 days, the modified CES-D was completed over the

$$PAR\% = \left(\frac{I_T - I_{NE}}{I_T} \right) \times 100$$

phone.

PAR% was calculated using a standard formula:

where I_T was the incidence rate in the total sample (consisting of exposed and nonexposed cohorts) and I_{NE} was the incidence rate in the nonexposed cohort. An assumption underlying this calculation is that the difference between these 2 incidence rates reflects the impact of the risk factor in the study population.

Results

Seventeen (19.8%) of the 86 exposed subjects and 5 (5.4%) of the 92 nonexposed subjects developed incident depressive symptoms during their stay in hospital. Hence the total incidence rate was 22/178 or 12.4%. There were missing data about income for 3 subjects (1.7%). Of the remaining 175 subjects, 20 (11.4%) were below the poverty line. Twenty-three (12.9%) of the subjects were unemployed. The crude relative risk (RR) for drug exposure (which is the ratio of the 2 incidence rates above) was 3.64 (95% confidence interval [CI] = 1.4 to 9.3), which resembled the relative risks associated with poverty (RR = 2.91, 95% CI = 1.29 to 6.56) and unemployment (RR = 3.14, 95% CI = 1.44 to 6.88).

Calculation of PAR% for drug exposure, as well as for the 2 psychosocial variables, is displayed in Table I.

The PAR% associated with drug exposure (56.0%) exceeded that associated with poverty (17.9%) or unemployment (21.7%). The reason was not that drug exposures were more strongly associated with depression, but rather that the frequency of exposure to the drugs exceeded that of the psychosocial variables.

Conclusions

This analysis suggests that drug exposures may have a considerable impact on the incidence of depressive symptoms in the medical inpatient population. In community populations, where the frequency of exposure to drugs is much lower than in the medical inpatient setting, the PAR% associated with drug exposure is expected to be much lower.

It should also be emphasized that the data collected in this project pertain to depressive symptoms and may have no direct relevance to the etiology of depressive disorders in this population. Depressive symptoms are only an approximate indicator of depressive disorders. Myers and Weissman (6) reported a false-positive rate of 6.1% and a false-negative rate of 36.4% for the CES-D in relation to Research Diagnostic Criteria for major depression in a community sample. In an early CES-D validation study (7), Weissman and others reported a 99% sensitivity in a sample of "acute depressives." The scale was not highly specific, however, in other psychiatric patient groups. The data reported in this study are best interpreted with reference to depressive symptoms rather than depressive disorders.

In epidemiology, measures of impact are usually calculated to evaluate the potential benefits of prevention programs. For example, PAR% is frequently used to estimate the percentage of disease within a population that could be prevented if exposure to the risk factor were removed by a preventive program. Since discontinuing exposure to these drugs is not a preventive option in the medical inpatient setting, the PAR% reported here has no direct implications for primary prevention. It may, however, have clinical implications for mental health programs that offer secondary prevention in the medical inpatient setting. Counselling designed to provide support for patients developing depressive symptoms in the medical inpatient setting should not focus exclusively on helping patients cope with the psychological and social challenges associated with their illnesses. Indeed, counselling may benefit from an educational component,

including the possibility that drugs can contribute to depressive symptomatology and that, with withdrawal of the medications, the depressive symptoms may abate. Awareness that medication exposures may contribute to feelings such as hopelessness, lethargy, pessimism, guilt, and despair may help some patients struggling to keep these experiences in perspective during a difficult hospitalization.

Clinical Implications

- Depressive symptoms have a biopsychosocial etiology in the medical inpatient population.
- Certain medications may be biological risk factors for depressive symptoms.
- Certain medications may significantly affect the incidence of depressive symptoms in the medical inpatient population.

Limitations

- The study evaluated the epidemiology of depressive symptoms rather than depressive disorders.
- Depressive symptoms are often not indicative of clinically significant depressive disorders.
- The duration of follow-up in this study was brief.

Acknowledgements

This study was supported by grants from the Canadian Psychiatric Research Foundation, Alberta Heritage Foundation for Medical Research, and the Calgary General Hospital.

References

1. Patten SB, Love EJ. Drug-induced depression, incidence avoidance and management. *Drug Saf* 1994;10:203-19.
2. Hengeveld MW, Ancion FAJM, Rooijmans HGM. Prevalence and recognition of depressive disorders in general medical inpatients. *Int J Psychiatry Med* 1987; 17:341-9.
3. Barnes GE, Prosen H. Depression in Canadian general practice attenders. *Can J Psychiatry* 1984;29:2-10.
4. Wells KB, Hays RD, Burnam MA, Rogers W, Greenfield S, Ware JE Jr. Detection of depressive disorder for patients receiving prepaid or fee-for-service care: results from the medical outcomes study. *JAMA* 1989;262:3298-302.
5. Patten SB, Williams JVA, Love EJ. Self-reported depressive symptoms following treatment with corticosteroids and sedative-hypnotics. *Int J Psychiatry Med* 1996;26:15-24.
6. Myers JK, Weissman MM. Use of a self-report symptom scale to detect depression in a community sample. *Am J Psychiatry* 1980;137:1081-4.
7. Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. *Am J Epidemiol* 1977;106:203-14.

Résumé

Objectif : L'exposition à certains médicaments — les inhibiteurs de l'enzyme de conversion de l'angiotensine, les β -bloquants, les inhibiteurs calciques, les corticostéroïdes, les inhibiteurs des récepteurs H₂ et les hypnotiques — peut être liée à un risque accru de dépression. Ces médicaments sont couramment utilisés pour traiter des malades hospitalisés. Puisque la fraction étiologique du risque (FER) est généralement liée au degré d'associa-

tion et à la fréquence de l'exposition à un facteur de risque, la FER des symptômes de dépression liés à l'exposition à ces médicaments est potentiellement élevée. Cette étude visait à évaluer le pourcentage de la fraction étiologique du risque (FER %) des symptômes de dépression dans une population de malades hospitalisés.

Méthodes : Dans cette étude, on a utilisé un plan à cohortes prospectives. Des sujets non déprimés et non exposés aux médicaments ($N = 178$) ont été choisis à partir d'une série de 369 malades nouvellement hospitalisés au Calgary General Hospital. Un des médicaments en question a été prescrit à 86 de ces 178 sujets, formant une cohorte exposée. Les autres sujets formaient une cohorte non exposée. Au cours de l'hospitalisation, on a mesuré les symptômes de dépression et les variables psychosociales connexes des 2 sous-groupes.

Résultats : Pendant leur hospitalisation, 17 des 86 sujets exposés et 5 des 92 sujets non exposés ont manifesté des symptômes rattachés à la dépression. Le pourcentage de la FER lié à l'exposition aux médicaments (56,0 %) dépassait les pourcentages liés à la pauvreté (17,9 %) ou au chômage (21,7 %).

Conclusions : L'exposition aux médicaments peut avoir une influence appréciable sur l'incidence des symptômes de dépression des populations de malades hospitalisés.