There is limited geriatrics-oriented clinical pharmacological information available to guide pharmacotherapy in late-life psychiatric disorders. In this paper, we review available data on interindividual differences in drug exposure and central nervous system functioning, amplified by drug–drug interactions in the elderly, that may contribute to variable responses to treatment and significant adverse drug effects. The inclusion of greater numbers of elderly persons in clinical trials and the vigorous application of clinical pharmacologic methodology (i.e., pharmacoepidemiology, population pharmacokinetic modeling, and pharmacogenetics) will be critical for improving safety and personalization of drug and dose selection for elderly patients.

LATE-LIFE PSYCHIATRIC DISTURBANCES

Although the rates of depressive symptomatology are comparable in younger and older adults (5–13%), the elderly face a chronic disease profile that is often not alleviated by treatment, is likely to recur/relapse, and frequently involves cognitive decline.1 Late-life anxiety disorders affect 2–19% of the community-dwelling elderly, with almost 20% additionally experiencing symptomatic antidepressants that does not meet diagnostic criteria. Also common in 10–70% of dementia sufferers are behavioral and psychiatric symptoms of dementia (BPSDs) such as agitation, aggression (physical and verbal), and psychosis.2 Late-life psychiatric disturbances result in a lower quality of life; an increase in disability rates; and a risk of dementia, placement in long-term care, and cognitive decline as well as a risk of extrapyramidal symptoms and mortality, which may include suicide.3–6

UNDERREPRESENTATION IN CLINICAL TRIALS

Antidepressant drug trials in geriatric patients are very sparse and limited to academic sites, as are studies in those with chronic psychotic illnesses (e.g., schizophrenia). By contrast, there have been a number of drug trials in dementia patients with BPSDs. To date, there have been only two significant trials of antidepressants in the “old-old.” A randomized, placebo-controlled trial of citalopram in those aged ≥75 years did not find a significantly different rate of remission between medication and placebo groups.7 Reynolds and colleagues determined that 65% of the depressed elderly who achieved initial response to paroxetine and psychotherapy remained in remission for up to 2 years during maintenance treatment.8 In contrast, in the case of atypical antipsychotic drugs, because there is a potential for achieving a specific indication for treatment of psychosis in dementia, there were at least 15 double-blind placebo-controlled trials (only 6 of which were published) from 1995 to 2005. Although efficacy was demonstrated in trials of risperidone and olanzapine, based on the pooled data, mortality was higher in patients treated with atypical antipsychotics as compared with those who received the placebo (3.5% vs. 2.3%).9

Variable interindividual drug exposure can contribute to mixed outcomes. For example, it is challenging to administer antipsychotics to acutely agitated patients. In the same patients, the variation in risperidone concentration exposure was found to be ~125% when they were in the acute in-patient unit and 70% when they were transferred to the long-term care setting.10 These variable exposures are potential contributors to the risk of adverse drug reactions (ADRs) and lack of response. The Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer’s Disease (CATIE-AD) included 260 dementia patients receiving treatment for BPSDs with olanzapine, quetiapine, risperidone, or placebo. Between 21 and 32% of the patients experienced improvement in their symptoms, whereas 5% (placebo) to 24% (olanzapine) of the patients discontinued treatment on account of intolerable side effects, thereby demonstrating an unfavorable risk-to-benefit ratio.11 This relatively low response rate in typical clinical studies may be secondary to relatively poor adherence to medication schedules in respect of antipsychotic drugs (<70% of the doses were taken correctly).12 This provides a significant challenge in interpreting the assignment of treatment, given the inconsistency of drug exposure inherent in these low adherence rates. The rationale for using risperidone

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Received 2 September 2008; accepted 30 September 2008; advance online publication 26 November 2008. doi:10.1038/clpt.2008.229
or other dopamine receptor–blocking drugs to treat BPSDs in patients who have existing dopaminergic deficits associated with dementia remains open to question. Serotonergic dysfunction in dementia patients has been associated with BPSDs, and further trials of serotonergic medications in the treatment of agitation are being sponsored by the National Institute on Aging.

PHARMACOEPIDEMIOLOGY

One in five community-dwelling elderly persons is prescribed psychotropic medications. Additionally, between 20.9 and 44.3% of long-term-care residents are dispensed antipsychotics. Psychotropic drugs are among one of the leading causes of preventable ADRs in long-term-care facilities. Pharmacoepidemiology has revealed safety concerns that are not apparent from efficacy trials or routine clinical use of psychotropics. Nursing-home residents have experienced cerebrovascular events and increased mortality consequent to the use of atypical antipsychotic drugs. The risk of falls and fragility fractures increase in community-dwelling elderly persons with long-term use of selective serotonin reuptake inhibitors (SSRIs). The elderly are at particular risk for upper gastrointestinal bleeding associated with the use of SSRIs. The bleeding may result from the direct effects of SSRIs on platelet aggregation and can be further compromised with the concomitant use of nonsteroidal antiinflammatory drugs or low-dose aspirin. While the US Food and Drug Administration found, from data in a pooled analysis from 372 efficacy trials, a decreased incidence of suicidal tendencies (thoughts and behaviors) in patients aged ≥65 years, a study based on prescription data found an increased risk of actual suicide in the depressed elderly within the first month of initiating SSRI treatment.

PHARMACOKINETICS

A significant proportion of ADRs (~70–80%) are related to concentration. Cholinergic events (e.g., nausea, vomiting, and diarrhea) can occur with higher doses of cholinesterase inhibitors and can become severe with rapid dosage increases or if metabolism by the cytochrome (CYP) P450 enzyme 3A4 is inhibited (e.g., with donepezil or galantamine). Variability in drug concentrations is often not evaluated, and in regulatory trials with younger, healthier subjects, medications are often administered at or close to their highest tolerable dose to ensure efficacy. In elderly patients, this translates into serious ADRs, such as are seen after the use of bupropion and clozapine (e.g., dose-related seizures) or fluoxetine and risperidone (e.g., dose-related agitation, akathisia, and extrapyramidal symptoms).

Pharmacokinetic analysis generally calls for the collection of numerous samples from a small number of volunteers (6 to 12 subjects). Single-dose studies generally fail to provide this type of analysis for elderly volunteers. Studies evaluating pharmacokinetics through multiple dosing reveal nonlinear relationships. Population pharmacokinetics, an alternative to traditional modeling, uses mixed-effects methods. Only a few samples (e.g., one or two) from each subject contributes to individual and population pharmacokinetic parameters, and heterogeneity among older adults is better accounted for by including covariates such as medication use, illness, and age. The results are more clinically relevant because a larger number of patients are included in the analyses. Population pharmacokinetic modeling has demonstrated that there is a linear decline in citalopram clearance from ages 22 to 93 years by 2.31/h per decade. Recent evidence from the CATIE found that elderly patients may have greater exposure to risperidone’s active metabolite, 9-OH risperidone, because of a 20% decrease in elimination. No age-associated changes in olanzapine or quetiapine pharmacokinetics were found in this study. Variability in the elimination of olanzapine was best accounted for by smoking status, with smokers clearing olanzapine 55% faster than nonsmokers. Quetiapine clearance was higher when there was concomitant use of bupropion, and body weight significantly influenced the volume of distribution. In general, there is a trend toward decreases in clearance in elderly individuals. Nonetheless, because there is greater interindividual variability of drug concentrations, which are difficult to predict in the elderly, dosages comparable to those administered to younger adults may be required for effective therapy in some older patients.

Many antidepressant drugs (e.g., nortriptyline, desipramine, paroxetine, venlafaxine) and antipsychotic drugs (e.g., perphenazine, thioridazine, and risperidone) are hydroxylated by the CYP2D6 isozyme. There does not appear to be an age-associated decline in the activity of this enzyme in older, unmedicated adults, although significant interactions can occur from common medications, either competitively (e.g., perphenazine) or noncompetitively (e.g., paroxetine, fluoxetine, bupropion), inhibiting CYP2D6. Within the Caucasian population, 7% of individuals are genetically poor CYP2D6 metabolizers. A study carried out in elderly subjects that used CYP2D6 identification prospectively found that poor metabolizers experienced more severe extrapyramidal side effects than extensive metabolizers did.

CYP2C19 metabolizes diazepam, escitalopram, mephentoin, and phenytoin. The demethylation of tertiary tricyclic antidepressants is partially dependent on this isozyme and is inhibited by fluvoxamine and fluoxetine. Some research shows that CYP2C19 functioning declines with age. Inhibition of CYP2C9 by fluvoxamine and fluoxetine decreases the clearance of warfarin’s active S-enantiomer. R-warfarin will accumulate with inhibition of CYP1A2 (fluvoxamine) and 3A4 (fluvoxamine, fluoxetine), also affecting S-warfarin clearance.

CYP3A4 drugs such as sertraline, mirtazapine, alpraxolam, and triazolam can be affected by age and gender (Table 1). This enzyme is inhibited significantly by fluvoxamine and fluoxetine, via its demethylated metabolite, norfluoxetine. CYP1A2 is induced in postmenopausal women receiving growth hormone treatment and is inhibited by estrogen replacement.

The accumulation of an antidepressant drug’s active hydroxylated metabolites (e.g., nortriptyline and bupropion) can have clinical consequences. Imipramine’s active metabolite, 2-OH desipramine, is twice as potent in eliciting arrhythmias as imipramine itself, and the concentrations of the metabolite have been associated with prolonged QRS intervals. The accumulation
of venlafaxine’s metabolite can impair cardiac conduction. Older patients with decreased renal or hepatic function may develop unexpected extrapyramidal side effects due to accumulation of 9-OH risperidone. The elderly are typically prescribed nonsteroidal antiinflammatory drugs and angiotensin-converting enzyme inhibitors, which potentially reduce lithium clearance.

**PHARMACODYNAMICS**

Older adults are more susceptible to increased pharmacodynamic effects at lower drug concentrations than younger adults are. In one of the first pertinent studies, Reidenberg and colleagues found that older adults showed greater sedation at lower diazepam concentrations than younger adults did. Even healthy elderly persons have been noted to have significant cognitive impairment as compared with younger volunteers at the same intravenous dose of scopolamine (0.5 mg). Obesity, poor nutrition, and high triglyceride levels can increase the risk of cardiovascular events with chronic use of antipsychotics in the elderly. In elderly patients, risperidone has a linear concentration side-effect profile, olanzapine demonstrates a curvilinear dose–response relationship, and quetiapine is administered across a very wide range of doses.

SSRIs have a much wider therapeutic index than tricyclic antidepressants; nonetheless, avoidable ADRs (e.g., cognitive and psychomotor events) occur when SSRIs concentrations become needlessly high. Bradycardia may intensify with the use of SSRIs in the elderly. Inappropriate antidiuretic hormone secretion consequent to the intake of SSRIs or venlafaxine is reported mainly in patients aged ≥65 years. Some degree of hyponatremia is experienced by up to 12% of older adults taking SSRIs and can occur at 13 days after commencement of treatment (range 3–120 days). Patients with idiopathic Parkinson’s disease have demonstrated parkinsonism or motor worsening after SSRI use. This may be a function of reduced dopaminergic transmission related to serotonin in a population with already compromised dopamine reserves. Higher concentrations of tricyclic antidepressants prolong QTc intervals and pose a greater risk of arrhythmias. Venlafaxine’s cardiovascular toxicity is increased by CYP2D6 inhibition, and, in older patients, dropout rates conform to an ascending dose–response model. The association between adherence to the medication regimen and response to the drug in elderly persons with depression may not be strictly related to the average exposure or the average number of tablets taken correctly. It may be that gaps in treatment are a significant contributor to poor treatment response.

Genetic variability may impact response to SSRIs in older adults. The number of geriatric studies examining receptor/transporter sites is limited, and these few have focused on the serotonin transporter (5HTT). A functional polymorphism in the promoter region of the 5HTT results in a short (s) or long (l) allele. The s variant has been associated with poorer SSRI response. However, in a Korean population of elderly patients with depression, those expressing the s/s allele and the l/l variant of the intron 2 variable number of tandem repeats polymorphism were found to be more likely to respond to treatment with fluoxetine or sertraline than those with other genetic combinations. Elderly persons who are heterozygous for the s allele experience greater side effects (gastrointestinal complaints,
fatigue, agitation, sweating, and dizziness) to paroxetine treatment than 1 allele carriers do.44

Neuronal changes with aging (e.g., decreased dopamine or acetylcholine) can lead to greater sensitivity to D2 antagonists and antimuscarinic agents. Age-related reductions in cortical D2 and 5HT2a receptors can also have implications on the effects of atypical antipsychotics as well as some antidepressants.45,46 Tardive dyskinesia from the use of conventional antipsychotic drugs has been shown to occur frequently and with rapid onset in older patients. Recent pharmacokinetic/pharmacodynamic studies using positron emission tomography have found that, after controlling for risperidone concentration, older schizophrenic patients will experience extrapyramidal symptoms when 60% of the D2 receptors are bound by risperidone, whereas younger adults do not have these side effects until binding occurs up to 80%.47

Anticholinergic effects, such as dry mouth, tachycardia, blurred vision, urinary retention, and constipation, can markedly impair quality of life in elderly patients. Cognitive manifestations may be slight (mild confusion, short-term memory impairment) or more severe (delirium). These effects are particularly problematic in patients with dementia, and even agents with modest anticholinergic activity can impact cognition in older adults. Serum anticholinergic activity (representative of overall anticholinergicity from all medications and their metabolites) was found in almost 90% of the samples from a group of community-based elderly persons, and even low levels of such serum activity were associated with impairment in cognition.48 Anticholinergic activity was assessed in a study of 107 medications commonly prescribed to the elderly and may help to guide medication selection and assess anticholinergic burden.49 Medications with noradrenergic properties can lead to dry mouth and urinary retention in elderly men, tachycardia, and aggravation of hypertension and tremor.

SUMMARY
In the absence of basic clinical pharmacologic information relating to geriatric patients, more intensive and standardized postmarketing studies are essential. Obtaining minimally invasive drug exposure data and DNA in both clinical trials and in postmarketing studies will assist in determining unanticipated drug interactions and ADRs, such as those seen with SSRIs (e.g., fragility fractures, hyponatremia, and risk for completed suicide after initial treatment). The inclusion of structural and functional imaging with genetic investigations and the capture of drug-exposure information provide opportunities to reduce heterogeneity and improve the efficacy and safety of psychotropic medications.

ACKNOWLEDGMENT
This work was supported by the Sandra A. Rotman Program in Neuropsychiatry (Toronto).

CONFLICT OF INTEREST
B.G.P. has received grants or research support from the National Institutes of Health and Janssen Pharmaceuticals. He serves on the advisory board of Forest Laboratories and Lundbeck Inc., and has consulted for Wyeth, Takeda Pharmaceuticals, and GlaxoSmithKline, and is a faculty member of the Lundbeck International Institute. Until 2005 he was a member of the speakers’ bureau for Forest and Lundbeck. The other authors declared no conflict of interest.

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