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Age-related Changes in Antidepressant Pharmacokinetics and Potential Drug-Drug Interactions: A Comparison of Evidence-Based Literature and Package Insert Information

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INTRODUCTION

Antidepressants are among the most commonly prescribed psychotropic agents for older patients. In particular, there has been a dramatic increase in the frequency at which antidepressants are prescribed to older nursing home patients. Specifically, antidepressant use has increased from 21.9% in 1996 to 47.5% in 2006.[1] Of potential concern is that antidepressants are associated with an increased risk for potentially clinically significant adverse drug events (ADEs) in the elderly such as falls and fractures.[2] The increased risk of ADEs might be due in part to dosing that does not take into account known age-related changes in antidepressant pharmacokinetics and/or drug-drug interactions (DDIs).[3–4] Indeed a recently published study in 877 older nursing home patients showed that 43.1% of antidepressant prescribing for those with depression was potentially inappropriate.[5] In particular, dosage problems were seen in 8.8% and DDIs in 25.9%. This latter point is

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CONFLICT OF INTEREST STATEMENT

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important, as DDIs may be more common in older adults due to the greater number of medications needed to treat persons with multiple comorbid conditions.[5]

Thus prescribers are faced with a tension that requires that they consider the potential benefits and harms with the use of antidepressants in older patients. Therefore clinicians need accurate up to date pharmacotherapy information sources to correctly dose antidepressants and avoid potential DDIs with antidepressants. One potential source of pharmacotherapy information is the Food and Drug Administration (FDA) approved package inserts (PIs) for marketed antidepressants. However, previous work has shown that PIs for medications commonly used in hospitalized older adults rarely contain comprehensive information about age-related changes in pharmacokinetics.[6] Moreover, two separate studies showed that only a minority of potentially clinically significant DDIs appear in the PI compared to other evidence-based sources.[7,8] To the best of our knowledge, no study has compared antidepressant PI's with the evidence-based primary scientific literature regarding the completeness of information about geriatric pharmacokinetics and DDIs.

Given this background, the objective of this study is to synthesize and contrast information in the PI versus that found in the scientific literature regarding antidepressants age-related changes in systemic clearance and potential pharmacokinetic DDIs.

METHODS

Included Antidepressants and PI Retrieval

Currently-marketed antidepressants were identified by searching the Martindale drug reference for drugs indicated for the treatment of depression. Those listed in the "drugs@FDA" database were included in this study.[9,10] Appendix A list the 26 agents available as of the start of our study (September, 2011). FDA-approved PIs were retrieved when possible for these 26 currently -marketed antidepressants from the 2011 Physicians' Desk Reference® (PDR).[11] In cases where we could find no relevant package insert in the PDR, one was retrieved from the National Library of Medicine's *DailyMed* website.[12]

Age-related Pharmacokinetic Changes with Antidepressants

We identified published studies examining age-related pharmacokinetic changes affecting antidepressants by searching MEDLINE and EMBASE from January 1975 through September 2011. The searches combined the generic names of each antidepressant with the term "*pharmacokinetics*" and limited the results to studies published in English that included persons age ≥65. Additional articles were found by a manual search of the reference lists of identified articles and the authors' files, book chapters, and recent review articles.[13–25] Two of the investigators (JTH and RDB) independently screened the search results for studies that compared the systemic clearance (Cl) of an antidepressant between the younger and older. We considered a drug to have an age-related change in Cl if any pharmacokinetic study reported a quantitative decrease in Cl in older adults as compared with younger adults. The same two investigators independently identified PI statements referring to age-related pharmacokinetic changes and reporting the quantitative difference in Cl of the antidepressant between the young and old study populations. PIs statements discussing the results of pharmacokinetic studies as "no effect" or "no change" were not included." Any discordances were resolved by another author (SMH).

Pharmacokinetic Drug interactions with Antidepressants

We identified published studies examining pharmacokinetic DDIs affecting antidepressants by searching MEDLINE and EMBASE from January 1975 through September 2011. The searches combined the names of each antidepressant with the terms "*clinical trial*", *"drug*

interactions", and *"interaction."* and the results were limited to studies published in English. Additional articles were found by a manual search of the reference lists of identified articles and the authors' files, book chapters, and recent review articles.[13–25] Studies involving precipitant drugs that are no longer marketed or cytochrome P450 (CYP) enzyme inducing agents were excluded. Two of the investigators (JTH and RDB) independently reviewed each study and included only those studies that measured systemic Cl and/or area under the concentration time curve (AUC) of the object antidepressant drug in the presence of a precipitant drug. A DDI was operationally defined as any increase in the AUC or decrease in Cl of an antidepressant in the presence of a precipitant drug. The same two investigators independently identified PIs for quantitative information regarding the impact of specific medications on antidepressant AUC and/or Cl. Any discordances were resolved by the another author (SMH).

Statistical Analysis

Descriptive statistics (i.e. percentages) were calculated for literature and PI derived studies showing evidence of age-related decline in systemic clearance and potential DDIs. Agreement between the literature or PI statements for both age-related pharmacokinetic changes and potential DDIs were calculated by the Kappa statistic (a measure of chance-adjusted agreement).[26] A Kappa statistic of >0.75 was ranked as "excellent" agreement, one between 0.40 and 0.75 was considered "good to fair," and less than 0.40 was considered to be "marginal" or "poor" agreement. The Kappa statistic was calculated using SAS (version 9.0, Cary, NC).

RESULTS

Table 1 shows the studies from the scientific literature regarding potential age-related changes in systemic Cl for the 26 antidepressants. It was determined that 13 of the 26 (50%) antidepressants had evidence of age-related decline in systemic Cl.[27–44]

Table 2 shows information about age-related changes in Cl from PIs. The PIs provided sufficient information on age-related decline in systemic Cl for four antidepressants.[45–48.] Overall, agreement between the literature and PI regarding age-related Cl changes was marginal or poor as indicated by a Kappa statistic of less than 0.40.

Our search also revealed 52 articles from the scientific literature involving 45 drug-antidepressant pairs that were deemed to be pharmacokinetic DDIs due to changes in AUC and/or Cl (Table 3).[49–101] In contrast, the PI shows that only 12 drug-antidepressant interactions involving 8 antidepressants as per changes in AUC or Cl parameter. (Table 4).[45–47, 102–106] Again, overall agreement between the PIs and literature was marginal or poor with a Kappa statistic of less than 0.40.

DISCUSSION

This study demonstrated that the scientific literature provides more complete information regarding age-related decline in antidepressant systemic Cl than does the PI (50% of antidepressants vs 15%). These findings are concordant with a study by Steinmetz et al. found that only 8% of the 50 PIs for commonly used medications in hospitalized older adults stated age- or disease-related pharmacokinetic changes quantitatively.[6] It is important to note that despite the marginal to poor overall agreement between the two information sources, the PI did identify two antidepressants with age-related decline in systemic Cl that were not identified in the literature (i.e., mirtazapine and duloxetine).[46,47]

This study also determined that the literature reported almost four times as many pharmacokinetic DDIs affecting AUC or Cl than did the PIs (47 vs 12). This is consistent with a study by Hines et al. that found that only 15% of the PIs for drugs commonly known to interact with warfarin stated so.[7] Similarly, Chao and Maibach found that PIs contained only between 13–48% of the known DDIs affecting four commonly-prescribed dermatologic drugs (i.e., dapsone, erythromycin, methotrexate, and prednisone).[8] In this study the PIs did however identify 4 potential DDIs not found in the literature (i.e., cimetidine-citalopram, ketoconazole-mirtazapine, cimetidine-sertraline, and ketoconazole-vilazodone).[46,104–106] Fortunately, neither cimetidine or ketoconazole are commonly used medications in older patients.[5]

Our review of the literature and PIs found twelve antidepressants that have evidence of both an age-related decrease in Cl and at least one Cl-reducing pharmacokinetic DDI. These include three SSRIs (citalopram, escitalopram, and sertraline), two SNRIs (duloxetine, venlafaxine,), four TCAs (amitriptyline, doxepin, imipramine, and nortriptyline) and three other newer antidepressants (bupropion, mirtazapine, and trazodone). Clinicians should be aware that the combination of two or more factors reducing drug clearance can increase the chance that their elderly patient will experience an adverse drug event.[4,107] This phenomena was seen in a study by Zint et al. that examined the association between benzodiazepines and hip fracture among older adults.[108] Specifically the association between alprazolam alone and falls was not statistically significant (Adjusted Relative Risk [ARR] 1.01, 95% confidence interval [CI] 0.92–1.11). However, the combination of alprazolam with an interacting drug resulted in a point estimate for risk that was increased by nearly 50% (RR 1.51, 1.34–1.69).[108]

Our study has a number of potential limitations. One potential limitation of this study is that we excluded drug interactions with possible pharmacokinetic and/or pharmacodynamic mechanisms that were found by observational studies. In addition, no distinction was made between age-related changes in free systemic clearance versus clinically important decline. Moreover, we included DDI studies that observed any decrease in Cl or increase in AUC, even if the difference between groups did not reach statistical significance ($p<0.05$). Nonetheless, we believe that using these more sensitive approaches for inclusion was justified due to the small number of subjects in these studies which could have limited their statistical power to detect meaningful differences. Finally, our search strategy might have missed some studies published in languages other than English, and studies available in unpublished technical reports, white papers, or other “grey literature” sources.

CONCLUSIONS

The evidence-based literature compared to PIs is the most complete pharmacotherapy information source regarding both age-related Cl changes and pharmacokinetic DDIs with antidepressants. Future rigorously designed observational studies are needed to examine the combined risk of antidepressants with age-related decline in clearance and potential DDIs on important health outcomes such as falls and fractures in older patients. [108,109]

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Table 1

Evidence from the scientific literature about age-related reduction in systemic clearance of antidepressants

Class/Agent	Age-related reduction in clearance	Reference
MAOI		
Isocarboxazid	N/A	
Phenelzine	N/A	
Selegiline	N/A	
Tranylcypromine	N/A	
Other Antidepressants		
Bupropion	Yes	[27]
Mirtazapine	N/A	
Nefazodone	N/A	
Methylphenidate	N/A	
Trazodone	Yes	[28,29]
Vilazodone	N/A	
SNRI		
Desvenlafaxine	Yes	[30]
Duloxetine	N/A	
Venlafaxine	Yes[+]	[30]
SSRI		
Citalopram	Yes	[31–33]
Escitalopram	Yes	[31, 32]
Fluoxetine	N/A	
Paroxetine	N/A	
Sertraline	Yes	[34]
Tetracyclics		
Amoxapine	N/A	
Maprotiline	No	[35]
Trimipramine	N/A	
TCA		
Amitriptyline	Yes	[36–38]
Desipramine	No	[39]
Doxepin	Yes	[40,41]
Imipramine	Yes	[35,39,42]
Nortriptyline	Yes	[43,44]

[*] renal clearance may be impaired with age; avoid use in creatinine clearance < 30ml/minute

[+] men only; dose reduction recommended with reduced creatinine clearance

Abbreviations: MAOI=monamine oxidase inhibitor; NA= none available; SNRI=selective norepinephrine reuptake inhibitor, SSRI= selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

Table 2

Evidence from the package insert about age-related reduction in systemic clearance of antidepressants

Class/Agent	Age-related reduction in clearance	Reference
MAOI		
Isocarboxazid	N/A	
Phenelzine	N/A	
Selegiline	N/A	
Tranylcypromine	N/A	
Other Antidepressants		
Bupropion	Yes	[45]
Mirtazapine	Yes*	[46]
Nefazodone	N/A	
Methylphenidate	N/A	
Trazodone	N/A	
Vilazodone	N/A	
SNRI		
Desvenlafaxine	N/A	
Duloxetine	Yes+	[47]
Venlafaxine	N/A	
SSRI		
Citalopram	N/A	
Escitalopram	N/A	
Fluoxetine	N/A	
Paroxetine	N/A	
Sertraline	Yes	[48]
Tetracyclics		
Amoxapine	N/A	
Maprotiline	N/A	
Trimipramine	N/A	
TCA		
Amitriptyline	N/A	
Desipramine	N/A	
Doxepin	N/A	
Imipramine	N/A	
Nortriptyline	N/A	

*Especially in males

+tested only in females

Abbreviations: MAOI=monamine oxidase inhibitor; NA= none available; SNRI=selective norepinephrine reuptake inhibitor, SSRI= selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

Table 3

Potential pharmacokinetic drug interactions with antidepressants from the scientific literature

Class/Agent	Potential Interacting Drug	↑AUC or ↓clearance	Reference
MAOI			
Selegiline	Alprazolam	No	[49]
Selegiline	Cabergoline	Yes	[50]
Selegiline	Citalopram	No	[51]
Selegiline	Itraconazole	No	[52]
Selegiline	Olanzapine	No	[49]
Selegiline	Risperidone	No	[49]
Other Antidepressants			
Bupropion	Cimetidine	Yes	[53]
Bupropion	Clopidogrel	Yes	[54]
Bupropion	Prasugrel	Yes	[55]
Bupropion	Ritonavir	Yes/No	[56, 57]
Bupropion	Ticlopidine	Yes	[54]
Mirtazapine	Amitriptyline	No	[58]
Mirtazapine	Cimetidine	Yes	[59]
Mirtazapine	Lithium	No	[60]
Mirtazapine	Paroxetine	Yes	[61]
Nefazodone	Cimetidine	Yes	[62]
Nefazodone	Desipramine	No	[63]
Nefazodone	Lithium	No	[64]
Nefazodone	Lorazepam	Yes	[65]
Trazodone	Clarithromycin	Yes	[66]
Trazodone	Ritonavir	Yes	[67]
SNRI			
Duloxetine	Fluvoxamine	Yes	[68]
Duloxetine	Paroxetine	Yes	[69]
Venlafaxine	Cimetidine	Yes	[70]
Venlafaxine	Diphenhydramine	Yes*	[71]
Venlafaxine	Ketoconazole	Yes	[72]
Venlafaxine	Terbinafine	Yes	[73]
Venlafaxine	Voriconazole	Yes	[73]
SSRI			
Citalopram	Ketoconazole	No	[74]
Escitalopram	Cimetidine	Yes	[75]
Escitalopram	Omeprazole	Yes	[75]
Escitalopram	Ritonavir	Yes	[76]
Fluoxetine	Alosetron	Yes	[77]
Fluoxetine	Desloratadine	Yes	[78]
Paroxetine	Cimetidine	Yes	[79]

Class/Agent	Potential Interacting Drug	↑AUC or ↓clearance	Reference
Paroxetine	Terbinafine	Yes	[80]
Sertraline	Donepezil	No	[81]
TCA			
Amitriptyline	Cimetidine	Yes	[82]
Amitriptyline	Diazepam	Yes	[83]
Amitriptyline	Divalproex	Yes	[84]
Amitriptyline	Fluvoxamine	No	[85]
Amitriptyline	Ketoconazole	Yes	[86]
Amitriptyline	Orlistat	No	[87]
Desipramine	Atomoxetine	No	[88]
Desipramine	Duloxetine	Yes*	[69]
Desipramine	Fluoxetine	Yes	[89,90]
Desipramine	Ketoconazole	No	[91]
Desipramine	Paroxetine	Yes*	[92,93]
Desipramine	Sertraline	Yes	[90,93]
Desipramine	Temsirolimus	Yes	[94]
Doxepin	Cimetidine	Yes	[95]
Imipramine	Cimetidine	Yes	[96–98]
Imipramine	Diltiazem	Yes	[99]
Imipramine	Fluoxetine	Yes	[101]
Imipramine	Labetolol	Yes	[99]
Imipramine	Ketoconazole	Yes	[91]
Imipramine	Paroxetine	Yes	[100]
Imipramine	Ranitidine	No	[97]
Imipramine	Verapamil	Yes	[99]
Nortriptyline	Cimetidine	No	[82,98]
Nortriptyline	Divalproex	Yes	[84]
Nortriptyline	Fluvoxamine	No	[85]
Nortriptyline	Paroxetine	Yes	[101]

*in extensive metabolizers only

Abbreviations: MAOI=monamine oxidase inhibitor; NA= none available; SNRI=selective norepinephrine reuptake inhibitor, SSRI= selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

Table 4

Potential pharmacokinetic drug interactions with antidepressants from FDA-approved drug package labeling

Class/Agent	Potential Interacting Drug	↑AUC or ↓clearance	Reference
MAOI			
Selegiline	Alprazolam	N/A	
Selegiline	Cabergoline	N/A	
Selegiline	Citalopram	N/A	
Selegiline	Itraconazole	N/A	
Selegiline	Olanzapine	N/A	
Selegiline	Risperidone	N/A	
Other Antidepressant			
Bupropion	Cimetidine	Yes	[45]
Bupropion	Clopidogrel	N/A	
Bupropion	Prasugrel	N/A	
Bupropion	Ritonavir	N/A	
Bupropion	Ticlopidine	N/A	
Mirtazapine	Amitriptyline	N/A	
Mirtazapine	Cimetidine	Yes	[46]
Mirtazapine	Ketoconazole	Yes	[46]
Mirtazapine	Lithium	N/A	
Mirtazapine	Paroxetine	N/A	
Nefazodone	Cimetidine	N/A	
Nefazodone	Desipramine	N/A	
Nefazodone	Lithium	N/A	
Nefazodone	Lorazepam	N/A	
Trazodone	Clarithromycin	N/A	
Trazodone	Ritonavir	Yes	[102]
SNRI			
Duloxetine	Fluvoxamine	Yes	[47]
Duloxetine	Paroxetine	Yes	[47]
Venlafaxine	Cimetidine	Yes	[103]
Venlafaxine	Diphenhydramine	N/A	
Venlafaxine	Ketoconazole	Yes	[103]
Venlafaxine	Terbinafine	N/A	
Venlafaxine	Voriconazole	N/A	
SSRI			
Citalopram	Cimetidine	Yes	[104]
Citalopram	Ketoconazole	N/A	
Escitalopram	Cimetidine	Yes	[105]
Escitalopram	Omeprazole	N/A	
Escitalopram	Ritonavir	N/A	
Fluoxetine	Alosetron	N/A	

Class/Agent	Potential Interacting Drug	↑AUC or ↓clearance	Reference
Fluoxetine	Desloratadine	N/A	
Paroxetine	Cimetidine	N/A	
Paroxetine	Duloxetine	N/A	
Paroxetine	Terbinafine	N/A	
Sertraline	Cimetidine	Yes	
Sertraline	Donepezil	N/A	
Vilazodone	Ketoconazole	Yes	[106]
TCA			
Amitriptyline	Cimetidine	N/A	
Amitriptyline	Diazepam	N/A	
Amitriptyline	Divalproex	N/A	
Amitriptyline	Fluvoxamine	N/A	
Amitriptyline	Ketoconazole	N/A	
Amitriptyline	Orlistat	N/A	
Desipramine	Atomoxetine	N/A	
Desipramine	Duloxetine	N/A	
Desipramine	Fluoxetine	N/A	
Desipramine	Ketoconazole	N/A	
Desipramine	Nefazodone	N/A	
Desipramine	Paroxetine	N/A	
Desipramine	Sertraline	N/A	
Desipramine	Temsirolimus	N/A	
Doxepin	Cimetidine	N/A	
Imipramine	Cimetidine	N/A	
Imipramine	Diltiazem	N/A	
Imipramine	Fluoxetine	N/A	
Imipramine	Labetalol	N/A	
Imipramine	Ketoconazole	N/A	
Imipramine	Paroxetine	N/A	
Imipramine	Ranitidine	N/A	
Imipramine	Verapamil	N/A	
Nortriptyline	Cimetidine	N/A	
Nortriptyline	Divalproex	N/A	
Nortriptyline	Fluvoxamine	N/A	
Nortriptyline	Paroxetine	N/A	

Abbreviations: MAOI=monamine oxidase inhibitor; NA= none available; SNRI=selective norepinephrine reuptake inhibitor, SSRI= selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

Appendix A

Antidepressants Included in This Study*

Antidepressant	Year first released	Pharmacologic Class
Methylphenidate	1955	Other
Isocarboxazid	1959	MAOI
Imipramine	1959	TCA
Tranylcypromine	1961	MAOI
Amitriptyline	1961	TCA
Desipramine	1964	TCA
Nortriptyline	1964	TCA
Doxepin	1969	TCA
Trimipramine	1979	Tetracyclic
Amoxapine	1980	Tetracyclic
Maprotiline	1980	Tetracyclic
Bupropion	1985	Other
Trazodone	1986	Other
Fluoxetine	1987	SSRI
Paroxetine	1992	SSRI
Venlafaxine	1993	SNRI
Nefazodone	1994	Other
Mirtazapine	1996	Other
Citalopram	1998	SSRI
Escitalopram	2002	SSRI
Duloxetine	2004	SNRI
Selegiline (patch form)	2006	MAOI
Desvenlafaxine	2008	SNRI
Vilazodone	2011	Other

* drugs@fda listed at www.accessdata.fda.gov/scripts/cder/drugsatfda/

MAOI=monamine oxidase inhibitor; SNRI=selective norepinephrine reuptake inhibitor, SSRI= selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant