Current Prescription Patterns and Safety Profile of Irreversible Monoamine Oxidase Inhibitors: A Population-Based Cohort Study of Older Adults

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Objective: To determine the prescription pattern and safety profile for irreversible monoamine oxidase inhibitors (MAOIs) in older adults over the past decade.

Method: A population-based observational cohort study of older adults was conducted from January 1, 1997, to April 14, 2007, utilizing large administrative health care databases in Ontario, Canada. We examined the prevalence and incidence of irreversible MAOI use, as well as the frequency of coprescribing of MAOIs with contraindicated medications such as serotonergic and sympathomimetic drugs. We reviewed the most responsible diagnosis of emergency department (ED) visits and acute care admissions to assess for serious adverse events that may occur during MAOI treatment (ie, serotonin syndrome and hypertensive crisis).

Results: Over a 10-year period, there were 348 new users of irreversible MAOIs. The majority of patients showed a previous treatment pattern consistent with recurrent major depressive disorder, including prior use of antidepressant treatment and electroconvulsive therapy. The yearly incidence of MAOI prescriptions remained low and decreased from a rate of 3.1/100,000 to 1.4/100,000. Concomitant exposure to at least 1 serotonergic drug occurred in 18.1% of patients treated with an MAOI. No ED visits or acute care admissions for serotonin syndrome or hypertensive crisis were identified.

Conclusions: The low prescription rate of MAOIs is not consistent with the continued recommendation of MAOIs by expert opinion leaders and consensus guidelines for use in atypical depression and treatment-refractory depression. While their use appeared safe, heightened awareness of the potential risk of concomitant use of serotonergic agents is necessary. Relative underuse of the MAOIs for a significant subgroup of depressed patients with atypical and treatment-refractory depression remains a concern.

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Irreversible monoamine oxidase inhibitors (MAOIs), as a class of antidepressants, were first discovered to have mood elevating properties among tubercular patients in the early 1950s, even before the widespread use of tricyclic antidepressants.[1] Tranylcypromine and phenelzine, both irreversible MAOIs, were widely prescribed, often in combination with phenothiazines (eg, the tranylcypromine and trifluoperazine combination Parstelin) until the mid-1960s when concerns about hypertensive crises associated with tyramine-containing foods became apparent.[2] With the emerging medico-legal consciousness, these drugs quickly began to fall out of favor. However, their use has persisted at low levels and has been advocated as a preferred treatment option for "atypical" depression[3,4] and treatment-refractory depression in mixed-age as well as older adults.[5,6]

A recent evidence-based review suggests that the MAOIs are indeed effective for major depressive disorder of various clinical presentations.[7] The safety profile concern, including the risk of hypertensive crisis and serotonin syndrome associated with drug interactions and specific food groups, has severely restricted their use. This has been compounded by the fact that irreversible MAOIs are not promoted by any major pharmaceutical company. Much work on the revision of the MAOI diet[8,9] has made it easier for patients to use irreversible MAOIs such as tranylcypromine and phenelzine by providing a balance of safety with practical concerns. The emergence of an MAO-A inhibitor (moclobemide)[10] and, more recently, a transdermally delivered MAO-B inhibitor (selegiline)[11] has also rekindled interest in MAOIs as a class of antidepressants. However, neither selegiline nor moclobemide has been shown to be effective for atypical or treatment-refractory depression.

Major consensus guidelines, including the American Psychiatric Association[12] and Canadian Network for Mood and Anxiety Treatments[13] (CANMAT) continue to list

For Clinical Use

- Monoamine oxidase inhibitors (MAOIs) continue to be recommended by official treatment guidelines for a variety of depressive conditions but especially for refractory depression, atypical depression, and bipolar depression.
- Clinicians must be especially vigilant with MAOIs to avoid interactions with serotonergic and adrenergic drugs.
- The use of updated dietary guidelines and attention to drug interactions create safe conditions for this underutilized class of antidepressants.

MAOIs as a second- or third-line option for treatment-refractory depression or atypical depression. MAOIs are recommended for treatment of depression in bipolar disorders in the consensus guidelines of the American Psychiatric Association,[12] CANMAT,[13] the Texas Algorithm project,[14] and the British Association for Psychopharmacology.[15] Despite safety concerns, including potentially serious food and drug interactions and a lack of industry promotion, irreversible MAOIs continue to be a treatment recommendation by expert clinicians.

METHOD

Study Design

We conducted a population-based observational cohort study utilizing large administrative health databases in Ontario to determine the prescription pattern and safety of irreversible MAOIs over the past decade. We reviewed the most responsible diagnosis of emergency department (ED) visits and acute care admissions to assess serious adverse events such as serotonin syndrome and hypertensive crisis. We tracked the incidence and prevalence of irreversible MAOI use (phenelzine and tranylcypromine) in a population of over 1.4 million older adults in Ontario over the past decade, 1997–2007. In addition, we examined the prescription of irreversible MAOIs concomitantly with interacting medications. We restricted our study to older adults over 65 years of age because there is no comparable drug database for younger adults in Ontario. We did not examine reversible MAO-A or MAO-B inhibitors because of the lack of evidence for their use in treatment-resistant or atypical depressions.

Data Sources

Ontario residents aged 65 years and older have universal access to physician services, hospital care, and selected prescription drugs. We used 5 population-based administrative health care databases that were linked using encrypted unique identifiers. The Ontario Drug Benefit (ODB) database includes government funded prescriptions dispensed to Ontario residents aged 65 years and older. Both irreversible monoamine oxidase inhibitors, phenelzine and tranylcypromine, were available on the Ontario drug formulary during the entire study period. The Ontario Health Insurance Plan (OHIP) includes data on all inpatient and outpatient physician billing claims. We obtained information on hospital admissions and ED visits from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database and the National Ambulatory Care Reporting System (NACRS), respectively. The Registered Persons database provided basic demographics and vital statistics.

The study was approved by the Ethics Review Board of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

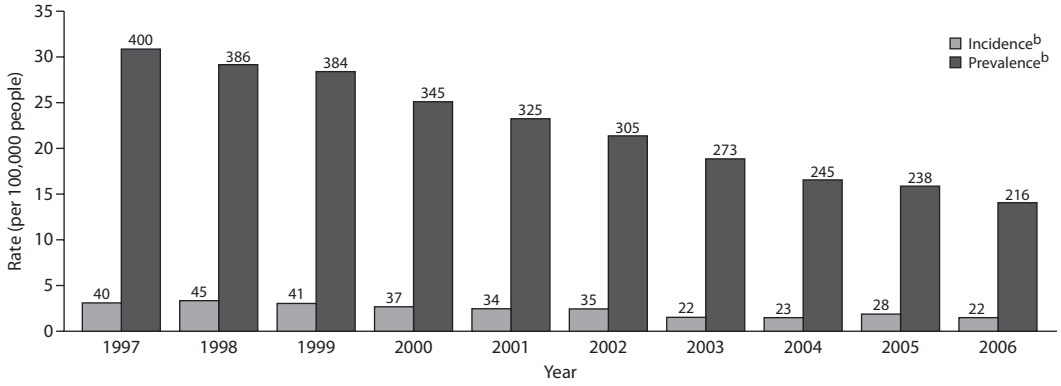
Incidence and Prevalence of MAOI Use

We identified all the adults aged 66 years and older who were dispensed an irreversible MAOI (phenelzine or tranylcypromine) between January 1, 1997, and December 31, 2006. We restricted the observations to patients aged 66 years or older in order to enable us to examine their drug use in the prior year. Incident use (new users) of irreversible MAOIs was defined as those patients who were not prescribed any irreversible or reversible (moclobemide) MAOIs in the previous year. Patients could have been included more than once in different years throughout the decade if they met all the inclusion criteria.

Irreversible MAOIs and Interacting Drugs

The frequency of coprescribing of MAOIs with contraindicated medications was examined. This cohort consisted of new continuous users of an irreversible MAOI who were aged 67 years and older, between April 1, 1997, and March 31, 2007. A new user was defined as having no prescription for irreversible MAOIs (phenelzine or tranylcypromine) in the 1 year prior to cohort entry, and the first prescription for an irreversible MAOI served as the study index date. We included only patients aged 67 years and older in order to be able to look back for a period of 2 years to examine previous drug use. Using the "days supply" field in the ODB, we defined patients as continuous MAOI users as long as they filled another MAOI prescription within a period of 120% of the days supply of the previous prescription. This allowed for a "grace" period of 20% days supplied to refill the prescription following the presumed end date of the initial prescription. We described baseline treatment characteristics of the MAOI users' cohort using OHIP physician fee

Figure 1. Incidence and Prevalence Rates[a] of MAOI Users



[a]Statistics Canada Ontario Population estimates (age ≥ 66 y).
[b]Numbers above bars indicate the absolute number of patients.
Abbreviation: MAOI = monoamine oxidase inhibitor.

claims to assess use of electroconvulsive therapy (ECT) in the 5 years prior to cohort entry and ODB for prior antidepressant use in the previous 2 years. We also described how many of the new users saw a psychiatrist in the year prior to cohort entry. As a measure of medical comorbidity,[16] we examined exposure to drugs in the year prior to cohort entry based on the number of unique drug identification numbers (DINs) dispensed.

We identified a list of contraindicated medications that should be avoided in combination with irreversible MAOIs (Appendix 1).[17] These interacting drugs were categorized as either serotonergic drugs (eg, serotonin reuptake inhibitors), which can, in combination with MAOIs, cause serotonin syndrome, or sympathomimetics (eg, methylphenidate, amphetamine), which may produce severe hypertension, seizures, arrhythmias, and death when combined with MAOIs. It is recommended that at least 14 days pass after MAOIs are discontinued before prescribing these serotonergic and sympathomimetic drugs. We followed patients while on continuous MAOI use and examined how many were dispensed an interacting drug while on treatments with MAOIs or within 14 days after the end date of the MAOI prescription. Patients in our study were followed until the end of the observation period (April 14, 2007), death, or discontinuation of the MAOI. If the follow-up was terminated due to MAOI discontinuation, we continued follow-up for 14 days after the presumed end date of the last prescription to look for the prescription of an interacting drug. In addition, we examined how many patients were dispensed another MAOI prescription within the days supply of the interacting drug.

Hospital Admissions and ED Visits During MAOI Treatment

Serotonin syndrome and hypertensive crisis are serious adverse events that may occur during MAOI treatment. These events may be coded in different ways. We reviewed the most responsible diagnosis of the hospital visits to determine if it was likely that the visit was due to one of these adverse events. We examined ED visits and acute care admissions while patients were on MAOIs for a subgroup of the cohort from July 2000 to March 2007 using CIHI and NACRS data. We examined all hospital admissions and ED visits while the patient was on continuous MAOI treatment with an extended follow-up period of 20% grace period after the presumed end date of the MAOI prescription. Because of privacy regulations, we reported cells of "less than 6" individuals by that phrase rather than recording the actual number of cases. All analyses were performed using SAS statistical software version 9.1.3 (SAS Institute, Cary, North Carolina).

The diagnostic categories recorded under hospital admissions and ED visits were reviewed independently by 2 of us (K.S., N.H.) and agreement was reached on the categorization of the diagnoses. If a patient was hospitalized following an emergency visit, this was counted as a hospital admission only.

RESULTS

The yearly incidence of MAOI prescriptions remained low (ranging from 45 to 22) while the prevalence decreased steadily over the study period from 400 in 1997 to 216 in 2006 (Figure 1). The incidence rate decreased from 3.1/100,000 in 1997 to 1.4/100,000 in 2006 while the prevalence rate decreased from 30.9/100,000 in 1997 to 14.0/100,000 (Figure 1). In the accrual period of April 1, 1997, to March 31, 2007, there were 348 new, continuous users in the cohort of irreversible MAOI users. Of these, 60.3% were female and the mean (SD) age was 74.7 (± 5.6) years. The mean number of unique DINs in the year prior to index date was 14 (± 7.2). The mean exposure time for patients who were

Table 1. Numbers of Hospital Visits by Diagnostic Category in 221 Patients Receiving MAOIs

Diagnosis	Hospital Admissions or ED Visits
Psychiatric (including overdose)	48
Neurologic	8
Syncope and orthostatic hypotension	8
Other cardiac	16
Pulmonary	9
Gastrointestinal	18
Infection	13
Fractures	9
Other	49
Total	178

Abbreviations: ED = emergency department, MAOI = monoamine oxidase inhibitor.

dispensed MAOIs continuously was 218.9 (± 407.1) days. The majority of patients showed previous treatment patterns that are consistent with recurrent major depressive disorder. Of the cohort of 348 patients, 272 received at least 1 other non–irreversible MAOI antidepressant in the 2 years prior to cohort entry, with a mean of 3.1 (± 1.8) other antidepressant drugs, a minimum of 1, and a maximum of 11. There were 94 patients (27%) who received ECT in the 5 years prior to index date, with the mean number of treatments being 33.5 (± 25.0). The number of ECT treatments ranged from 1 to 138 per patient. There were 233 patients who had seen a psychiatrist in the year prior to starting the MAOIs. Less than 6 patients were exposed to contraindicated sympathomimetic drugs while on MAOI treatments. Concomitant exposure to at least 1 serotonergic drug occurred in 63 (18.1%) patients, and, of those, 24 patients were prescribed a serotonergic drug only once. Of the 63 patients who were dispensed serotonergic drugs, 23 patients were dispensed an additional MAOI after the serotonergic drug.

Hospital visits were examined in 221 patients who were on MAOIs after and including July 2000. A review of hospital admissions revealed a total of 84 during the observation period involving 52 unique patients, while there were 94 ED visits involving 47 unique patients. Table 1 describes the diagnostic categories identified as the primary diagnosis for both hospital admissions and ED visits. The majority of events were of a psychiatric nature, including overdose. The 8 hospital admissions or ED visits for neurologic causes included diagnoses of delirium, cerebral infarction, transient ischemic attack, hydrocephalus, brain injury, and unspecified migraine. None of these diagnostic categories were specific for serotonin syndrome or hypertensive crisis secondary to MAOI use. Eight cases involved syncope or orthostatic hypotension, a more common and well-known side effect of MAOIs. However, this cohort of patients typically had multiple comorbidities including a mean of 14 drugs, which could also contribute to the lowering of blood pressure and syncope. The 9 fractures recorded were of a wide range, typically seen in an ED. Finally, the category "Other" was carefully reviewed and also reflected a typical range of minor conditions seen in an ED.

DISCUSSION

Over a 10-year period in the province of Ontario, with an average population of over 1.4 million older adults, we identified only 348 new users of irreversible MAOIs. As expected, the incidence of MAOI prescriptions in Ontario has remained low with a steadily falling prevalence. This decrease occurred during a time period when antidepressants were being prescribed at an increasing rate, up to 10.9% (10,900/100,000) of older adults in 2002.[18] To put this into perspective, during the same year, the prevalence rate for prescription of MAOIs was 21.3/100,000. Thus, only about 1/500 older adults who were prescribed an antidepressant received an MAOI. However, our data also show that MAOIs continue to be used in a subgroup of seriously ill depressed unipolar and bipolar patients who have a high rate of prior use of other antidepressants as well as ECT. This population-based elderly cohort is typical of other mood cohorts[19] with significant medical comorbidities, as reflected by the number of other drugs prescribed (DINs) and a mean age of 75 years. Consequently, the diagnostic codes recorded in the ED visits and hospital admissions are consistent with this patient population.

Of concern is the apparently high concomitant exposure of these patients to at least 1 serotonergic drug (18.1%). However, a limitation of our methodology is that on the basis of dispensed prescriptions, we cannot assess if the patients were told to stop their MAOI prior to starting the serotonergic or sympathomimetic agent. Therefore, we also examined how many patients had another MAOI prescription dispensed following the interacting drug. Despite this apparent concomitant exposure to serotonergic drugs, no adverse events that might represent a serotonin syndrome were identified. Exposure to sympathomimetics was minimal, and we did not identify any episode specific for a hypertensive crisis or other cardiac or neurologic event as part of an ED visit or hospital admission. This may reflect the recent use of safe and practical MAOI diets developed over the past decade.[9]

While the incident use of MAOIs remains very low in Ontario (approximately 25 new patients per year), this contrasts with the continued recommendation by opinion leaders in the field of mood disorders[4,7] and by consensus guidelines published since 2000. If MAOIs were being used as recommended, we would be seeing higher prescription rates for them. The atypical depression subtype of mood disorder represents 1%–4% of the population and 15%–29% of all patients with major depressive disorder.[4] Recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D) data suggest a prevalence of at least a third of patients with major depressive disorder who meet criteria for stage 2 treatment-refractory depression, ie, failure to achieve remission after 2 courses of adequate antidepressant treatment.[5] These 2 subtypes of depression represent a very significant proportion of the overall population of

depressed patients. Tranylcypromine was used as a step 4 treatment in the STAR*D trial and produced predictably modest results similar to the combination of mirtazapine and venlafaxine.

Irreversible MAOIs maintain a special place in the antidepressant armamentarium, which may correspond with their unique pharmacologic properties compared to other classes of antidepressants. A finding that levels of MAO tend to increase with age[6,20] may also be relevant to this unique function. Recent positron emission tomography findings confirm the presence of high MAO-A levels during major depression.[21] Although it is appropriate that MAOI use is limited, this class of antidepressant maintains a potentially important role for individuals with atypical and treatment-refractory depressions who may be condemned to suffer without access to MAOIs.

Our analysis of ED visits and acute care admissions does not create a signal of major concern. However, despite our use of a population-based cohort, a limitation of our study is the relatively small number of patients included. This is compensated by a relatively long observation period. Nonetheless, there is no room for complacency, and, although we did not find evidence of the most serious medical consequences of using MAOIs, namely hypertensive crises or serotonin syndromes, we cannot completely rule out the possible contribution of MAOIs to the common conditions seen in an elderly cohort such as syncope and falls. Younger patients should be less vulnerable than this older cohort to these common medical conditions.

Current dietary approaches combined with continuing education about the need to avoid concomitant exposure to serotonergic and sympathomimetic agents should provide a good balance of risk-benefit for irreversible MAOIs.[22] Our pharmaco-epidemiology study covering a period of 10 years did not find evidence of serotonin syndrome or hypertensive crisis associated with the use of MAOIs. This may be a limitation of a population-based database approach. However, given the low use of MAOIs, no single-center or even multi-site study is likely to capture a sufficient number of such patients for clinical study.[23] Continued vigilance and surveillance by individual case reports of adverse events is still necessary. Moreover, expanded use of MAOIs would have to come with clear guidance and careful monitoring.

Our study suggests that we may not be achieving the potential benefit for a significant cohort of older patients with atypical and treatment-refractory depressions. We suspect that the same concern holds true for a larger mixed-age population.[24] MAOIs, like lithium carbonate, are not actively promoted. It appears that an older, inexpensive class of drugs such as MAOIs has been forgotten in the lucrative market for new and much more expensive agents. Cheap drugs for common conditions such as refractory depressions are dependent on the recommendations of expert clinicians, official psychiatric guidelines, and insurers rather than pharmaceutical marketing and promotion. If we are to implement these recommendations, then the next generation of clinicians needs to be familiar and comfortable with the use of irreversible MAOIs. This should be a formal requirement in the pharmacologic training of psychiatric residency programs. Otherwise, drugs such as MAOIs with the potential to benefit a substantial subset of refractory mood disorders will be relegated to an historical footnote to the detriment of our patients.

Drug names: benzphetamine (Didrex and others), brompheniramine (Bromfed, Myphetane, and others), buspirone (BuSpar and others), citalopram (Celexa and others), dextroamphetamine (Adderall, Dextroamp, and others), dextromethorphan (Bromfed, Promethazine, and others), diethylpropion (Tenuate and others), duloxetine (Cymbalta), ephedrine (Semprex, Bromfed, and others), escitalopram (Lexapro and others), fluoxetine (Prozac, Sarafem, and others), fluvoxamine (Luvox and others), meperidine (Demerol and others), methamphetamine (Desoxyn), methylphenidate (Focalin, Daytrana, and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), phendimetrazine (Bontril and others), phenelzine (Nardil), phentermine (Adipex and others), phenylephrine (Prometh, Cyclomydril, and others), pseudoephedrine (Semprex, Bromfed, and others), selegiline (Emsam, Eldepryl, and others), sertraline (Zoloft and others), sibutramine (Meridia), tramadol (Ultracet, Ultram, and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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Appendix 1. Contraindicated Medications in Patients Taking Irreversible MAOIs [a]

Serotonergic drugs
Buspirone
Citalopram (hydrobromide)
Dextromethorphan
Duloxetine (NA)
Escitalopram (not in ODB)
Fluoxetine
Fluvoxamine
Meperidine
Mirtazapine
Paroxetine
Sertraline
Sibutramine (not in ODB)
Tramadol (not in ODB)
Trazodone
Venlafaxine
Sympathomimetic drugs
Amphetamines, cocaine (NA)
Benzphetamine (NA)
Dextroamphetamine
Diethylpropion
Dopamine (not in ODB)
Ephedrine
Isometheptene (NA)
Mazindol
Metaraminol (NA)
Methamphetamine (not in ODB)
Methylphenidate
Phendimetrazine (NA)
Phentermine
Phenylephrine
Pseudoephedrine
Brompheniramine and phenylephrine and phenylpropanolamine[b]
Azatadine maleate and pseudoephedrine sulfate[b]

[a]Some drugs have not been available throughout the whole study period; however, since they do not serve to define the cohort, it was decided to include contraindicated drugs irrespective of availability throughout the study period. Some contraindicated drugs are not available in Canada (NA) or not in ODB, as specified above; however, the list includes all the drugs listed as contraindicated based on *The Top 100 Drug Interactions: A Guide to Patient Management*.[17]
[b]Combination drug.
Abbreviations: MAOI = monoamine oxidase inhibitor, NA = not available, ODB = Ontario Drug Benefit.

For the CME Posttest for this article, see pages 1749–1750.