Pharmacokinetic and pharmacodynamic alterations in older people with dementia

Abstract

**Introduction:** The number of people with dementia internationally is increasing. Older adults with dementia are prescribed multiple medications, both to treat dementia symptoms and to manage their other medical conditions. Dementia is correlated with increasing age and frailty; this provides insight into how the efficacy and toxicity of medications may be altered in people with dementia.

**Areas covered:** This review discusses the current evidence of the alterations in pharmacokinetics that can occur with aging, frailty and in people with dementia. The evidence is presented via the four primary pharmacokinetic processes (absorption, distribution, metabolism and elimination). Additionally, distribution into the brain, sex considerations and potential pharmacodynamic alterations in older people with dementia are discussed.

**Expert opinion:** While the evidence is limited, people with dementia appear to be at a higher risk of toxicity of some medications due to altered pharmacokinetic processes and pharmacodynamics. There are a number of limitations to the research and there are still significant gaps in knowledge in this field. Proactive, ongoing review of the appropriateness of choice of medication, dose and whether or not a medication is required at all is necessary for achieving quality use of medications in people living with dementia.

**Key words**
Blood Brain Barrier, Dementia, Frailty, Older adults, Pharmacodynamics, Pharmacokinetics
1. Introduction

In 2015, internationally, 46.8 million people lived with dementia. This number is estimated to increase to 131.5 million by 2050 (1). As Fontana, Kennedy and Longo (2) states, “The problems of old age come as a package”. Most people with dementia have additional medical conditions, such as cardiovascular disease, depression, diabetes, chronic obstructive pulmonary disease and musculoskeletal disorders (3,4). Therefore, people with dementia are often prescribed multiple medications, both to treat dementia symptoms and to manage their other medical conditions. Although the number of medications taken by people with dementia vary by study population and country, most who live in the community take approximately 4-5 different regular medications (3,5,6), while those in nursing homes take approximately 6-12 (4,7). The purpose of this narrative review is to examine the potential alterations in pharmacokinetics and pharmacodynamics that may affect the efficacy and toxicity of medications used by people with dementia.

1.1 Dementia

Dementia is an inclusive term for a syndrome characterized by a progressive decline in cognition, functioning and behavior. Dementia is caused by neuronal damage leading to symptoms of memory loss, impaired reasoning and judgment, difficulty with language and communication and other cognitive skills (8). In the most recent Diagnostic and Statistical Manual of Mental Disorders (DSM-V) the condition previously called ‘dementia’ is now termed ‘Major Neurocognitive Disorder’. Its core feature is change in an individual’s cognition to the extent that it interferes with their ability to carry out important every day activities (9). As such dementia is associated with both cognitive and functional decline.

Dementia has many causes, with the most common single etiology being Alzheimer’s disease (AD, 60-80% of cases), followed by vascular dementia and dementia with Lewy Bodies. Although, at autopsy, mixed pathologies are seen most commonly, this fact has variable impact on how much dementia research is categorized, so that single causes still receive the most attention (8). Additionally, dementia is a progressive disease with severity ranging from mild to very severe. Transition through these stages is highly variable, and since the advent of widespread use of symptomatic treatment (i.e. cholinesterase inhibitors and memantine) it is common to see patients who combine features that cross stages as they were defined in the pre-treatment era (10).

1.2 Representation of people with dementia in clinical trials

It is necessary to consider potential changes in pharmacokinetics and pharmacodynamics in people with dementia to help extrapolate the results of large randomized controlled drug trials to this population. People with dementia are commonly excluded from the trials to establish the efficacy of medications to treat conditions like diabetes, heart failure and hypertension, despite these being common co-morbidities. For example, the prevalence of diabetes in people with dementia is 6-39% (11). There are many reasons why people with dementia may be under-represented in clinical trials, although these issues can be overcome with careful planning and increased resources (12). Narrow inclusion criteria improves the homogeneity of the population, which reduces the variability in outcomes measured, producing a clearer result that is easier to attribute to the intervention (often sought in drug development). Additionally, older age, multiple co-morbidities and medications are risk factors for mortality and other adverse outcomes; therefore, excluding this population minimizes drop-out rates and reduces the complications of drug-drug and drug-disease interactions. There are also feasibility issues to address when including people with dementia in clinical trials, such as reminders to attend multiple follow-ups and assessments that can be validly completed by a person with dementia. There may also be ethical and legal dilemmas surrounding recruitment of people...
without capacity to consent for participation in clinical trials. However, having this as an exclusion criteria may actually threaten the ethical principles of autonomy and justice (12,13). Furthermore, it limits the ability of health care professionals to make evidence-based treatment decisions for their patients who have dementia with multiple morbidities and polypharmacy.

Dementia is most prevalent in the oldest old and it has been reported repeatedly that older adults are under-represented in clinical research, although this is improving with time and greater recognition of this issue (13,14). While upper age limits are disappearing, eligibility criteria may still disproportionally affect older individuals and those with dementia. A systematic review of inclusion of older adults in randomized controlled trials found that almost half of the studies did not include an upper age limit, but had exclusion criteria that would limit involvement of the older population, e.g., decreased life expectancy (22% of studies), physical disability or functional limitations (18%), inability to give informed consent (11%) and age-related cognitive impairment (5.5%) (14). This review also identified that subgroup analyses based on age were not routinely conducted and often underpowered. Where sub-group analysis was conducted a small but substantial proportion (17%) did find a difference in treatment effect by age.

Even in clinical studies on the effect of medications used to treat dementia, exclusion criteria commonly limit generalizability to the wider population of people with dementia. A systematic review of dementia protocols recorded in a Dutch online registry found that most studies focused on people with less severe stages of dementia, who were still living at home and were otherwise healthy (15). Exclusion criteria included upper or lower age limits (60% of protocols), inability to consent (51%), residence in a nursing home (22%), severe dementia (78%), visual or hearing impairment (22%), medication use (38%), somatic co-morbidities (54%) and neurological conditions (56%). Overall, only 14% of the protocols had none of these exclusion criteria. A recent systematic review of Alzheimer’s disease clinical trials conducted between 2000 and 2015 identified that only 8% of participants were greater than 85 years old, despite approximately one third of people with dementia falling into this age category (16). It can, therefore, not be assured that the results of clinical trials are generalizable to all people with dementia, particularly those with multiple morbidities, taking multiple medications (13).

2. Altered pharmacokinetics in people with dementia

2.1 Aging, frailty and dementia

Little research was identified which specifically studied changes in absorption, distribution, metabolism and elimination in people with dementia, compared to those without. There are, however, two key pieces of information about people with dementia that provide insight into using medications safely and effectively in this population. Firstly, dementia is correlated with increasing age, and secondly, it is associated with increased frailty (figure 1).

The incidence of dementia is approximately doubled every 6.3 years from the age of 60 (1). In the United States, 96% of people with dementia are aged 65 years or older (17). Almost one in ten people over the age of 65 have dementia, and three out of every ten people over the age of 85 (18).

Frailty is a condition of cumulative reduction in function of multiple organs and systems. It is typically described and measured either as a phenotype (characterized by combinations of unintentional weight loss, exhaustion, grip weakness, slow walking speed and low physical activity)(19) or a cumulative deficit model (i.e. the Frailty Index) (20). Individuals categorized as frail are highly vulnerable to external stressors and have less ability to recover after an event (poor
resolution of events that perturb homeostasis). The development and progression of frailty is highly correlated with age (21). Frailty has been found to be independently associated with dementia and reduced cognitive function in a number of studies, although there is heterogeneity present in the dementia-frailty link (22–26). It has been suggested that dementia and frailty may share a common underlying etiology (22) for which aging itself appears to be implicated (2). Approximately 15% of community dwelling older adults with dementia can be classified as frail (27). This may increase to 50% in those greater than 85 years (28,29) and up to 80% amongst those residing in residential aged care facilities (30,31). Another consideration about how frailty relates to dementia extends into its prodrome, often to as “Mild Cognitive Impairment” (MCI) (32). The notion of MCI has even been grouped with the frailty phenotype (19) (which does not include cognition as a defining feature) into an entity referred to as “cognitive frailty” (24,33,34). Whether the grouping of the two suggests a distinctive new condition or the manifestation of shared causal features is controversial (35).

2.2 Absorption

Hypochlorhydria (reduced gastric acidity) due to gastric mucosal atrophy is more common in older adults and this may theoretically reduce the absorption of weakly basic drugs (e.g., ketoconazole)(36,37). Hypochlorhydria can also be caused by medications commonly used by older adults, e.g. anti-ulcer medications (38). Prescription of anti-ulcer medications in older adults has been found to be independently associated with use of cobalamin supplements, indicating that this alteration in gastric acidity through medication use in older adults can have important implications for absorption of essential nutrients (39). Transit time and passive permeability are most likely unchanged purely by the effect of aging, while carrier mediated permeability has been reported to be decreased (40,41). Age-related changes may affect the absorption of certain nutrients such as glucose, calcium and Vitamin B12, however, the clinical importance has not been confirmed (42,43). The effect of aging on the transport of drugs back into the gut lumen via P-glycoprotein (P-gp) (which results in decreased absorption) has not been extensively studied (41,44). In a single study in humans, no alteration in P-gp activity was observed to occur with increased age, however, this study involved healthy volunteers between the ages of 19 and 34 (45). More research is needed in this area.

The most clinically significant change in absorption that has been associated with aging is a reduction in first pass metabolism due to alterations in the liver structure and function (discussed further below). This is important for medications with a high first pass metabolism and a narrow therapeutic index. For example a significant difference between older and younger adults has been observed in the bioavailability of nifedipine (61% versus 46% respectively) (46). However, not all studies have found consistent changes in bioavailability of drugs with a high first pass metabolism with aging (40).

Ahmed et al. (47) investigated the pharmacokinetics of delta-9-tetrahydrocannabinol in ten older people with dementia. They found that there was a delayed time to maximum concentration (1-2 hours) in people with dementia and in healthy older adults, compared to younger adults (30 minutes to 1 hour). This indicates that there is an alteration in absorption of delta-9-tetrahydrocannabinol in older adults compared to younger adults, but no additional change in people with dementia. They did, however, observe high levels of heterogeneity in their results and more research is needed to determine whether other drugs have altered absorption in people with dementia.

Also relevant to oral administration of medications is the composition of intestinal microbiota which secrete a varied range of enzymes. At least thirty drugs are known to be substrates for these bacterial enzymes, with particular concern focused around the toxicity of the metabolites (48). Older adults have been found to have substantially altered gut microbiota than that of younger adults (49).
Additional changes have been found in older adults with high frailty scores, for example, reduced lactobacilli and increased Enterobacteriaceae (50). Use of medications can also affect the microbiota, in particular antibiotics. More investigation is required into this area to determine the clinical significance of these changes on drug toxicity in older adults and those who are frail (41,48).

2.3 Distribution

Several changes in body composition associated with aging can affect the distribution of drugs throughout the body, that is, its availability at target (and toxicity) sites as well as metabolizing and eliminating organs. In general, aging is associated with a relative reduction in total body water and muscle mass and a relative increase in body fat (51,52). The classification of frailty is often defined by weight loss and reduced muscle strength (e.g. hand grip, reduced walking speed) or as a sum of clinical deficits (which can include physical impairments such as impaired mobility) (19,53). The definition in itself indicates that frail older adults will be those with the most exaggerated of these body composition changes. In a study of older adults with frailty classified via phenotype, frail older adults had reduced BMI and arm muscles (54). Frailty has also been associated with obesity and therefore greater body fat (55).

Older adults with AD are more likely to experience weight loss than the general population of older adults and people with dementia in residential aged care facilities have a two fold increase in the risk of anorexia than those without dementia (56). Various mechanisms have been proposed including abnormal feeding behaviors, pharmacological treatment (e.g. cholinesterase inhibitors causing anorexia), biological disturbances and medial temporal cortex atrophy (56,57).

How the aforementioned changes in body composition affect drug distribution depends on the properties of the drugs themselves, with water-soluble drugs having a reduced volume of distribution while lipophilic drugs will have increased volume of distribution. In terms of the potential effect of these changes on toxicity, a reduced volume of distribution (water soluble drugs) may lead to increased peak serum concentrations while lipophilic drugs may take longer to be cleared from the body (40,58). However, these changes in body composition are likely to have minimal, if any, effect on the total exposure to the drug as increased serum concentration leads to increased clearance (59). Therefore, these alterations may not be clinically important.

In addition to body composition, the volume of distribution of drugs (the theoretical volume of liquid that corresponds to the concentration of a drug in the blood after administration of a dose) can be influenced by the extent to which the drug binds to plasma proteins. The two main proteins which drugs bind to are albumin (usually acidic drugs) and alpha 1-acid glycoprotein (usually basic drugs). Only the unbound concentration of the drug is available to exert its therapeutic effect, therefore, changes in levels of these proteins may potentially affect efficacy and toxicity in an individual (60).

Older adults have been observed to have a reduced concentration of albumin compared to younger adults by approximately 5-15% (61–63). Albumin is further reduced in frail older adults by another 5% (54,62) and has been termed a ‘biomarker of aging’ due to its relationship with a number of negative health outcomes including heart attack, stroke, functional decline, mortality and cognitive decline (64). In a study of general medical inpatients in Italy, an increase in levels of cognitive impairment was associated with a decrease in serum albumin levels (65) and Ng et al. found low albumin (bottom quintile) to be independently associated with poor cognitive performance (66). Additionally, studies have found that older adults with dementia have, on average, approximately 10% lower albumin levels than healthy older adults (63,67).

The protein alpha 1-acid glycoprotein is generally unchanged in healthy older adults, however, may be increased in a number of chronic inflammatory diseases (40,68). Alpha 1-acid glycoprotein has
been found to be lower in people with dementia versus controls in some studies (69,70) but not significantly different in others (67).

As with changes in body composition, these changes in serum drug-binding proteins which are observed in older adults, frail adults and people with dementia may not produce clinically important changes in drug pharmacokinetics or necessitate dosing changes (40,59,71). Increased levels of the unbound drug (due to reduced albumin) at metabolism and excretion sites leads to a proportionate increase in elimination and therefore total exposure to the drug is unchanged (59). Drugs for which changes in protein binding may lead to clinically relevant effects are hepatically cleared drugs with high extraction ratios when given intravenously such as diltiazem, fentanyl and erythromycin (59). Drugs that are highly protein bound, have a high clearance and are not titrated to effect (e.g. antibiotics) may also be clinically affected by altered protein binding (60). If therapeutic drug monitoring is being conducted, allowances need to be made based on altered plasma protein levels as it is only the unbound concentration that will be relevant and not the total serum concentration (which is often the value measured in laboratory testing) (68,72).

2.4 Changes in the blood-brain barrier

The ability of drugs to reach the brain has important implications for people with dementia, both in treatment of the disease as well as cognitive side effects (73). The Blood Brain Barrier (BBB) is a layer of tight endothelial cells which function as a protective barrier, limiting the access of hydrophilic and large molecules, while still allowing movement of essential substances such as oxygen and carbon dioxide (74). It is believed that alterations in the BBB may, in fact, contribute to the onset and the progression of dementia (74).

Farrall and Wardlaw (75) conducted a systematic review in 2009 of the changes in BBB permeability with age and in certain disease states, including dementia. The majority of included studies used biochemical techniques (such as CSF/plasma albumin ratio) while a smaller number employed imaging techniques. Their meta-analysis of younger adults versus older adults found that increasing age was significantly associated with increased BBB permeability. They identified nineteen studies which compared people with dementia to age matched controls without dementia. Ten of these reported increased BBB permeability in dementia, while the remaining nine found no significant difference. Their analysis of available numeric data showed an overall significant increase in BBB permeability. When directly comparing patients with vascular dementia (VD) versus patients with AD, increased BBB permeability was found in those with VD. Their review was limited by significant heterogeneity between the studies and limitations of the included studies themselves. Due to the limited studies which assessed BBB permeability with disease duration or severity, this review was not able to ascertain if the changes in BBB permeability are causal or consequential (75).

Recently, attention has also been directed towards the activity of the efflux transporter P-glycoprotein (P-gp) at the BBB (74,76). P-gp plays a protective role by transporting substances immediately out of the brain, restricting uptake (77). Toornvliet et al (77) investigated whether the activity of P-gp is changed with age by studying the pharmacokinetics of (R)-[11C]verapamil in five young healthy volunteers (aged 21-27 years) and five healthy older adults (aged 59-68 years). They concluded that their data supports a decreased P-gp activity in the BBB in older adults. In contrast to this study, no difference was observed in P-gp expression at the BBB in aging rodents (78).

As with BBB permeability, P-gp changes have been proposed to play a role in the development of neurodegenerative diseases. A study, again using (R)-[11C]verapamil, investigated the activity of P-gp at the BBB in thirteen participants with AD versus fourteen age matched controls. They found altered brain pharmacokinetics in the AD participants suggesting that the activity of P-gp at the BBB
is compromised in these patients (79). These results were replicated in 2014, with the suggestion that impaired P-gp activity may contribute to development and progression of AD (through reduced clearance of beta-amyloid) (80).

These changes in the integrity of the BBB in older adults and people with dementia may lead to increased access of drugs to the brain and be responsible for the increased risk of adverse drug reactions in this population (76). A study utilizing a mouse model of AD, aimed to determine if BBB alterations change the distribution of therapeutics in the brain (81). They identified reduced P-gp expression, but no alteration in the brain uptake of several P-gp substrates (digoxin, loperamide and verapamil). The authors concluded that other BBB alterations in the AD mouse model (such as increased microvascular basement membranes) may have counteracted the effect of altered P-gp activity on the distribution of these drugs. Clinical studies support the hypothesis that alterations in the BBB in older adults and people with dementia increases the risk of adverse drug reactions (76).

For example, older adults have been found to be more sensitive to the cognitive effects of scopolamine than younger adults, although other factors such as a decline in the cholinergic system and reduced drug elimination may complicate the interpretation of these results (82). Additionally, increased permeability of the BBB has been identified as a predisposing factor for beta-lactam antibiotic neurotoxicity (83). In a preliminary report, Reeves reports a clinically significant effect and adverse drug events in older adults with AD prescribed very low doses of amisulpride. The levels of amisulpride in the blood were low as expected by the dose (lower than optimal blood levels in younger adults), indicating increased distribution of amisulpride into the brain (84).

2.5 Metabolism

Prior to elimination from the body, many drugs are metabolized to detoxify the substance and increase its solubility in water, aiding elimination via the kidneys. Metabolism can also result in a more toxic metabolite or may be responsible for converting the drug into its active form (85). The majority of metabolism occurs in the liver, however, metabolizing enzymes can be found throughout the body (86). Aging has been shown to affect Phase I metabolism (oxidation, reduction and hydrolysis) and Phase II metabolism (glucuronidation, acetylation and sulfation) differently (85).

In general, Phase I metabolism via Cytochrome P450 (CYP) enzymes reduces with increasing age (40,85,87–89). This reduction in metabolizing capacity is thought to be mostly due to a reduction in the size of the liver and reduced blood flow to the liver. It has been observed that older adults have a 20-30% reduction in liver mass and a 20-50% reduction in liver blood flow (85,89,90). This is especially true for drugs with a high extraction ratio, as their rate of metabolism is dependent on the rate at which the drug is delivered to the liver (more than the speed at which the drug is metabolized in the liver). Butler and Begg (88) conducted an extensive review and re-analysis of data on the alterations in metabolism in older compared to younger adults based on the unbound plasma concentration. They found that medications with high extraction ratios had approximately 30-50% reduction in metabolism. For example, metabolism of levodopa is reduced by 39% in old age, while that of amitriptyline is 62% lower.

Additionally, alterations in liver structure may reduce the ability of certain substances to cross from the blood into hepatocytes, contributing to observed reductions in metabolism. Pseudocapillarization describes endothelial thickening, defenestration and collagen deposition which has been observed to occur with aging (91,92). Animal studies have found that fenestrations in the sinusoidal endothelium may be important determinants of hepatic pharmacokinetics of liposomal formulations (e.g. liposomal doxorubicin) and that in old age, with pseudocapillarisation, there is reduced transfer of drugs that are highly protein bound (e.g. diazepam) (93,94), with a smaller but significant impact on acetaminophen transfer (95).
Studies are not consistent, but it is generally considered that the metabolizing capacity of CYP enzymes does not decrease with age (40,96). This was however, challenged by the same review by Butler and Begg (88) who found that drugs with a low extraction ratio (i.e. those that are capacity limited in their metabolism rate) also had reduced metabolism of degrees up to 60%. This may be explained due to reduced liver size and reduced entry of oxygen due to pseudocapillarization into hepatocytes (as CYP enzymes require oxygen as a co-substrate) (92). However, animal studies have not found evidence of reduced oxygenation of hepatocytes in old age (97,98).

Increasing frailty has been associated with increases in multiple inflammatory makers such as C-reactive protein (CRP) and interleukin-6 (IL-6) indicating either a contributory role of inflammation in aging and frailty, or an outcome of it or a shared pathway (99,100). High levels of inflammation are known to down-regulate drug metabolism and transporter pathways (101,102). Infection and inflammation (for example due to auto-immune diseases, trauma or burns) can reduce the metabolizing activity of CYP enzymes by 20-70% (102). Rivory et al (103) investigated the activity of CYP3A4 enzyme in patients with lung and breast cancer using the antibiotic erythromycin. Participants in an acute inflammatory stage (measured by CRP > 10 mg/L) had a reduced metabolic clearance of the CYP3A4 substrate. In this study, CRP and IL-6 were significantly correlated and they also found an inverse association between CRP and metabolism of erythromycin. The levels of the inflammatory markers CRP and IL-6 in frail older adults found in the study by Hubbard et al. (99) is comparable or greater than those of the participants in the study by Rivory et al (103) (mean 16.9mg/L and 47.67 pg/mL versus median 13.0mg/L and 5.6 pg/mL respectively). Schwartz (104) investigated whether CYP3A4 metabolism was decreased in frail older adults (independent of aging), again using erythromycin as the test substrate. They were, however, not able to show an additional reduction in metabolism of erythromycin in frail versus robust older adults. Although these conclusions are limited as erythromycin is an imperfect probe of CYP3A4 activity since it also reflects P-gp activity (105).

In addition to CYP enzymes, the activity of esterases, also Phase I metabolizing enzymes, has been investigated in older and frail older adults. Using over 100 healthy participants aged 18 to 85, Abou-Hatab and colleagues (106) found no relationship between age and activity of esterases in the plasma. This was replicated by Hubbard et al. in 2008 (99) who hypothesized that activity is maintained in healthy older adults but reduced in frail older adults. They found that plasma acetylcholinesterase, butyrylcholinesterase and benzoylcholinesterase reduced significantly with increasing frailty. Aspirin esterase, however, was unchanged. The esterases are also responsible for converting several drugs administered in an inactive form (so called pro-drugs) to their active form, e.g. enalapril (107). It is therefore possible, that frail older adults might have reduced conversion to the active form and therefore, reduced efficacy of such drugs.

Phase II metabolism is considered to be unaltered in healthy older adults. However, recent studies indicate that it is reduced in frail older adults. The clearance of acetaminophen (which undergoes Phase II metabolism) was investigated in 19 young adults, 20 fit older adults and 9 frail older adults. Metabolism to the glucuronide conjugate was found to be preserved in the older compared to the younger adults, but significantly reduced in the frail participants (108). Similarly, the clearance of metoclopramide, which is metabolized by sulfation and glucuronidation, is significantly reduced in frail compared to fit older adults and fit younger adults (109). Frail older adults may also be at greater risk of toxicity, above that expected by the reduced clearance (greater levels of exposure to the drug). For example, the reduced glucuronidation of acetaminophen can lead to production of a toxic intermediate via an alternative Phase I metabolic pathway. This toxic metabolite is quickly neutralized via conjugation with glutathione, however, frail older adults can have reduced glutathione stores.
A recent study by Kane et al. investigated acetaminophen toxicity in older and frail mice. They found a negative correlation between frailty and albumin and the liver enzyme alkaline phosphatase (ALP), however, observed no difference in hepatotoxicity between the young, old or frail mice (111). This is consistent with observational clinical data that found no evidence of an increased risk of elevated liver enzymes with therapeutic doses of paracetamol between younger, older robust and older frail acute inpatients, despite higher paracetamol levels in the frail older patients (112).

Liver enzymes including ALP, alanine transaminase (ALT) and gamma-glutamyltransferase (GGT) are often used as markers of liver disease. Low ALT has been associated with frailty (62) as has high GGT and ALP (55). High GGT activity has been found in 25% of people with AD (113). The impact, if any, of these findings on drug metabolism in frail older adults and people with dementia is yet to be determined.

2.6 Renal elimination

The kidneys are responsible for elimination of the majority of drugs and/or their metabolites from the body. It is generally considered that an increase in age is associated with a reduction in kidney function and therefore reduction of the renal excretion and increased toxicity of renally excreted drugs (114). However, it may not be purely aging that is responsible for the effect seen. Older adults are highly heterogeneous and they commonly have co-morbidities that can negatively affect renal function, such as diabetes and hypertension (115). Recent reviews have concluded that there is an overall reduction of kidney function and reduced clearance of renally excreted drugs with increasing age, but not to the same magnitude as previously suggested and likely contributed to by co-morbidities and medications common in older adults (116,117). Renal function reserve may be reduced in older adults, that is, they have reduced capacity to respond to and recover from an acute assault on their renal function (118,119). This impaired ability to recover homeostasis is a hallmark of the definition of frailty. In accordance with this, older adults who are classified as frail, have been found to have poor renal function and reduced clearance of renally excreted drugs (55,100,120–122).

Shubert et al. found that renal failure was more common in people with dementia in primary care than those without (11.2% versus 8.3%) (3). In hospitalized people with dementia, Zuliani et al. identified that renal failure was more commonly reported as a primary reason for admission in people with dementia than in control cases (123). A number of cross-sectional and longitudinal studies report that chronic renal failure, and perhaps even moderate renal impairment is an independent risk factor for cognitive decline (124–126). Because of this, renal function should be assessed regularly in people with dementia, especially when initiating a new medication. However, serum creatinine and standard formulas for calculating renal function may not be accurate in frail older adults with dementia (127). Creatinine is a product of muscle breakdown and as such the levels in the serum are dependent not only on the rate of elimination via the kidneys but also muscle mass. As discussed, frail older adults and people with dementia often have reduced muscle, and therefore reduced production of creatinine (128). This masks a reduction in renal function when viewed on its own. Formulas such as the widely used Cockcroft and Gault equation adjust for body weight but have been shown to be inaccurate in older adults (118,129–131). The Cockcroft and Gault equation has been historically, and is still, used in guidance for drug dosing in many standard pharmacopeias (130,131) and does reflect gentamicin clearance accurately in frail and robust older people (122).

2.7 Sex considerations

In addition to considering the potential alterations in pharmacokinetics with aging and frailty, safe and effective treatment of people with dementia needs to also consider potential sex differences. The prevalence of dementia is higher among women than men (up to 32% higher in some countries) (1).
While this may be because women live longer than men, in the oldest age category alone, prevalence is still higher in women than men indicating that it is not purely due to increased life-expectancy (1).

An early study using radiolabeled cellulose demonstrated that gastric emptying, small intestinal transit and colonic transit did not differ between men and women (132). However, subsequent examination of gastric transit suggested that gastric and colonic emptying is slowed in women (133) which may increase bioavailability. Gastric pH has been observed to be higher in females (134) which may increase absorption of basic medications such as cholinesterase inhibitors. Absorption of some drugs is also influenced by intestinal CYP concentration and activity. CYP3A4 substrates such as verapamil and midazolam demonstrate increased bioavailability in women, indicating a potential reduction in CYP3A4 metabolism in the gut (135,136). However in 2005, a detailed analysis of duodenal pinch biopsies from 48 men and 45 women was unable to find any clinically meaningful difference in intestinal CYP3A4 content (137). Similarly P-gp differences in the intestinal lumen have been hypothesized to contribute to differences in absorption between sexes, however this was not demonstrated in a clinical study (137).

In older adults, males remain larger than females with increased height, body mass index and waist circumference while women have increased adiposity (138). This difference in body composition has failed to show much difference in actual drug distribution and any differences attributable to this can largely be explained by differences in total body mass (139).

Hepatic metabolism variations by sex have been observed for several of the CYP enzymes, however, there is large variability in the findings. CYP2D6 activity was predicted to be up to 20% reduced in females (140) however this has been contradicted by other researchers (141–143). CYP2C19 activity does not display a consistent difference between men and women. For CYP2C9, sex does not seem to produce any effect (143–145). CYP1A2 was found to be slower in women than in men in Chinese populations (146) while in Nigerian and American populations significant sex-related differences could not be demonstrated (143,147). CYP3A4 activity measured using lidocaine levels failed to demonstrate any variation in pre-menopausal women, postmenopausal women or men (148). The variability in whether or not these studies found an effect of gender on activity of CYP activity may be explained by the differences in study designs. Notably many of the studies may have been underpowered to detect a small difference in activity. Additionally, different drugs were used, many of which undergo metabolism through multiple CYP metabolism pathways, making it difficult to draw conclusions about a single enzyme.

Renal clearance is also linked strongly to body weight and therefore the aforementioned sex difference in body composition may lead to altered clearance. Pharmacokinetic studies have confirmed this finding for many drugs including digoxin which has slower clearance in females (149).

Overall, study results exploring sex-related differences in pharmacokinetics fail to show consistent findings. As absorption is potentially increased and metabolism is potentially slowed in women this does suggest that women may be exposed to higher concentrations of medication than men at the same dose. This, and their smaller size, is in keeping with the experience of women being more likely to experience adverse drug reactions (150) and does support clinicians using the lowest possible doses of medication in older women and to titrate to desired response.

3. Altered pharmacodynamics

In addition to pharmacokinetic alterations related to age, frailty and dementia, the efficacy and safety of medications is affected by altered pharmacodynamics. The pharmacodynamics of a drug describes
the interaction of the drug with the receptor or biological site of action and the resulting clinical effect (151–153). While the changes in pharmacokinetics with aging described above can be somewhat predictable and measurable, altered pharmacodynamics are more complicated to investigate and to predict in individual cases (153). There are several known increases and decreases in efficacy and toxicity of certain drugs in older adults (152). In 2007, Bowie and Slattum reviewed this (152) finding several studies reporting altered pharmacodynamics with CNS and cardiovascular drugs. For example, older adults have a decreased sensitivity of their cardiac beta-1 and beta-2 adrenergic receptors and therefore a decreased response to beta agonists (152,154). Studies have found no difference between younger and older adults in the effect of alpha antagonists and angiotensin-converting enzyme inhibitors, and an inconsistent effect with sulfonylureas (152). This review concluded that older adults, in general, have a greater sensitivity to drugs, which can lead to greater toxicity. However, more research with specific drug classes is needed to explore and understand this phenomenon.

There is little investigation, if any into the effect of frailty, above and beyond chronological age, on pharmacodynamics (87). However, it is conceivable, that in older adults with reduced baseline function and reduced homeostasis, the effect of drugs at their site of action may be exaggerated.

Use of drugs with anticholinergic effects is of particular concern in people with dementia. A reduction in acetylcholine in the brain has been directly linked to the presence of AD and severity of the disease (155–157). In 1988, Sunderland et al found that participants with AD displayed a significantly greater response to administration of an anticholinergic drug than older adults without AD that could not be attributed to altered pharmacokinetics (157). They also found, however, that there was no altered response in the participants with dementia to administration of the benzodiazepine, lorazepam. Older adults have been found to be more sensitive to the sedative effects of benzodiazepines than younger adults (152), but this study indicated that there is no additional sensitivity conferred by the presence of AD (157).

The reduction in acetylcholine, coupled with increased permeability of the BBB discussed previously, places people with dementia at a greater risk of the central adverse effects of anticholinergics (151,155). Salahudeen et al conducted a systematic review into the effect of withdrawal of anticholinergics on cognition (158). Of the four studies identified, the two cohort studies showed improved cognition upon withdrawal of these agents, while the two randomized studies found no effect. Studies with larger sample sizes, longer follow-up and robust assessment of cognition and behavior are required to determine whether or not a clinically significant benefit occurs upon withdrawal of anticholinergics (158).

Antipsychotic drugs (neuroleptics) may be prescribed to people with dementia to control negative behavioral and psychological symptoms. Neuroleptic sensitivity (specifically extrapyramidal reactions) is significantly more common in patients with Lewy Body dementia (up to 80%) (159) than in patients with Alzheimer’s disease (160). This predisposition to severe neuroleptic sensitivity in patients with Lewy Body dementia may be due to a relative loss of dopaminergic neurons and failure to up-regulate Dopamine-2 (D2) receptors in response to D2 antagonists and/or the anti-muscarinic properties of the drugs (159,161). Additionally, the risk of cerebrovascular events in patients using risperidone is greater in people with vascular or mixed dementia than in those with AD (OR = 5.26, 95% confidence interval = 1.18-48.11 versus OR = 2.23, 95% confidence interval = 0.85-6.88 respectively). It is not clear whether this increased risk represents a pharmacodynamic difference or differences in the susceptibility and co-morbidity profile of people with vascular dementia (162).

Because of their minimal effectiveness in treating these symptoms and established harms (increased risk of mortality and cerebrovascular events), antipsychotics should generally only be used short term (less than 3 months) in people with dementia (regardless of the underlying etiology) (163).
Multiple studies have found that a significantly lower proportion of people with dementia are prescribed analgesic medications than older adults without dementia (7). There is a possibility of alterations in the pain pathways in people with dementia, leading to reduced pain. However, Cole et al. found that participants with AD had preserved pain-related brain activity as measured via functional MRI (164). Additionally, a reduction in cognitive function has been associated with reduced placebo response to administration of analgesics (165). These findings have led to concerns about under-detecting and under treatment of pain in people with dementia (7,87).

4. Conclusion

In conclusion, there is limited knowledge on whether there are specific systemic physiological changes in people with dementia and any impact on the efficacy and safety of medications in this population. Knowledge about the observed changes in pharmacokinetics and pharmacodynamics in robust and frail older adults may provide insight into quality use of medications in people with dementia. The most clinically important changes associated with aging are changes in body composition, liver structure and function and kidney function. In general people with dementia may have reduced clearance of drugs due to reduced metabolism and renal excretion and therefore may be more at risk of toxicity. Additionally, alterations in the BBB in people with dementia can lead to increased central exposure to therapeutic agents.

5. Expert opinion

This review has discussed ‘older adults’ versus ‘younger adults’, ‘frail’ versus ‘robust’ and ‘people with dementia’ versus those without. In reality, care of patients is never this black and white. An individual might have dementia, but not be chronologically ‘old’ or ‘frail’. Older adults show a great deal of inter-individual variability in the physiological characteristics discussed in this review (58,166,167). There may be a further increase in this variability within the category of ‘frail older adult’ (168), although this may be in comparison to those categorized as a ‘healthy older adult’. While aging and frailty are concepts defined by a reduction in functioning of body systems, neither is a dichotomous category; indeed, frailty finds its rationale in a way of understanding the heterogeneity in the risk of adverse health outcomes of people of the same age. In relation to safe use of medications, it may be best to consider aging and frailty as continuous states of increasing susceptibility to risks of medication use. That being said, there is still a large potential for older adults with dementia to benefit from medication use. Additionally, not all body systems/organs will be affected at the same rate, if at all. That is, an individual may have reduced lung function while maintaining good renal clearance (although there may still be reduced ability of the organs to recover from an acute event, e.g. dehydration). Alterations in pharmacokinetics and pharmacodynamics in people with dementia is highly dependent on the characteristics of individual drugs. Whether or not the drug is protein bound, its metabolic pathway and route of elimination will determine if there is likely to be a change in overall drug exposure.

The medications used to treat dementia symptoms (cholinesterase inhibitors and memantine) have varied pharmacokinetics and elimination pathways. Donepezil and galantamine undergo Phase I metabolism via CYP 2D6 and 3A4, rivastigmine is metabolized by esterases while memantine is mostly excreted unchanged in the urine (see review by Noetzli and Eap(169)). Knowledge about an individual with dementia (e.g. level of frailty or renal function) may influence drug selection, and an
alteration in an individual’s condition may necessitate review of ongoing appropriateness of cholinesterase inhibitors or memantine. Additionally, pharmacogenetics may play a role in guiding treatment choices for people with dementia (170). For example, those with the normal CYP2D6 function allele may have a better response to donepezil than those with the increased function CYP2D6 allele (171). However, the cost-effectiveness (including impact on patient relevant outcomes) of CYP genotyping in regular practice is unclear (170).

There are a number of limitations of the evidence discussed above. Interpretation of studies on frailty is complicated by the various ways in which frailty is assessed. This is true also for people with dementia. There is no definitive test for AD and other dementia types (8) and inclusion criteria for recruitment of people with dementia can vary between studies. Additionally, underlying disease pathology discovered on autopsy does not always agree with living diagnosis (172). There have been important improvements in studying frailty and dementia in animal models in recent years, however, limitations in the translatability of finding to humans still exists (173,174).

When reviewing the evidence discussed above, it is difficult to determine if statistically significant alterations in absorption, distribution, metabolism and elimination actually result in clinically meaningful changes in drug efficacy and toxicity. Whether or not these changes amount to increased toxicity or reduced efficacy and therefore whether dose adjustments are required can be hard to determine. Pharmacoepidemiological studies show that increasing age, frailty and cognitive impairment are all associated with an increased risk of experiencing adverse drug reactions (ADRs) (153,175). This increased susceptibility may be due to altered pharmacokinetics and pharmacodynamics but may also be contributed to by other factors associated with these conditions. People with dementia are likely to have multiple co-morbidities and polypharmacy which can lead to an increased risk of drug-drug and drug-disease interactions (153,175). There are a number of clinically important drug-drug interactions which can occur in people with dementia, for example the co-administration of ketoconazole (a strong CYP3A4 inhibitor) with donepezil (a CYP3A4 substrate) results in an increase in donepezil plasma concentrations (176) (see review by Pasqualetti et al (151)).

In a study of hospitalized geriatric patients with dementia in France, presence of a drug-drug interaction was significantly associated with occurrence of a serious ADR (177). Contrary to the studies mentioned above (153,175,178), a study of almost 17,000 participants in hospitals across Italy found that after adjusting for confounders, cognitive impairment was associated with a reduced risk of reported ADRs (179). However, when examining only neuropsychiatric ADRs, people with dementia were at greater risk than those without dementia (OR=2.23). It is possible than non-neurological ADRs go unrecognized in people with dementia due to their reduced ability to report these symptoms (179). Alternatively, health care professionals may not specifically ask about ADRs, or they may go unrecognized as an ADR and instead attributed to worsening condition (179).

Safe and effective evidence based treatment of people with dementia would benefit from greater inclusion of people with dementia, multiple morbidities and polypharmacy in trials. Where this is not possible, robust post-marketing pharmacoepidemiological surveillance should be conducted and reported routinely. Trials of new therapeutic agents should include greater investigation into appropriate dosing in various populations as current recommendations for reducing the dose in older adults are rarely evidence based. Ongoing investigations into the alterations in different pharmacokinetic processes in frailty and dementia (both human and animal models) is warranted, but there needs to be a greater emphasis on the system as a whole and mediating factors to clinical outcomes.

Overall, pharmacological treatment of people with dementia needs to be individualized. A ‘start low and go slow’ approach is a practical way of translating the knowledge about altered pharmacokinetics
and pharmacodynamics in this population. There are, however, circumstances in which this is not suitable. Appropriate dosing of antibiotics in severe infections would not follow this approach and instead should utilize therapeutic drug monitoring where possible. Additionally, use of analgesics, as discussed is underutilized in people with dementia, should be optimized with appropriate dementia specific pain monitoring. Further, due to the large inter-individual variability as well as the vastly different properties of different drugs a reduced maximum dose of all medications in older adults with dementia is not recommended.

Clinicians should monitor for both benefits and harms of medication use, not just following initiation of therapy but throughout treatment. Dementia is, in general, a progressive disease. As a person ages, their body composition, liver and renal function, co-morbidities and medications will change. Additionally, as the severity of the dementia increases the goals of treatment will change. Generally, the aims of treatment will switch from a focus on reducing future morbidity to managing symptoms and improving or maintaining quality of life. In the treatment of dementia, it is important to focus treatment monitoring towards symptoms which are important to the individual, in addition to using validated tools to objectively measure cognition and severity of dementia. Symptoms which are troubling to people with dementia and their caregivers (e.g. verbal repetition) may respond to treatment with cholinesterase inhibitors and this may not fully correlate with measures of cognition (180).

Proactive, ongoing review of the appropriateness of choice of medication, dose and whether or not a medication is required at all is necessary for achieving quality use of medications. Lists of medications which are considered potentially inappropriate in people with dementia and people with advanced dementia are available to assist clinicians in prescribing and deprescribing decisions (181–183). Deprescribing (supervised withdrawal) of medications which have become inappropriate over time with changes in physiology and treatment goals may reduce unnecessary harm, and allow for initiation and optimization of treatments that are appropriate (184). There are a number of barriers to achieving this ideal in practice such as a lack of guidelines, fragmentation of care and consumer values, beliefs and preferences (185), but it is a state of practice which researchers and clinicians should strive towards.

**Article highlights**

- Little research was identified which specifically studied changes in pharmacokinetics in people with dementia compared to those without. However, knowledge of the alterations that occur with aging and frailty can help inform using medications safely and effectively in this population.
- Several physiological changes were identified which may alter the pharmacokinetics of medications (additional to those associated with aging). People with dementia have an increased risk of weight loss as well as reduced albumin and possible reduced alpha 1-acid glycoprotein which can alter the volume of distribution of drugs. Reduced renal function is also common in this population.
- People with dementia (specifically Alzheimer’s disease and vascular dementia) have increased permeability of their blood brain barrier and reduced P-glycoprotein activity. These changes may lead to increased access of drugs to the brain and be responsible for the increased risk of adverse drug reactions in this population.
- Pharmacodynamically, reduced acetylcholine in the brain (observed in people with dementia) increases susceptibility to adverse cognitive side effects of anticholinergics.
Clinicians should monitor for both benefits and harms of medication use, not just following initiation of therapy but throughout treatment. Dementia is, in general, a progressive disease. As a person ages, their body composition, liver and renal function, co-morbidities and medications will change. Additionally, as the severity of the dementia increases the goals of treatment will change. Therefore, the efficacy, necessity and toxicity of medications may change in an individual over time.

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Conflicts of Interest

The authors declare no potential conflicts of interest with this manuscript. KR founded and has shares in DGI Clinical, a company that has contracts with pharma for individualized outcome measurement and advanced data analytics in Alzheimer disease, Parkinson disease and other disorders.

References


<table>
<thead>
<tr>
<th>Absorption</th>
<th>Older adults</th>
<th>Frail older adults</th>
<th>People with dementia</th>
<th>Comment</th>
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<tbody>
<tr>
<td></td>
<td>Hypochlorhydria is more common, may reduce absorption of basic drugs. Reduced first pass metabolism. Other alterations are unknown or unlikely to be clinically relevant.</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Use of medications which can alter gastric pH is common in all three populations. May affect absorption of certain medications and nutrients.</td>
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| Distribution | Reduced total body weight (water and muscle mass), relative increase in body fat. 5-15% reduction in albumin, alpha 1-acid glycoprotein is generally unchanged. | Increased risk of anorexia and weight loss. 10% further reduction in albumin*. Alpha 1-acid glycoprotein may be lower or unchanged. | Unknown | Alterations in distribution alone are unlikely to have clinically important implications. |

| Distribution to the brain | Increased permeability of the BBB. Possible decreased P-gp activity. | Unknown | Increased permeability of the BBB.* Possible decreased P-gp activity.* | These alterations likely increase access of drugs to the brain, increasing the risk of neurological ADRs. |

| Metabolism | Reduced Phase I metabolism (via CYP enzymes). Phase II metabolism unchanged. | Possible further* reduction in Phase I CYP mediated metabolism. Possible reduction in Phase I esterase activity. Likely reduction in Phase II metabolism. | Unknown | Drug-drug interactions (via inhibition and induction of CYP enzymes) in these populations are common. |

| Elimination | Some reduction in renal function. | Likely reduced.* | Impaired renal function is common. | Serum creatinine and standard formulas for calculating renal function may not be accurate in frail older adults with dementia |

*compared to healthy older adults

BBB=Blood Brain Barrier, P-gp=P-glycoprotein, ADRs=Adverse Drug Reactions, CYP=Cytochrome P450 enzyme

Table 1: Summary of the potential pharmacokinetic alterations in older adults, frail older adults and people with dementia
Figure 1: Schematic portrayal of the relationship between aging, frailty and dementia.

Fig 1a: Prevalence of dementia and frailty in increasing age groups. Figure for illustrative purposes only.

Fig 1b: Associations between aging (increase in hazard rate over time), frailty and cognitive impairment.