Best Practice for Antipsychotic Medication Management in Community Dwelling Older Adults with Schizophrenia

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Dedication

This evidence-based project is dedicated to my wonderful and supportive husband, father-in-law, children, sister, brother-in-law, “sisters-in-law,” and friends. Without their love and understanding, this project would not have been possible. Thank you for your patience as I know there were times along the way I was lost on the academic highway of papers and clinicals. I hope the value and thirst for education will remain with my children as a lesson I taught them well.

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Abstract

Schizophrenia, aging, and medication factors combine to present a very complex clinical presentation in caring for the elderly population with schizophrenia. The aging body displays a slowing of physiological processes, which alters the pharmacokinetics and pharmacodynamics of medications prescribed. Multiple comorbid health factors and the medications recommended for treatment may become detrimental to the overall body health, causing more problems for the older individual. This evidence based practice project reviewed literature and evidence to focus on the question, "In community dwelling older adults with schizophrenia, what is best practice for antipsychotic medication management?" The literature search resulted in classifying 16 articles as relevant to medication management in older adults with schizophrenia. The results of this project were limited by the paucity of available quality research material on the subject. Few studies were inclusive of the 65-years and older population. However, the literature analysis resulted in several recommendations to guide decision-making and promote the safe incorporation of antipsychotic medications in the plan of care to treat schizophrenia in older patients. These may be used by Psychiatric-Mental Health Nurse Practitioners in the clinical reasoning process.

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Chapter 1 Introduction

Schizophrenia is on the rise among the elderly in the United States. The prevalence of schizophrenia in people age 65 and over is 0.5% of the total population (Reeves et al., 2011). With the impact of medical advances through research, life expectancy is projected to continue its upward trend ("Explaining divergent," 2011). This results in the population of elderly schizophrenic patients doubling over the next two decades. Mental health practitioners will be caring for the greater proportion of these older patients in mental health clinics. Preparations are necessary to plan for the best care focusing on this special population and their unique needs.

Schizophrenia is a chronic mental health problem characterized by a mixture of positive and negative symptoms. Positive symptoms include excess or distortions of thought content, perception, language, thought processing, and self-monitoring. Negative symptoms are restrictions in range and intensity of emotion, fluency and productivity of thought and speech, and initiation of goal-directed behavior. For the diagnosis to be made these symptoms must be present for the majority of one month or some persisting symptoms should be present at least six months. These symptoms are associated with marked social or occupational dysfunction as well as a range of cognitive, emotional and communication dysfunction ("Schizophrenia," n.d.). Schizophrenia is usually diagnosed

between the ages of 10 to 25 years for men and 25 to 35 years for women (Sadock & Sadock, 2007). These individuals can expect a lifetime of challenges including unmet health care needs, lessened quality of life and higher mortality rates (Saha, Chant, & McGrath, 2007).

As with the general population, the number of older adults with schizophrenia is increasing. Currently there are 2.2 million Americans suffering from schizophrenia (Reeves et al., 2011). The disease and aging factors combine to present a very complex situation for the context of care and action and side effects of drugs. The clinical picture is confounded by multiple medical comorbidities, physiological changes of aging, polypharmacy issues, and alcohol and substance abuse. This chapter examines these factors, describes the synergy among them complicating medication management, and presents the evidence-based practice (EBP) question with definitions. This evidence-based project's focus is safe and effective medication management for the aging population with schizophrenia.

Background and Significance

The core symptoms of schizophrenia arise from dysfunction in many areas of the brain. Effective treatment involves targeted medication therapy aimed at the specific areas of the brain involved. Timely treatment may prevent or delay the full-syndrome onset of schizophrenia (Miller, 2009). Studies of schizophrenia in the elderly population suggest that consistency of treatment and medication are a predictor of successful symptom management (Sapra, Vahia, Reyes, Ramirez, & Cohen, 2008; Farley, Wang, Hansen, Voils, & Maciejewski, 2011). Currently clinicians are aware that older adults with schizophrenia have complicated management issues because of the multiple levels

of medication necessary to care for the spectrum of health needs including both mental and physiological illnesses commonly associated with aging. Unless a best practice approach is used, this predicted load on the mental health system into the next decade will result in more adverse physical health problems.

Context of Care

A majority of the elderly population with schizophrenia today dually is eligible to receive both Medicare and Medicaid. Medicare has been further divided into Part A (hospital insurance coverage), Part B (medical provider insurance coverage), and Part D (prescription drug coverage). Medicare Part D is available from multiple insurance companies that offer a variety of coverage dependent on patient preference. Medicaid is a jointly funded state and federal funding health care for low income and disabled individuals ("Eligibility," n.d.). Appropriate medication management is made more difficult within the government systems because of fragmented mental health care, fewer trained providers, complicated and restrictive insurance management, decreasing funding, and increased caseloads.

Fragmentation of care. Due to shortages in the community of health care professionals trained to provide safe and effective care for older people with schizophrenia, medical problems often go unnoticed or are misdiagnosed (Bartels, 2004). It is estimated that one half of this population have co-occurring medical and substance abuse disorders, and almost half of these disorders are either not diagnosed or are inappropriately treated (Rosenberg, Woo, & Roane, 2009). Medical clinics are not equipped to manage the care of patients with chronic severe mental illnesses because of the complexities of psychiatric issues. Mental health clinics only focus on the psychiatric

issues. Additionally, physical illnesses and early signs of physical or emotional problems are often incorrectly assumed to be part of the delusional symptoms of the mental illness (Csernansky, 2002). This misdiagnosis delays the onset of effective treatment, which may in turn lead to severe or life-threatening conditions. Dementia symptoms may also be misinterpreted as a part of the psychiatric presentation resulting in inappropriately prescribed or adjusted medications (Csernansky, 2002). This fragmentation of care is only one pressing concern.

Fewer trained providers. Most elderly patients with schizophrenia receive the majority of their psychiatric care from local mental health centers in the community. As funding cuts occur in each state, the amount of money supporting mental health treatment has decreased. Funding for schools with mental health nurse practitioner curricula has also decreased, resulting in the closure or suspension of many programs and declining numbers of providers entering the workforce. This lack of support leaves fewer trained providers with specialization in mental health to staff the community centers to care for the needs of the population with schizophrenia. Patients also often lack support to navigate the insurance system.

Complicated and restrictive insurance. The healthcare system makes acquiring the necessary medication complicated for the provider as well as the elderly patient with schizophrenia. Medicare insurance has a limited formulary and protocol that must be followed by prescribers that still may result in denial or less than full coverage for antipsychotic medications. When the newest medications gain Food and Drug Administration (FDA) approval, the co-pay often results in a higher level of coverage

requiring more personal outlay of money. Although these drugs may be better tolerated with fewer side effects, thereby desired for this patient population, the cost is prohibitive.

Even if Medicare approves a drug, acquiring the medication is still fraught with additional system problems. Quantities of prescribed medications could be limited to 30 pills a month making a preferred multiple dosing per day protocol problematic. Recommendations made to prescribers by the insurance company for alternative choices of drugs, or tiers, are often not suitable for the elderly patient with schizophrenia because of negative side effects. Practitioners may be directed to follow step therapy requiring the patients documented history of failed attempts on other drugs preferred by the insurance company to be filed in a lengthy review. This process takes precious time away from patient care and delays the introduction of needed medication that will alleviate suffering and eliminate symptoms.

Economic challenges. A monthly Supplemental Security Income (SSI) check, intended to support a base subsistence, is provided to the elderly person with schizophrenia at age 65 years old or prior if disability was determined. The average SSI monthly check in 2013 was $423.02 with 2,092,000 recipients. Of this group, 919,000 received this SSI as their only support ("Monthly statistical," 2013). This meager amount must be used to pay for all supplemental costs of healthcare as well as living expenses. Following up with all providers and paying Medicare Part D costs for drug coverage both pose additional financial strain on already tight budgets.

Additionally, many provider practices want co-payment for service. This is not easily affordable to a population also struggling to pay for medications prescribed for treatment. With multiple providers, the costs can be compounded by each specialist

attending to the needs of the elderly patient with schizophrenia. Once Medicare Part D has paid for a preset maximum amount, the patient must pay "out of pocket" until a maximum amount is paid which is sometimes thousands of dollars. This is referred to as the "donut hole" of coverage. The Affordable Care Act (ACA) is scheduled to gradually reduce the amount of co-payment and percentage of "out of pocket" expense through 2020. In 2013, the ACA offered the elderly a 52.5% discount on name brand drugs and a 21% discount for generic drugs (Kaplan, 2011). Incremental decreases over the next seven years will be small and slow leading to an end point of 25% responsibility for both generic and name brand name drugs in 2020 and a $903 annual cost as the enrollee's responsibility (Kaplan, 2011).

Alternative options for patients to acquire the necessary medication for treatment of schizophrenia are few, despite the potential risks to self and others when individuals receive inadequate treatment. The patient must rely on samples or patient assistance programs designed by the drug companies to assist during this "donut hole" of coverage. With the increased cost, elderly patients with schizophrenia often economize by taking the medication less often than ordered or not filling the prescription. This irregular or absent dose may lead to decompensation with psychosis, instability, and potential harm to these elderly patients. Utilization of emergency services, admissions to acute care hospitals, and interventions resulting from this destabilization further increase the cost of mental health. Cost concerns are also often compounded with the issue of limited providers.

Limited providers. Methods used to manage resources include limiting reimbursements to providers for services and placing restrictions on prescribing practices

for medications. The percentage of Medicare patients per practice is capped in many offices to buffer the overall decreased repayment for care paid by this plan. This reduced Medicare reimbursement provides a disincentive for providers to accept new geriatric patients (Rosenberg et al., 2009). These issues, along with the lack of knowledgeable providers willing to negotiate and maintain both the medical and psychiatric needs of this elderly population, are some of the flaws of the healthcare system that severely impact the care options of the elderly population with schizophrenia. Having examined the complicated context in which elderly patients with schizophrenia seek care, the actions and side effects of psychopharmacology follows.

Actions and Side Effects of Drugs

Just as the health care context is complex, so too are the action and side effects of antipsychotic drugs. Psychopharmacological intervention involves modulation of multiple neurotransmitters aimed at a remission of symptoms of schizophrenia. These antipsychotic drugs are known to be "the most complex pharmacological mechanisms of any drug class in the field" (Stahl, 2008, p. 328). Prescribing practice for the older population with schizophrenia is focused on identifying the specific neural pathways of the brain to target treatment for optimum symptom management with minimum side effect potential. Table 1.1 reviews the major neural pathways affected by the most commonly prescribed antipsychotic in each class of medications prescribed for the older population with schizophrenia.

Table 1.1

Neural Pathways and Side Effects of Antipsychotic Drug Classes

Drugs by Class	Neural Pathways Effected	Common Side Effects
• Typical (Conventional)	• Alpha – 1	• Dizziness, drowsiness, and decreased blood pressure.
	• Dopamine- (D2 antagonist)	• Apathy, lack of motivation, anhedonic, movement disorders, and elevated prolactin (galactorrhea, amenorrhea, demineralization of bones, weight gain).
	• Histamine (H1)	• Weight gain, drowsiness.
	• Muscarinic (M1)	• Constipation, blurred vision, dry mouth, and drowsiness.
• Atypical	• Serotonin Dopamine Antagonists* • D2 antagonists with rapid disassociation* • Serotonin -Dopamine Partial Agonist* • Serotonin partial agonist at 5HT1A receptor*	• Weight gain • Dyslipidemia • Diabetic risks • Anxiety • Prolonged QT interval • Elevated prolactin levels • EPS • Sedation

Note. Adapted from *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (3rd ed.), by S. M. Stahl, 2008, p. 342.

* The pharmacologic methods that serotonin and dopamine interact within the D2 receptor to elicit the desired antipsychotic effect are found in these four types of agonist. They are unique to the atypical psychodynamic profile.

Schizophrenia is a disorder affecting many areas of functioning including cognitive, affective, negative, positive, and aggressive symptoms (see Figure 1.1). It is difficult to envision one medication effectively treating all these areas (Stahl, 2008). The five-dopamine pathways and symptoms associated with each are illustrated in Figure 1.1.

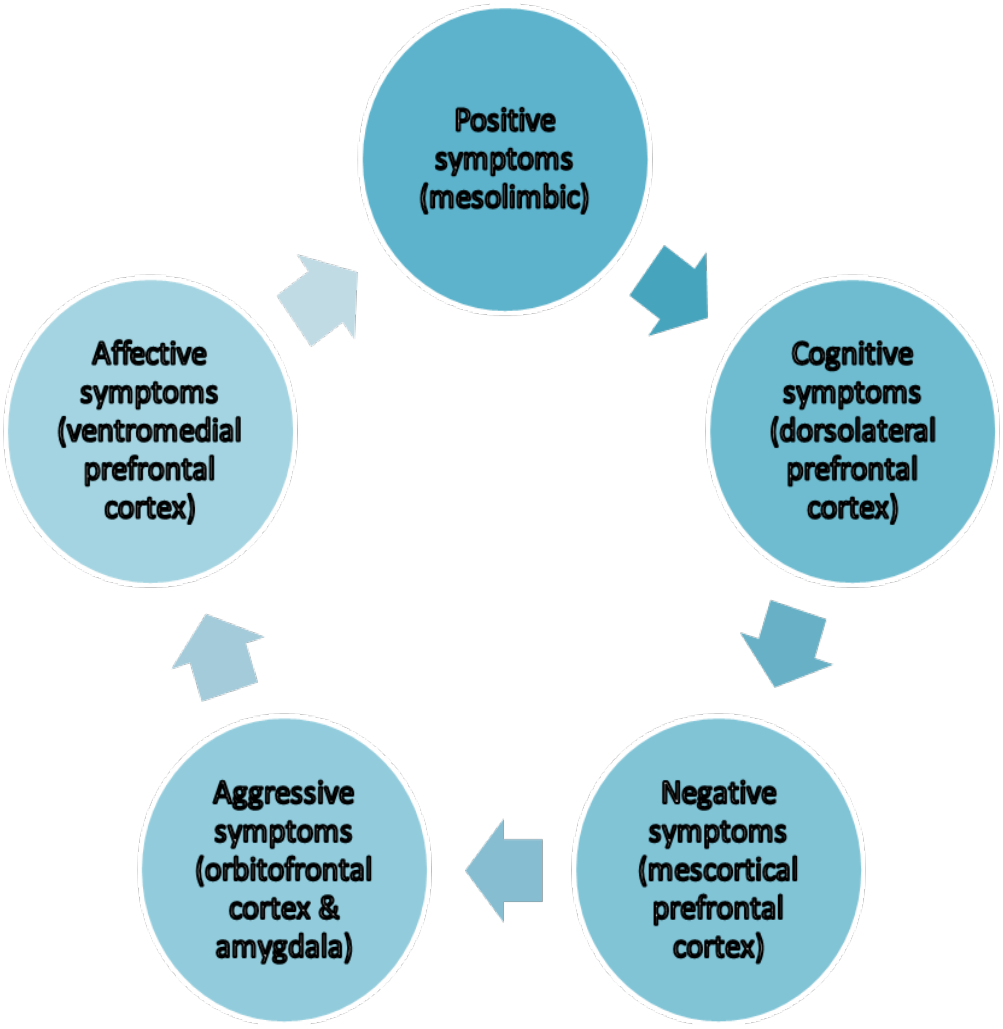

Figure 1.1 Schizophrenia model of dopamine output. Adapted from *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (3rd ed.) by S.M. Stahl, 2008, p. 262.

Antipsychotic medications are responsible for a higher risk potential of major side effects in the elderly population with schizophrenia. The cause of side effects in some cases is known, as in the case of movement disorders associated with dopamine antagonism in the nigrostriatal dopamine track (Leon et al., 2010). However, for some side effects the cause is not known. These include causes of neuroleptic malignant syndrome (NMS) as well as sudden cardiac death and strokes (Novick, Haro, Bertsch & Haddad, 2010). Table 1.2 highlights the movement disorders and symptoms of each.

Movement disorders, also called pseudo-Parkinsonian symptoms, can be classified in two types: extrapyramidal symptoms (EPS) and tardive dyskinesia (TD). EPS includes a variety of symptoms characterized by changes in muscle tone, poverty of voluntary movements (akinesia) or abnormal involuntary movements (dyskinesia). EPS is associated with both conventional (typical) and atypical antipsychotic medication administration. Symptoms may be acute or chronic, or delayed as in TD. Their presence may spontaneously resolve or be permanent.

Tardive dyskinesia is a disorder of involuntary repetitive body movements that can be delayed or slow in onset, which appears after high dose use of antipsychotics (Lieberman & Tasman, 2006). Aging of the brain decreases dopamine functioning in the corticostriatal pathway causing an increased prevalence of both extrapyramidal

Table 1.2

Antipsychotic Drug Side Effects

Name	Category	Symptoms
• Movement Disorders	• Extrapyramidal Symptoms	• Change in muscle tone, poverty of voluntary movements (akinesia), abnormal involuntary movements (dyskinesia)
	• Tardive Dyskinesia	• Involuntary repetitive body movements: Grimacing, tongue protrusion & movements, lip smacking, puckering or protrusion, rapid eye blinking, grunting, tics and/or movements of limbs, torso, or fingers.
• Neuroleptic Malignant Syndrome	• Neurological	• Life threatening disorder: Rigidity, autonomic instability, altered level of consciousness and hyperthermia, elevated creatine, kinase, and leukocytosis

Note. Adapted from "*Incidence of extrapyramidal symptoms and tardive dyskinesia in schizophrenia"* by D. Novick, J. Haro, J. Bertsch, and P. Haddad, 2010, *Journal of Clinical Psychopharmacology, 30*(5), pp. 531-540.

symptoms and tardive dyskinesia (Meyers & Jeste, 2010). As a result, TD and EPS symptoms may also occur with lower doses and can be more persistent and severe (Leon et al., 2010).

Neuroleptic malignant syndrome (NMS) is a life-threatening neurological disorder associated with antipsychotic medications. Symptoms of NMS are rigidity, autonomic instability, altered level of consciousness, hyperthermia, and elevation of creatine kinase and leukocytosis (Lieberman & Tasman, 2006). The onset can be sudden, occurring usually in the early course of the medications. Understanding the potential risk and recognizing these possibly life-threatening syndromes is critical to safely prescribing antipsychotic medications to this older population with schizophrenia (Novick et al., 2010).

General side effects of antipsychotic medications are varied and unique, as one individual's response to treatment may be quite different from another's response to the same medication. Some antipsychotics trend towards common side effects in a larger portion of the population treated with the medication. Sedation is a common side effect of specific medications and can be better tolerated with a bedtime dosing pattern. While providing symptom relief of schizophrenia, practitioners need to be aware of the potential of side effects to provide optimum care as safely as possible.

Table 1.3 reviews the major medications used in the treatment of schizophrenia with information about metabolism, classification, dosing, excretion, peak level of drug concentration (C-Max), half-life, protein binding, and special considerations for the older adult population with schizophrenia.

Table 1.3

Medication Data

Drug Name	Available Route/Dosing	Half-Life	Peak Concentration (Cmax)	Absorption & Excretion	Absorption Issues and Special Notes
Serotonin-dopamine antagonist — SDA/SGA					
Brand: Zyprexa (Generic is Olanzapine)	Oral daily dosing	21 to 54 hours	5 hours	85% GI / 40% inactivated by first pass hepatic metabolism. Excreted 57% renal, 30% by GI. Protein binding 93%.	No absorption issues with food. Luvox and tagamet increases serum carbamazepine and decreases phenytoin levels. Alcohol increases absorption by 25%.
Brand: Relprevv (Generic is Olanzapine)	IM (Depot) administer every 2 to 4 weeks.	30 days	14-45 min	Absorption rapid. (IM)	Post injection delirium sedation syndrome (PDSS) potential — must be observed for 3 hours after IM.
Brand: Seroquel (Generic is Quetiapine)	Oral (regular 2 times a day dosing)	7 hours	1-2 hours	Rapidly absorbed from GI/ Excretion 73% renal, 20% GI. Protein binding 83%.	Marginal effect with food. Phenytoin increased clearance 5 times normal.

Brand: Seroquel XR	Oral (delayed release, daily dosing 3-4 hrs. prior to sleep)	9-12 hrs.	6 hours	Rapidly absorbed from GI/ Excretion 73% renal, 20% GI. Protein binding 83%.	Absorption slowed with high fat foods (22-52%)
Brand: Geodon (Generic is Ziprasidone)	Oral (2 times daily dosing recmd.)	5-10 hrs.	2-6 hours	Bioavailability doubles when taken with food (300 cal) -absorption rapid. Excretion 20% renal, 66% GI. Protein binding < 99%	Interactions with other drugs that prolong QT intervals.
Brand: Invega (Generic is Paliperidone)	Oral (daily dosing)	4-5 days	24 hours	Bioavailability 28%. 74% protein binding. Limited hepatic metabolism. Excretion 11% GI, renal 80%. Protein binding 74%	With or without food. Reduce dose in renal impairment. Avoid with other drugs that prolong QT.
Brand: Invega Sustenna (Generic is Paliperidone palmitate)	Depo (every 4 weeks)	25-49 days	1 day	Bioavailability 28%. 74% protein binding. Limited hepatic metabolism. Excretion 11% GI, renal 80%.	2 initial doses required. #1- in deltoid (28% higher absorption), #2.5-7 days later in muscle of choice.

Brand: Risperdal (Generic is Risperidone)	Oral (daily dosing)	Up to 17 hours	1-3 hours	Bioavailability 70% Excretion: 70% renal, 14% GI. Protein binding 90%	May inhibit active metabolite when used with strong SSRIs and elevate prolactin level.
Brand: Risperdal Consta	Depo - IM (every 2 weeks)	3-6 days	3 weeks	Bioavailability 70% Excretion: 70% renal, 14% GI. Protein binding 90%	Requires 3 doses to reach steady state (6 weeks). Supplement with oral medication until after 3rd dose.
Brand: Clozaril (Generic is Clozapine)	1 to 2 times a day	12 hours	2 hours	Bioavailability 50-60%. Excreted 30% GI, 50% renal. Protein binding 97%.	Unaffected by food
Brand: Fanapt (Generic is Iloperidone)	Oral (2 times a day dosing)	(1) 18-26 hrs. (2) 31-37 hrs.	2 - 4 hours	Hepatic metabolism excretion. Protein binding - 95%. Excreted via renal -58-45% and 20-22% GI	1) CYP 2D6 extensive metabolizers, 2) CYP 2D6 poor metabolizers. Dose adjustment needed. No interaction with food.

Brand: Latuda (Generic is Lurasidone)	Oral (daily dosing)	18 hours	1-3 hours	Renal and GI excretion. Protein binding – 99%	Should be taken with food (350 cal). Without food absorption impaired. Grapefruit products should be avoided.
Brand: Abilify (Generic is Aripiprazole)	Oral (daily dosing)	75 hours	3-5 hours	Readily absorbed. Excretion 25% renal, 55% GI. Protein binding <99%. Steady state achieved in 14 days.	Absorption unaffected by food. 99% protein bound. Clearance reduced in elderly. Modulates dopamine rather than blocks. Parent compound is the aripiprazole, major metabolite, dehydro-aripiprazole may take longer ½ life (94 hrs.)
Brand: Abilify Maintena (Generic is Aripiprazole)	Depo- IM	29.9 days	5-7 days	Hepatic excretion. Steady state achieved after 4 injections. 29% protein bound.	Not tested or recommended in 65 years or older.

Brand: Saphris (Generic is Asenapine)	Sublingual (2 times a day)	24 hours	1 hour	Protein binding 95%. Bioavailability 35%. Extensive hepatic metabolism. Excretion- 40% GI, renal 50%.	No food or liquid for 10 min. Caution with Luvox.
Drug Name	Available Route/Dosing	Half-Life	Peak Concentration (Cmax)	Absorption & Excretion	Absorption Issues and Special Notes
Dopamine Receptor Antagonist- DRA/FGA					
Brand: Haldol (Generic is Haloperidol)	Oral	10 to 37 hours	20 minutes	Protein bound 90% Bioavailability 60-70% 33-40% renal excretion, 15% GI. High potency	Well absorbed from GI tract. Smoking, coffee, antacids and food interfere. Clearance inhibited by SSRIs, TCAs, cimetidine, beta-blockers, isoniazid, methylphenidate, erythromycin, triazolo-benzodiazepines, ciprofloxacin, and ketoconazole.

Brand: Haldol Decanoate	Depot, IM	3 wks	2-6 hours	Peak concentration 6 days	Smoking, coffee, antacids and food interfere with absorption. Clearance inhibited by SSRIs, TCAs, cimetidine, beta-blockers, isoniazid, methylphenidate, erythromycin, triazolo-benzodiazepines, ciprofloxacin, and ketoconazole.
Brand: Trilafon (Generic is Perphenazine)	Oral (2-4 times a day dosing)	9-12 hrs.	1-3 hours	Bioavailability 20%. Metabolism in liver, GI tract. Protein binding 90%. Medium potency.	2-3 weeks for desired results. Lithium formulation may decrease serum concentration of antipsychotic.
Brand: Thorazine (Generic is Chlorpromazine hydrochloride)	Oral (2-4 times a day dosing)	6 hours	2.8 hours	Bioavailability 32%. Protein binding 90-99%. Low potency.	May cause gynecomastia, hyper- or hypo glycemia.
Brand: Prolixin (Generic is Fluphenazine)	(1-2 times daily dosing)	33 hours	1-4 hours	Bioavailability 2.7%. Metabolized via hepatic system. Protein binding 90%. High potency.	Report CNS effects (blurred vision, altered gait, excess sedation urinary retention)

Brand: Prolixin Decanoate	Depo, IM (every 2-4 weeks)	6.8-9.6 days	48-96 hours	Bioavailability 2.7%. Metabolized via hepatic system. Protein binding 90%. High Potency.	IM response may last up to 6 weeks.
Brand: Stelazine (Generic is Trifluoperazine)	1-2 times a day dosing	24 hours	2-4 hours	Bioavailability readily available. Metabolism via hepatic. Protein binding >90%. Medium Potency.	Lower dose with more gradual increase for elderly.

Note. Adapted from *Physicians' Desk Reference* (67th ed.) by E. Strompf, 2012. Copyright 2013 by PDR Network.

Definitions for Table 1.3

Atypical antipsychotic medications: synonymous with second-generation antipsychotic medications (SGA).

Bioavailability: The fraction of the total amount of administered medication that can be recovered from the bloodstream for use by the target tissue.

Half-life: The amount of time it takes for metabolism and excretion to reduce the particular plasma concentration by 50%.

First-pass metabolism: The initial metabolism of orally administered medications within the portal circulation of the liver referring to the fraction of absorbed drug reaching the systemic circulation unmetabolized.

Metabolism: The liver being the principle site of drug metabolism, with feces, bile and urine being the major routes of excretion. Antipsychotic drugs are also excreted in saliva, sweat, tears and breast milk.

Protein binding: Percentage of drug bound to a protein molecule (albumin, lipoprotein, glycoprotein, and globulins). Unbound portion of drug is readily metabolized and or excreted whereas bound portion has higher half-life and slower release.

Potency: The amount of drug required for the drugs' specific effect to occur.

Peak concentration (C-max): The maximum concentration a drug achieves prior to a second dosing and a point to which short-term side effects are more likely to occur.

Neuroleptic medication: Synonymous with antipsychotic medication both typical and atypical factors.

Typical Antipsychotic medications: Synonymous with first generation antipsychotic medications (FGA)

In Table 1.3, the drug classes are grouped according to drug classes, listed as the effect the medication has on the dopamine receptors in the brain. Further examination of antipsychotic medications will continue in Chapter 2, as the effects of antipsychotic medications by body systems will be examined in detail. Before moving on, it is essential to take into consideration the many confounding factors of pharmacology.

Confounding Factors of Pharmacology

Medical comorbidities, physiologic changes of aging, polypharmacy, and alcohol abuse, are common in the elderly patient. These concerns place older individuals with

schizophrenia at elevated risk for adverse drug reactions from medication prescribed to control symptoms. With the complexity of multiple issues co-occurring, the problems increase for safe prescribing. Awareness of these issues is essential.

Medical Comorbidities

Long-term use of atypical antipsychotic medication is associated with a cluster of related risk factors. Coronary heart disease had a significant increase over a 10 year span of study for middle age and older adult schizophrenia patients (Jin et al., 2011). Metabolic syndrome (MetS), which, when co-occurring with other disorders, increases an individual's risk of developing cardiovascular disease and insulin resistance leading to various diabetic states and cardiovascular disease in adults was also a concern (Kisely, Cox, Campbell, Cooke, & Gardner, 2009). Patients with schizophrenia had a higher incidence of diabetes for the youngest adult age group when compared to the general population (Hsu, Chien, Lin, Chou, & Chou, 2011). In a meta-analysis representing 48 studies of adults, clozapine and olanzapine had the highest risk of producing metabolic issues including weight gain, altered glucose metabolism, and elevated triglycerides within the class of atypical antipsychotics (Rummel-Kluge et al., 2010). The general features of metabolic syndrome include elevated blood pressure, atherogenic dyslipidemia, insulin resistance, and abnormal body fat distribution (Alberti, Zimmet, & Shaw, 2006).

Other factors contributing to MetS include physical inactivity, aging, proinflammatory state, hormonal dysregulation, and genetic predisposition (Alberti et al., 2006). A high fat carbohydrate rich diet often associated with limited income also increases the risk for MetS. Hyperlipidemia, obesity, and nicotine abuse contribute to

medical comorbid health issues as well by further compounding the problems with respiratory, musculoskeletal, and peripheral vascular issues.

Physiological Changes of Aging

Patients with schizophrenia often have metabolic issues that cause aging changes to occur earlier than in the population without schizophrenia. Premature intracellular deterioration in the older adult with schizophrenia precedes many metabolic health issues (Jeste, Wolkowitz, & Palmer, 2011). The origin of this premature aging remains debatable. There are several theories that try to explain this event. The first theory outlines a course of declining health secondary to the cumulative systemic effects of psychotropic medication. A second theory examines the contributing effect of the inflammatory response with oxidative stress as a focal point. This response increases C-reactive protein, cortisol, insulin, and suppresses certain anabolic hormones. Individuals with schizophrenia were found to have increased T-cell activity (pro-inflammatory activation), which is upregulated in acute inflammatory process, metabolic, and cardiovascular disease (Suvisaari et al., 2011). These biochemical reactions create the perfect environment for deterioration of the telomerase that is the protective cap at the end of the DNA chain. Results of this loss link diabetes, insulin resistance, higher cardiovascular disease, obesity, hypertension, and dyslipidemia to schizophrenia (Epel, 2009).

Early aging problems in the elderly brain associated with schizophrenia also cause unique and confusing neurocognitive changes. Decreasing gray matter volumes in the frontal and parietal lobes occur in the aging brain with schizophrenia (Jeste et al., 2011). This cognitive change decreases the older adults' ability to live alone and work

successfully within healthy boundaries of self-care. Recognition of key medical issues may also be diminished by the cognitive deficits of schizophrenia (Karim, Overshott, & Burns, 2005).

Two additional factors that can impair cognition are directly within the control of the practitioners prescribing skill. Antipsychotic medication decreases the positive symptoms of schizophrenia by blocking the dopamine (D2) receptors. But blocking too many receptors (greater than 80%) not only increases the risk of EPS, but also raises the risk of cognitive impairment (Sakurai et al., 2013). The total percentage blocked was estimated by measuring plasma levels of the antipsychotic concentrations using a pharmokinetic model developed for the study. Although this level of analysis is not common practice, the impact of antipsychotic medications in amounts high enough to cause these symptoms is important for practitioners to recognize. Prescribing anticholinergic medications to the older patients to reduce the symptoms of EPS becomes the second factor that can damage cognition. A study of 1,780 patients aged 70 years and older found using drugs with anticholinergic properties associated with low cognitive performance (Lechevallier-Michel, Molimard, Dartigues, Fabrigoule, & Fourrier-Reglat, 2004). Recognition and achieving the correct balance of receptor blocking would minimize the side effects while relieving symptoms. Choosing the correct medication, dose, and monitoring for physical and cognitive changes is important for this older population.

Physiologic changes as a product of aging place the elderly patients with schizophrenia at elevated risk for adverse drug reactions. Two major organs of excretion, liver and kidney, deteriorate with aging. This atrophy results in pharmacodynamic

changes that may alter the expected response of either organ to the effect of a medication (Hutchison & O'Brien, 2007). This atrophy is further complicated when the patients' renal and hepatic system is additionally challenged by disease that further confounds the process. Uncontrolled diabetes and hypertension are known to damage the kidneys when symptoms management over time has been poor. This may lead to dialysis with severe drug and dietary restrictions. As noted previously, hepatic function becomes impaired by the ravages of hepatitis and cirrhosis secondary to disease, alcohol or drug use, or poor lifestyle choices (Bowie, Serper, Riggio, & Harvey, 2005).

Fluid balance and the ability of the aging body to absorb, process, and excrete successfully the antipsychotic medications both require close supervision. Diabetes, heart failure, or instances of dehydration can alter the excretion and concentration of medications by impacting blood levels of medications (Kaufman, 2011). Liver impairment or disease may affect the efficiency of the metabolism of the drug (Sadock, Sadock, & Kaplan, 2011). These examples may result in failure of the medications to manage psychotic symptoms as the quality of the organ function is impaired by the atrophy or disease.

Polypharmacy

In addition to the antipsychotic medications used to treat their mental illness, aging patients with schizophrenia are more likely to be prescribed statins, non-steroidal anti-inflammatories, insulin, antibiotics, diuretics, and modulators of kidney filtration and hypoglycemic agents. Estimates indicate that 60% of drug reactions in older patients with schizophrenia are caused by the following medications: glucocorticoids, hypoglycemics, nonsteriodal anti-inflammatories and antibiotics (Perry, 2011). As these

multiple medications are absorbed into the body, the neural pathway in which the medication activates becomes overloaded causing conflicting medication efficiency. It is critical for practitioners to carefully assess the combined pharmacological profile of medical and psychiatric medications and their interactions within the aging body.

Substance Abuse

The comorbidities associated with schizophrenia in the elderly population may also be exacerbated by alcohol and/or drug use. Binge drinking and non-medical use of prescription drugs rank high in the elderly population (Blazer & Wu, 2011). A decreased percentage of water in the aging body means less alcohol is necessary to cause intoxication (Flood & Buckwalter, 2009). Alcohol and other drug use in the elderly may compound age-related declines in mental abilities. Memory lapses, changes in sleep patterns, and sleep deprivation may be more common in those who use alcohol and other drugs. Consequently, it is essential to identify substance abuse problems. However, it is important to be aware that symptoms associated with substance abuse such as confusion, forgetfulness, poor diet, neglect of personal appearance, and hoarding may be misinterpreted as symptoms of schizophrenia (Flood & Buckwalter, 2009).

Substance use may also result in falls or other accidents, especially in individuals with pre-existing impairment of vision, balance, or mobility. Prolonged use of alcohol in particular can contribute to the development or exacerbation of conditions that alter the successful metabolism of medications (e.g. cirrhosis and chronic pancreatitis) or complicate the overall health of the aging patient in general (e.g. compromise immunity and hepatitis) (Hipwell, Singh, & Clark, 2000). The use of alcohol in combination with antipsychotic medications alters the desired therapeutic effect of the antipsychotics

allowing break through psychosis to occur and an increased occurrence of side effects. Research examining the effect of alcohol on neuropsychological functioning noted a more severe decline in cognition (Mohamed, Bondi, Kasckow, Golshan, & Jeste, 2006). Additionally, a higher level of depression and non-compliance with prescribed medications were found in the substance abusing elderly population with schizophrenia (Margolese, Malchy, Negrete, Tempier, & Gill, 2004).

The occurrence of medical comorbidities within the elderly population is an expected part of the aging process, but the degree of understanding that practitioners exercise in prescribing for these conditions can greatly alter the final desired outcome. The monitoring of MetS symptoms and cardiovascular disorders, the awareness of all medications within the aging body and of the potential for alcohol and substance abuse are important factors in caring for this population. Knowledge of the effects these issues have on older patients' physical health will help provide the necessary identification to increase positive healthcare outcomes.

Synergy Among Factors Influencing Medication Management

Maximizing all of the resources available to cope with health concerns in caring for the older population with schizophrenia may be the best approach for practitioners. Under-recognition and under-treatment of medical risk factors, the patients' sedentary lifestyle or poor diet, and the contribution of adverse metabolic side effects from antipsychotic medications (weight gain, dyslipidemia, and hyperglycemia) can combine to undermine this population's health outcomes. By combining the behavioral, medical, and psychiatric interventions available, presenting issues can be treated more efficiently as a group rather than individually.

Additionally, a synergistic use of medications for treatment of the older population with schizophrenia would maximize the pharmacologic outcome with a minimum of complications from overloading the brain circuitry with polypharmacy. For instance, use of one medication for psychosis as well as sleep or prescribing medication more energizing with less sedentary side effects for issues related to weight gain or ahedonia utilizes a synergistic approach. Management of schizophrenia for the older population requires a delicate balance of pharmacology skills and knowledge of the patient to achieve the optimum potential possible.

Along with symptoms management of schizophrenia, there are many additional factors to be considered that may enhance the outcome of treatment. Arranging more frequent monitoring and offering targeted symptom management and behavioral components of treatment influences outcomes. Blending medical and psychiatric visits for an all-inclusive picture of the older adult with schizophrenia for continuity of care would bring the most gain for the least output. For example, additional medication is indicated at times for depression, anxiety, mood stability, or co-occurring psychiatric condition. Practitioners must then choose the proper medication to provide symptom control without causing further complications. Following up with the necessary monitoring of clinical indices for physical as well as mental areas of concern is indicated as part of the best practice care practitioners can provide.

Addressing the necessary monitoring and points of concern that may alter the current path of treatment is part of synergistic assessment. This approach may draw from a variety of sources inside and outside practice to provide best care options for older patients with schizophrenia. The focus is the patient as a whole. Choosing what

components to initiate in addressing several issues at one time can maximize the limited resources in the ever-narrowing mental health arena.

Project Focus

This project involves a detailed analysis of the literature on medication management of older adults with schizophrenia in the community setting. The objective of this project is to increase practitioners' understanding of medication management by increasing the ability to provide comprehensive, quality-focused care for this special population. The literature is analyzed and ranked according to the strength and quality of the evidence by examining the relevant research in aggregate to determine the strength of the evidence, using the hierarchal method proposed by Melnyk and Fineout-Overholt (2005). The hierarchy contains seven levels with I being highest quality and VII lowest quality. The levels are based on the ability of the design to protect against threats to internal and external validity. An evidence table will show the available literature analysis with the strongest data chosen as best practice recommendations.

Evidence-based question. Creating evidence-based practice inquiry begins with a specific format. This format, labeled PICOT (patient population, intervention of interest, comparison intervention or status and outcome, time), produces the best evidence and most relevant information (Melnyk & Fineout-Overholt, 2005). The PICOT definitions are seen in Table 1.4. The EBP question is "In community dwelling older adult with schizophrenia, what is the best practice for antipsychotic medication management?"

Table 1.4

PICOT Definitions

Population	Intervention	Comparison	Outcome	Time
Community dwelling older adults with schizophrenia	Medication management for schizophrenia	Changes in medication management because of drug actions and side effects, co-morbidities, physiological changes due to disease and age	Safe and effective medication management	Current

Summary

The expanding population of elderly individuals with complex health problems requires extensive comprehensive care. Understanding the ever changing mental health system continues to provide challenges both providers and patients must navigate in order to be successful. The lack of clinical guidelines to manage older adults with schizophrenia will present unprecedented challenges for health care providers as this population grows. The aging bodies' many ongoing changes, co-occurring medical and

psychiatric issues, multiple medications and providers, side effects, and the potential of substance abuse and non-compliance all cloud this navigation.

Selection of medications for the aging patient with schizophrenia requires careful analysis of factors including the patient's age, the duration of time the patient was been treated with antipsychotic medication, and the individual patient's health profile. Determination of appropriate antipsychotic medication presents the practitioner with myriad options. Patient exposure to decades of antipsychotic medications with subsequent side effects warrants special practitioner attention. However, use of medications within the older population, with aging body systems, requires extra scrutiny and vigilance to provide safe effective care.

Therefore, it is important for providers to be equipped with the knowledge to maximize patient outcomes. Compiling, evaluating, and ranking the scattered literature relevant to the care of older adults with schizophrenia will provide clarity regarding the best clinical medication management. In the following chapter, normal aging, schizophrenia, and medication issues will be examined by body systems to provide a context for the analysis of best-practice medication management for community dwelling older adults with schizophrenia.

Chapter 2 Physiological Analysis

Patients who are 65 years and older with schizophrenia provide practitioners with multiple pharmacological challenges. Although the speed at which aging occurs within the body is unique to each individual, aging ultimately results in a gradual slowing of the systems that govern the pharmacokinetic profile of medications. Providers must consider these changes when prescribing medications for aging adults. Coupled with the complexity of antipsychotic medications, the task of prescribing for this population may seem daunting. Pharmacological research focusing specifically on this population is historically limited because of the complicated health issues and polypharmacy presentations, as well as researchers' ethical concerns over the manipulation of this more fragile group (Howard, 2010; Perry, 2011). However, in preparation for the expansion of the geriatric population over the next quarter century, pharmacology research involving older adults is beginning to grow. Geriatric psychopharmacologists suggest the relationship between the general medical and neurological conditions are closely associated with aging. Careful focus on this connection may provide practitioners with improved options when choosing medications using this knowledge (Meyers & Jeste, 2010). In this chapter, the core points of antipsychotic medication management for older adults with schizophrenia are explored and common physiological issues important to safe and effective prescribing practice are identified.

The three major focal points impacting medication efficacies for older patients with schizophrenia are physiological changes of normal aging (see Appendix A), physiological changes in schizophrenia (see Table 2.1), and effects of antipsychotic medications (see Table 2.2). The effects of these three points on the person as a whole are discussed in the chapter's narrative. Table 2.3 presents a comparative examination of the interactions of normal aging, schizophrenia, and antipsychotic medications to explore the commonalities that complicate medication management in this population. An understanding of these issues will provide a basis for an exploration of the literature to determine best practice to improve medication success and positively impact the quality of care provided to this population.

Physiological Changes of Normal Aging by Body System

Pathophysiology researchers have found alterations in body function associated with aging (see Appendix A). Certain physiological changes of aging specifically influence the pharmacological treatment of older patients with schizophrenia.

An understanding of changes within the aging adult's body is essential when considering medical interventions for older patients with schizophrenia. First, aging leads to a gradual diminished functional capacity of the organ systems. Cardiovascular, central nervous system, and respiratory changes have the largest effect with reduction of blood flow, lack of oxygen, and diminished stimulation to target organs. The net effect is reduced size, decreased function, altered absorption, and regeneration issues leading to loss of efficient cellular function of the organs.

The reduced cellular functions within the organs predispose the older patient to reduced capacity or failure of the systems. These changes can result in myocardial

infarctions (MI's), coronary artery disease (CAD), hyperglycemia, and a higher potential for fractures and falls. The bases of the lungs are less ventilated resulting in an ineffective redistribution of blood to compensate. This results in falling oxygen levels that become worse when the older adult is lying down, causing a risk for respiratory failure. Surgery, bed rest, pulmonary edema, trauma, burns, or environmental events exacerbate this hypoxic condition (McDaniel, 1992).

The altered physiology within the cellular functioning also impacts the pharmokinetic values in the elderly. The distribution of medication is altered by the change in the proportion of water and body fat present. Hydrophilic drugs may have a smaller volume of distribution and concentrations could be higher than normal. Lipophilic drugs could have an increased volume of distribution with a potentially prolonged half-life (Shi & Klotz, 2011). Decreased serum albumin concentrations could increase unbound plasma concentrations of highly protein-bound medications. Decreased hepatic and renal function could also slow the clearance of metabolites and drugs from the liver and kidneys to increase the drugs' half-life (Cusack, 2004).

The addition of disease pathology overloads the system. Similarly, lifestyle choices affect the baseline wellbeing of the individual. Polypharmacy issues may complicate or overwhelm the entire system as medical and psychiatric medications are prescribed. All of these factors would have a compounding negative effect on the overall body of the aging patient. Alterations in physiological functioning associated with schizophrenia have the potential to exacerbate changes individuals are already experiencing as an expected result of the aging process. The physiological changes of schizophrenia by body system are examined next.

Table 2.1

Physiological Changes in Schizophrenia by Body System

Cardiovascular
• Increased risk of cardiovascular comorbidity, coronary artery disease, hypertension, and altered lipid levels (Saha et al., 2007)
• Decreased estrogen levels associated with increased blood pressure and decreased nitric oxide, increasing the risk of CV disorders and myocardial infarctions (Hennekens et al., 2005)
• Peripheral endothelial tissue dysfunction increases morbidity (Israel et al., 2011)
Hematologic
• Increased presence of hyperlipidemia, hyperprolactinemia, and hyperglycemia (Halbreich, Kinon, Gilmore, & Kahn, 2003)
• Impaired peripheral glucose metabolism with elevated glucose levels and hemoglobin A1C (Steiner et al., 2012)
Respiratory
• Increased risk of chronic obstructive pulmonary disease (COPD), deteriorating lung capacity, and respiratory problems (Leucht, Burkard, Henderson, Maj, & Sartorius, 2007)
• Small increase in lung cancer risk (Barak, Achiron, Mandel, Mirecki, &Aizenberg, 2005)
Gastrointestinal
• Increase in BMI and central adiposity (Steiner et al., 2012)
• Small decrease in risk for colorectal cancer (Barak et al., 2005)
Urinary
• Neurogenic bladder associated with Neuroleptic Malignant Syndrome (NMS) (Caroff, Campbell, & Sullivan, 2007)

Endocrine
• Increased risk of hypothyroidism (Carney, Jones, & Woolson, 2006)
• Increased risk of diabetes mellitus
• Increased occurrence of insulin resistance (Steiner et al., 2012)
Neurological
• Impaired cerebral glucose metabolism, especially the frontal lobe (Ward, Friedman, & Schulz, 1996)
• Right lateral fusiform gyrus dysfunction causing impairment of facial recognition and processing, contribute to social dysfunction (Quintana, Wong, Ortiz-Portillo, Marder, & Mazziotta, 2003)
• Oligodendrocyte and myelin dysfunction associated with changes in synaptic function and formation lead to progressive, mild cognitive impairment (Takahashi, Sakurai, Davis, & Buxbaum, 2010)
• Decreased muscarinic and nicotinic receptors in caudate-putamen, hippocampus, and selected regions of prefrontal cortex impair regulation of cognitive neurotransmitters (Eyler, Kemp, Mirzakhanian, & Jeste, 2009)
• Loss of GABAenergic neurons and inhibitory interneurons is associated with hippocampus hyperactivity, ventral hippocampus regulates dopamine neurons responsivity (Grace, 2012)
• Decreased 5-HT2A receptors, increased striatal D2 receptors with increased dopamine content or metabolism (Wong & Tol, 2003)
• Selective neuronal degeneration within the norepinephrine reward neural system contributing to ahedonia (Karim et al., 2005)
• Loss of brain volume from reduced density of the axons, dendrites, and synapses mediating brain's associative functions (Ward et al., 1996)
• Lateral and third ventricular enlargement and reduction in cortical volume (grey matter) by up to 25% (Pantelis et al., 2005)

• Grey Matter Volume (GMV) in superior temporal gyrus (STG) associated with positive symptom severity, white matter impairment increases negative symptoms, GMV reduced in temporal and mediofrontal cortex involved in positive symptoms
• Increased density of interstitial white matter neurons correlates to grey matter interneuron deficit in the cortex (Rusch et al., 2007)
• Reduced symmetry in temporal, frontal, and occipital lobes
•Decreased amygdala, hippocampus, temporal and parahippicampal gyrus sizes cause disturbance in limbic system and glutamate transmissions causing difficulty filtering out incoming data, brain responds by releasing dopamine (Baiano et al., 2007)
• 30-45% thalamus volume reduction and sub nuclei neuronal loss (Ettinger et al., 2001)
• Dysfunction of anterior cingulate basal ganglia thalamocortical circuit (positive psychotic symptoms) and dorsolateral prefrontal circuit (negative symptoms)
•N-acetyl asparatate were lower in hippocampus and frontal lobes impairing neural metabolism (Wong & Tol, 2003)
• Abnormal EEG with increased sensitivity to activation procedures, increased theta and delta activity, decreased alpha activity, causing epileptiform activity, and more left-side abnormalities (Nuechterlein & Dawson, 2002)
• Eye movement dysfunction with inability to follow moving target accurately, disinhibition of saccadic eye movements (Alain, Hargrave, & Woods, 1998)
• Dysdiadochokinesia, astereognosis, primitive reflexes, and diminished dexterity (Irani et al., 2011)
Immune
• Decreased T-cell interleukin (IL)-2 production, reduced number and responsiveness of peripheral lymphocytes, abnormal cellular, humeral reactivity to neurons, and presence of brain-directed (antibrain) antibodies
• Increased concentration of IL-1, IL-6, TGF-β, state markers and IL-12, IFN-λ, TNF-α, and sIL-2R are trait markers of the disease
• Elevated C-reactive protein, oxidative stress markers (Steiner et al., 2012)

• Increased apoptosis may account for tumor resistance with tumor suppression indicating a decreased incidence of cancer (Barak et al., 2005)
• Hyperprolactinemia alters the modulation of mononuclear cells of immune-cell function (Halbreich et al., 2003)
• Reduced length of telomeres causing cellular degeneration and premature cell death (Jeste et al., 2011)
Musculoskeletal
• Increased prolactin levels causing hypogonadism increasing risk of osteoporosis (Halbreich et al., 2003)
• Abnormal performance on cerebellar-dependent tasks with decreased complexity of postural sway; abnormal changes in association with removal of visual input causing a disturbance of gait (Kent et al., 2012)
• Decreased risk of rheumatoid arthritis (Leucht et al., 2007)
Reproductive: Female
• Small increased breast cancer risk at younger age, and higher risk for post-menopausal women (Barak et al., 2005)
• Increased prolactin levels cause decrease in estrogen levels with potential decreased libido or anorgasmia (Halbreich et al., 2003)
Reproductive: Male
• Increased prolactin levels cause decreased estrogen levels and libido, ED, delayed orgasm, anorgasmia, retrograde or painful orgasms (Halbreich et al., 2003)
• Small to medium decrease in prostate cancer (Barak et al., 2005)
Sensory: Vision & Olfactory
• Elevated blink rate (hyperdopaninergic) (Ross et al., 1999)
• Abnormalities in olfactory receptor neurons with decreased ability to detect and identify odors (Turetsky et al., 2003)

Skin & Hair
• Small to medium decrease of malignant melanoma (Barak et al., 2005)

Physiological Changes in Schizophrenia by Body System

Studies have shown schizophrenia to be a life-altering disease. Compared to the general population, individuals with schizophrenia experienced accelerated physical aging with increased and premature medical comorbidities and mortality (Jeste et al., 2011). Researchers have identified several common physiological changes inherent in patients with schizophrenia. In younger patients with schizophrenia, a high proportion of deaths are caused by suicide and accidents. Yet a substantial remaining proportion of mortalities is due to physical illness (Brown, 1997). These illnesses may be influenced by physiological changes associated with schizophrenia (see Table 2.1).

The main changes that occur within the body systems with the presence of schizophrenia begin in the brain. Many of these changes bring about the positive and negative symptoms of schizophrenia by affecting dopamine levels within the cortex. Other changes affect the transmission of the neurochemicals within the brain, causing alterations in cognition, the capacity to feel pleasure, and the ability to identify people, objects, and events. Throughout the cardiovascular system there are increased risks of heart disease, hypertension, and dyslipidemia with premature cellular death and lessened immune responses to protect the vascular system from damage. Hyperglycemia and insulin resistance occur at a higher level in this population, which leads to a higher percentage of diabetics.

The etiology of the physiological changes associated with schizophrenia is unclear. Questions remain regarding whether individuals with schizophrenia develop health issues contributing to reduced life expectancy and comorbid health issues, or whether there are associated factors. These would include unhealthy lifestyle choices, antipsychotic medications, or disease-inherent derangements predisposing them to these problems. With the knowledge of aging and the effects of schizophrenia on the body systems of the older individuals, an understanding emerges that provides insight for practitioners to guide practice decisions. Table 2.2 examines medication commonly prescribed for the treatment of schizophrenia and the many ways the presence of this medication alters the functioning of body systems. This additional layer will complement the total knowledge compiled and provide a basis for targeted analysis of problem areas important for best practice care.

Effects of Antipsychotic Medications

In considering the prescribing practices for older patients with schizophrenia, it is important to be aware of medication side effects, actions, and class warnings. The information given by the FDA helps providers monitor potential side effects, offer cautions for harmful drug/drug interactions, and guides precautionary details necessary for safe prescribing practice. This section provides a table illustrating these factors and a narrative overview of the most important findings. The two classes of antipsychotic medications are examined through the effects, both positive and negative, on each body system. Special warnings governing the prescribing practices for specific drugs are noted within the table.

The FDA's Warnings

The Food and Drug Act of 1906 prompted the formation of the Food and Drug Administration (FDA), the governing public health and consumer protection agency in the USA. Under the approval and sanctions of this office, prescribers operate and utilize FDA guidelines for safe use of medication. Drugs are subjected to rigorous testing with proof of safety carefully examined.

The FDA issues warnings or alerts on the package inserts (PI) that accompany all drugs to market and guide labeling and Physician Desk Reference (PDR) listings. The strongest warning is the boxed warning (also called a bolded or black box warning). This indicates that the drug carries a significant risk of serious or even life-threatening adverse effects. Warning and precautions do not meet the definition of serious adverse reaction, but are clinically significant events that may: (a) lead to potentially serious outcomes unless dosage or regimen is adjusted, (b) require monitoring to prevent or manage the potential of an adverse reaction, and (c) affect patient compliance when compliance has potentially serious consequences ("Guidance for industry," 2011). When the warning extends to all the drugs in one class of medications, it is called a class warning. Class warnings are typically issued when an across-the-board side effect is noted.

In 2003, the FDA issued a black box warning on all antipsychotic medications written for the elderly with dementia because of sudden cardiac death risk (Leon et al., 2010). Initially, the concern was an increase in cerebral vascular accidents including strokes. The warning was amended to include increased risk of mortality related to sudden cardiac death (Jouk et al., 2006). Further study revealed a risk of death in drug-

treated patients between 1.6 and 1.7 times the risk of death in placebo-treated patients (Strompf, 2012). Questions arise as to the best practice for treatment of the elderly patient with schizophrenia who additionally suffer from dementia, as both disorders must be addressed to provide quality care (Harris, Heaton, Schalz, Bailey, & Patterson, 1997).

Warnings regarding medications are areas continually revised and updated by the FDA. The FDA sponsors contact sites via the web, consumer phone reporting, and professional med watch e-lists to keep prescribers up to date on recalls, shortages, and amendments to the PI ("MedWatch," 2013). Safe medication prescription depends on knowing the latest information and applying this information to the care of individual patients.

It is also critical for prescribers to understand the effects of antipsychotic medications on the body. The actions and side effects (see Table 2.2) from the first generation antipsychotic, dopamine 2-receptor antagonist (D2RA) class, to the newer generation of neuroleptic medications, serotonin dopamine antagonist (SDA) class, are different in many ways with a few similarities. The degree the patient experiences these side effects is also patient specific, but the trend tends to follow the side effect potential in Table 2.2.

With the discovery of the first antipsychotic medication in the mid-twentieth century, the potential for enhancing the lives for patients with schizophrenia opened up to new possibilities. However, over time, adverse response to these new medications became apparent.

Table 2.2

Effects of Antipsychotic Medications by Body System

Cardiovascular		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Alpha-1 receptor antagonist • Increased risk of events in elderly dementia patients (Stahl, 2008)	• Class warning (all)	• Decreased blood pressure, orthostatic hypotension • Fainting, falls
• Elevated prolactin level (Miller, 2004)	• Class warning (all) • Cigarettes and alcohol consumption may also impact outcome	• Low estrogen, higher blood pressure, and decreased nitric oxide increase chance of myocardial infarction
• Disrupted enzyme contractility in cardiac cell, decreased cardiac contractility, increased circulating catecholamines, prolonged arterial and ventricular conduction refractory periods (Stahl, 2008)	• Lower potency DRAs more cardio toxic than high potency drugs • Caution with other drugs that may increase QT interval to compound the event (Thorazine, Haldol, Mellaril drug specific)	• Arrhythmias, postural hypotension, cardiac arrest • Torsades de Pointes (TdP) (with IV use and or higher doses) • Thorazine specific: T-wave blunting, depression of the ST segment

Serotonin-dopamine antagonist (SDA)		
Side effects	Interactions	Adverse reactions
• Weight gain, glucose dysregulation, and lipid abnormalities	• Class warning (all)	• Increased cardiovascular events
• Alpha-1 receptor antagonist	• Class warning (all)	• Fainting, falls
• Increased risk of events in elderly patients with dementia (Strompf, 2012)	• Class warning (all)	• Death
• Increased visceral obesity (Steiner et al., 2012)	• Increased pro-inflammatory cytokines and elevated C-reactive protein (CRP) levels	• Increased complications
• Clozapine specific: Increased risk of myocarditis, pericardial effusion, congestive heart failure, and cardiomyopathy, (Strompf, 2012)	• 25% tachycardia noted	• Associated with higher risk during first month of treatment
• Clozaril, Invega, Saphris, Fanapt, Geodon, Seroquel, Saphris specific: Prolonged QT interval	• Caution with other drugs that may increase QT interval to compound the event	• Arrhythmias, cardiac arrest

• Risperidone, Invega, Latuda, Seroquel specific: Elevated prolactin (Strompf, 2012)	• Cigarettes and alcohol consumption may also impact outcome	• Increased risk of cardiovascular disorders
Hematologic		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Agranulocytosis, thrombocytopenia or nonthrombocytopenic purpura, hemolytic anemia, pancytopenia can occur (rarely) • Leukopenia, neutropenia, and agranulocytopenia (Strompf, 2012)	• Class warning (all)	• Mortality rate is 30%
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions
• Leukopenia, neutropenia,and agranulocytopenia	• Class warning (all)	• Compromised immune system
• Elevated fasting triglycerides, insulin resistance	• Class warning - Initial symptoms of metabolic syndrome	• Increased appetite and weight gain (variable by drug)

• Clozaril specific: Significant risk of potentially life-threatening agranulocytosis	• Drop in white blood cells (WBC) and absolute neutrophil count (ANA)	• Compromised immune system and possible death
• Seroquel, Zyprexa specific: Hyperlipidemia (Strompf, 2012)		• Increased risk of cardiovascular events
Respiratory		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Blockage of muscarinic cholinergic receptors (Stahl, 2008)	• Decreased bronchial secretions	• Mucous occluding small airways in patients with asthma or bronchitis
• Increased risk of bronchial pneumonia (Strompf, 2012)	• Sedation, decreased secretions, hypoventilation, dehydration, and hemoconcentration contribute	• Compromised respiratory system
• Mellaril specific: Central nervous system depression (Strompf, 2012)	• Enhanced by use with sedative/hypnotic	• Respiratory depression with distress potential
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions
• Blockage of muscarinic cholinergic receptors (Stahl, 2008)	• Decreased bronchial secretions	• Mucous occluding small airways in patients with asthma or bronchitis

Gastrointestinal		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Muscarinic cholinergic receptor blockade (less with Haldol) (Stahl, 2008)	• Decreased salivation	• Dry mouth, constipation, dental caries, ulceration of gums, and buccal mucosa
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions
• Drug specific bias (espy. Clozapine, Zyprexa, Saphris, Latuda, Seroquel): Weight gain (Strompf, 2012)	• May be compounded by other weight-causing drugs	• Weight gain - Frequently a cause of discontinuation
• Muscarinic cholinergic receptor blockade (Stahl, 2008)	• May be compounded by other drying medications	• Decreased salivation
• Esophageal dysmotility	• Drug specific: Seroquel	• Blockage, N/V
• Invega specific: gastric narrowing		• Blockage and stricture potential when GI disease present

• Risperidone specific: Dysphagia (Strompf, 2012)		• Difficulty swallowing
Urinary		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Muscarinic cholinergic receptors blockage	• Difficulty urinating	• Bladder distention, urinary retention
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions
• Muscarinic cholinergic receptors block. (Stahl, 2008)		• Bladder distention, urinary retention
Endocrine		
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions
• Endocrine bioactivity from excess visceral adipose tissue increasing systemic inflammation (Buckley, Miller, Singer, Arena, & Stirewalt, 2005)	• Synthesize and release bioactive molecules: Interleukin (IL)-1, Il-6, Tumor Necrosis Factor (TNF), increased monocytes and CRP	• Reduced insulin resistance, induce insulin resistance of the insulin-sensitive glucose transporter in the peripheral tissue • Elevated triglycerides (with or without weight gain)

• Postsynaptic M3 muscarinic cholinergic receptor blockage (high probability with Olanzapine, Clozapine) (Lipscombe et al., 2011).	• Reduces insulin release- Beta cell failure	• Hyperglycemia, diabetic ketoacidosis (DKA) and hyperosmolar syndrome (HHS)
• Hyperglycemia, diabetes mellitus risk increased (Okumura et al., 2010)	• Class warning (all)	• Metabolic syndrome
Neurological		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Blockade of the D2 receptors in the mesolimbic dopamine pathway, reducing the hyperactivity of the pathway	• Reduction of the positive symptoms of schizophrenia	
• Blockage of the D2 receptors in the nigrostriatal DA pathway	• Blockage by dopamine may allow acetylcholine levels to become overactive. Class warning. Receptors become sensitive over time and upregulate	• Increased risk of EPS and TD High discontinuing rate due to unacceptable side effects
• D2 antagonist reduced in the tuberinfundibular pathway	• Prevents dopamine from binding to D2 receptors	• Elevated prolactin levels

• D2 receptor antagonist in the mesocortical pathway to the dorsolateral prefrontal cortex	• Reduced dopamine	• Cognitive and negative symptoms
• D2 receptors blocked in mesocortical DA pathway to ventromedial prefrontal cortex (Stahl, 2008)	• Reduced dopamine	• Affective and negative symptoms
• Neuronal brain changes (Dean, 2006)	• Neurotoxicity, apoptosis, DNA fragmentation, deficits in DNA repair, deficits in function of the mitochondrial respiratory chain, and changes in levels of Neurotrophic factors (NTF) (observed in rodents)	• Unknown
• Histamine 1 receptor antagonist.		• Drowsiness, increased appetite, with high discontinuing rate as a result
• Alpha 1 inserted		• Dizziness, drowsiness
• Block D2 receptors in the mesocortical and mesolimbic DA pathway (Stahl, 2008)		• Causes or exacerbates negative or cognitive symptoms
• Blockage of muscarinic cholinergic receptors (Strompf, 2012)	• Class warning (all)	• Cognitive blunting, drowsiness, memory impairment, and confusion

• Lower seizure threshold	• Class warning (all) • Lower potency drugs are higher epileptogenic	• Higher incidence of seizures if pre-existing seizure disorder present
• Neuroleptic Malignant Syndrome potential (Strompf, 2012)	• Class warning (all)	• Death possible without treatment and rapid recognition of symptoms
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions
• 5HT2A antagonist occupies 5HT2A receptors on mesolimbic dopamine neuron causing dopamine release.	• Cognitive, affective, and negative symptoms are reduced	
• 5HT1A (inhibitory) and 5HT2A (excitatory) regulate the dopamine release. 5HT2A antagonist blocks serotonin excitation of the cortical pyramidal cells decreasing glutamate release, reducing the hyperactive drive on the mesolimbic dopamine pathway downstream	• Reduced hallucinations and positive symptoms • Reduced binding (disinhibition) at D2 receptor also decreased EPS	
• Dopamine regulation in the mesocortical	• Mediate affective, cognitive, and negative	

pathway	symptoms	
• D2 receptors blocked in the nigrostriatal DA pathway (Stahl, 2008).	• Class warning/Drug specific: All in class except Clozaril • Receptors become hypersensitive or upregulate	• Initially hyperkinetic movements, over time developing into TD
• Increase in seizure activity (Clozaril highest).	• Class warning: Incidence occurs with higher doses	• Higher incidence of seizures if pre-existing seizure disorder
• Potential for cognitive and motor impairment	• Class warning (all)	• Impaired use of motor equipment
Immune		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Elevated prolactin level	• Class warning	• Decreased immune response
• Leukopenia, neutropenia, and agranulocytosis	• Class warning (all)	• Immunocompromised
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions
• Bioactive activity from visceral adiposity (Steiner et al., 2012)	• Synthesize and release bioactive molecules: Interleukin (IL)-1, Il-6, Tumor Necrosis Factor (TNF), increased monocytes and CRP	• Pro-inflammatory response

• Leukopenia, Neutropenia, and Agranulocytosis (Strompf, 2012)	• Class warning (all)	• Immunocompromised
• Elevated prolactin level (Halbreich et al., 2003)	• Class Warning/Drug specific: Invega, Risperdal, Seroquel, and Latuda	• Decreased immune response
Musculoskeletal		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Elevated prolactin level (Meaney, 2004)	• Class warning (all): hypogonadism	• Increased risk of osteoporosis
• Blockade of the dopamine receptors in the basal ganglia (Strompf, 2012)	• Class warning/Drug specific: All in class except Clozaril	• Movement disorders: Akathisia, TD, EPS, and hyperkinesis
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions
• Blockade of the dopamine receptors in the basal ganglia (Strompf, 2012)	• Class warning/ Drug specific- All in class but Clozaril Incidence less than D2RA	• Movement disorders: TD

• Potential for akathisia	• Drug specific: Abilify, Risperdal	• Restless legs with "inner restlessness" causing inability to sit
• Elevated prolactin level (Strompf, 2012)	• Class warning/Drug specific (Risperdal, Invega, Seroquel, Latuda): hypogonadism	• Increased risk of osteoporosis
Reproductive (Male)		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Elevated prolactin level	• Class warning: Disruption of the hypothalmis-pituitary-gonadal system	• Decreased libido and arousal, un- or hypo-orgasmia, galactorrhea
• α-1 adrenergic antagonist activity (Strompf, 2012)		• Priapism, painful orgasm
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions
• Elevated prolactin level (Invega, Risperdal, Seroquel, and Latuda specific)	• Class warning: Disruption of the hypothalmis-pituitary-gonadal system	• Decreased libido and arousal, un- or hypo-orgasmia, and galactorrhea
• Increased risk of priapism	• Drug specific: Fanapt, Seroquel, Risperdal, and Invega	• Requiring medical attention

• Blockage of muscarinic cholinergic receptors (Strompf, 2012)		• Sexual side effects
Reproductive (Female)		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Elevated prolactin level	• Class warning: Disruption of the hypothalmis-pituitary-gonadal system	• Disruption of the menstrual cycle, anovulation, galactorrhea, low estrogen level, increased risk of breast cancer (post-menopausal, pre-menopausal), and decreased libido
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions
• Elevated prolactin level (Invega, Risperdal, Zyprexa, and Latuda specific)	• Class warning: Disruption of the hypothalmis-pituitary-gonadal system	• Decreased libido and arousal, un- or hypo-orgasmia, galactorrhea, low estrogen levels, increased risk of breast cancer (post-menopausal, pre-menopausal), and decreased libido
• Increased risk of priapism	• Drug specific: Fanapt, Seroquel, Risperdal, and Invega	• Requiring medical attention

• Elevated prolactin level (Invega, Risperdal, Zyprexa, and Latuda specific) (Strompf, 2012)	• Disruption of the hypothalmis-pituitary-gonadal system	• Decreased libido and arousal, un- or hypo-orgasmia, galactorrhea, low estrogen levels, increased risk of breast cancer (post-menopausal, pre-menopausal), and decreased libido
Sensory		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Blocked muscarinic cholinergic receptors		• Blurred vision
• Retinal pigmentation	• Drug specific: Most associated with Mellaril	• Early symptoms are nocturnal confusion related to night vision, may progress to blindness
• Closed angle glaucoma, ocular dystonia, and cataracts (Strompf, 2012)	• Usually associated with high dose and prolonged use especially Thorazine and Mellaril	• Blurred vision, loss of vision, and blindness if untreated
• Dysregulation of the bodies' core temperature. (Strompf, 2012)	• Class warning	• Caution in conditions that may elevate core temperature (e.g., exercising strenuously, exposure to extreme heat, dehydration)
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions
• Closed angle glaucoma, ocular dystonia		• Blurred vision, loss of vision, and blindness if untreated

• Dysregulation of the bodies' core temperature. (Strompf, 2012)	• Class warning	• Caution in conditions that may elevate core temperature (e.g., exercising strenuously, exposure to extreme heat, dehydration)
• Increased chance of cataracts (Strompf, 2012)	• Drug specific (Geodon, Seroquel) with long time treatment	
Skin		
D2 receptor antagonist (D2RA)		
Site/action specific	Interactions	Adverse reactions
• Photosensitivity, allergic dermatitis	• Drug specific: Thorazine has high correlation to skin changes	• Severe sunburn appearance or long-term blue-grey discoloration of skin resolves when medication discontinued
• Macularpapular, urticarial, petechial, and edematous eruptions (Strompf, 2012)	• May resolve spontaneously	
Mood and Behavior		
D2 receptor antagonist (D2RA)		
Side Effects	Interactions	Adverse Reactions
• Increased risk of suicide	• Class warning (all)	
• Elevated prolactin level	• Class warning causing decreased estrogen	• Hostility, anxiety, and depression
Serotonin-dopamine antagonist (SDA)		
Site/action specific	Interactions	Adverse reactions

• Increased risk of suicide	• Class warning (all). Special caution with antidepressant use	
• Drug specific: Invega, Risperdal, Seroquel, Latuda elevated prolactin level (Strompf, 2012)	• Class warning causing decreased estrogen	• Hostility, anxiety, and depression

Both classes of antipsychotic medications, D2RA and SDA, have a major impact on the overall health of the patient with schizophrenia. As a class in general, the D2RA historically had more issues with movement disorders, prolactin elevations, and cardiac arrhythmias. The SDA have been associated with more metabolic issues including weight gain, dyslipidemia, and insulin resistance. Over time, the SDA have had added prolactin issues and movement disorders associated with use. It is paramount to see knowledge of antipsychotic medications as an evolving process.

The FDA web site offers updates to each drug with letters and addenda listed with changes to the PI by date. Frequent updates of prescriber knowledge are necessary to keep up to date with the newest findings of the FDA. Seminars and web-casts are offered to providers and most states require continuing hours of education for license renewal in medication updates. Drug representatives of specific antipsychotic medication are usually a good source of new information on their products as well. Changes occur on a continuous basis and safe prescribing practice requires practitioner attention.

In reviewing the depth to which these medications affect the body systems, the age-related changes in peripheral and central pharmacokinetics contribute to the variable degree of drug sensitivity in older age patients. Age-related changes contribute to

increased sensitivity to side effects along the treatment pathway. However, absorption factors and plasma concentration of antipsychotic medication are subject to the influencing factors of smoking and renal dysfunction as causative factors of altered clearance levels of medication. Pharmacodynamic changes within the dopaminergic system interfere with antipsychotic sensitivity, and dosing for this population may need adjustments to compensate.

Knowledge of the data in this medication table and performing careful assessments of the older patient with schizophrenia allows a safety net to develop. Once in place, guidelines can be set and patients can be monitored for individualized changes. With the use of medication, the patient has the chance of functioning free of the positive symptoms of the disease. Awareness of negative symptoms and system involvement is the cornerstone of best practice care.

Cross Correlation of Aging, Schizophrenia, and Antipsychotic Medications

Elderly patients with schizophrenia are susceptible to the compounding factors of age, disease state, and the onboard effect of prescribed medications. Research examined many of these factors, but stopped short, in many cases, of closely inspecting how these factors may interact to create treatment challenges. Table 2.3 illustrates correlations across the previous tables to identify key focal points for practitioners. Included in the table are items that appear in two or more tables across one body system, indicating areas that require particular attention or monitoring by providers because of their potential to interact in ways that complicate patient treatment. Table 2.3 supports this paper's premise that the best practice focus is on medication management considering drug actions, side effects, and comorbidities along with physiological changes associated with

both aging and schizophrenia. Geriatric psychopharmacologists must explore all aspects of the older patient with schizophrenia — physical, medical and psychiatric— to determine best practices for medication management.

Five main areas of concern for practitioners treating this population require greater attention: metabolic syndrome, immune system depression, increased risk of respiratory disease, cognitive impairment, and cardiovascular disease.

Table 2.3

Correlations Identified by Body System

Normal Aging	Schizophrenia	Antipsychotics
Cardiovascular		
• Increased risk of morbidity, MI, CAD	• Increased risk of morbidity, MI, CAD	• Increased risk of morbidity, MI, CAD
• Decreased blood to brain, kidneys	• Decreased diameter of vessels	
•Increased blood pressure	•Increased blood pressure	• Increased blood pressure
Hematologic		
	• Increased risk of hyperlipidemia	• Increased risk of dyslipidemia
	• Increased glucose, A1C	• Increased glucose, A1C
	• Increased prolactinemia	• Increased prolactinemia
Respiratory		
• Less sensitive to hypoxemia, increased risk of respiratory failure, nocturnal hypoxemia, and decreased vital capacity	• Decreased lung capacity and increased respiratory problems	• Increased risk pneumonia (hypoventilation, dehydration, sedation)
Gastrointestinal		
	• Increased BMI & central adiposity	• Weight gain
• Decreased saliva, taste	• Decreased saliva	• Decreased saliva
• Increased dental problems with loss of teeth		• Increased dental caries, ulcerated gums and buccal mucosa

• Decreased colonic muscle tone and motor function		• Constipation
Urinary		
• Decreased bladder capacity and residual urine, with increased nocturnal frequency		• Dysuria, bladder distention and retention
Endocrine		
• Increased insulin resistance	• Increased risk of DM	• Increased risk of DM, DKA & hyperosmolar syndrome (HHS)
Neurological		
• Cognitive impairment with anticholinergic effects of meds	• Progressive mild cognitive impairment, impaired neurotransmitters of cognition	• Cognitive, affective and negative symptoms, cognitive blunting
• Decreased energy production, blood flow, and glucose consumed	• Impaired glucose metabolism—especially in the frontal lobe	
• Decrease in dopamine and dopamine receptors	• Increased dopamine content or metabolism • Limited dopamine neurons that can be activated	• Decreased dopamine with D2RA & SDA •Prevention of dopamine from binding to D2 receptors
• Reduced brain size density	• Reduced brain density	• Reduced brain size
Immune		
• Reduced antibody/antigen response	• Reduced immune response	• Reduced immune cell response
• Reduced thymic hormones	• Increased C-reactive protein and O2 stress markers	• Increased pro-inflammatory response
Musculoskeletal		
• Increased risk of osteoporosis	• Increased risk of osteoporosis	• Increased risk of osteoporosis
Reproductive		

• Decreased libido	• Decreased libido	• Decreased libido

Metabolic Syndrome

Metabolic Syndrome (MetS) is a metabolic disturbance formed from a cluster of problems including hypertension, insulin resistance, dyslipidemia, and obesity. If left unchecked, MetS can increase a patient's risk for cardiovascular disease and diabetes (Alberti et al., 2006). For an older patient with schizophrenia these risks are compounded when poor nutritional food choices and budget constraints contribute to unhealthy diets.

Immune System Depression

Aging impacts the antigen/antibody system and the body's speed of response to invading organisms. The age-influenced reduction in thymic activity, depression of immune cell response, and humeral response are all influencing factors (Solana, Pawelec, & Tarazona, 2006). Elevated levels of prolactin in the body have both direct and indirect impact on various pathological states as indicated by the prevalence of osteoporosis, depressed immune response, increased cardiac events, and decreased libido. Having a depressed immune system slowing the body's ability to mount an immune response can also have detrimental effects.

Increased Risk of Respiratory Disease

Medical practitioners should be aware that this population is at greater risk of respiratory disease and respiratory failure. This results from several factors. Polysubstance use and difficulty sleeping may predispose the older patient to use more sedating agents or anticholinergic agents at night. Anticholinergic drugs or antipsychotic drugs also cause serious side effects such as cognitive impairment (Lieberman, 2004) and

block the muscarinic cholinergic receptors in the brain. This dries the mucous membranes and further depresses respirations. These factors would be particularly harmful if a patient had a pre-existing condition such as asthma or COPD.

Cognitive Impairment

Aging, the history of schizophrenia, and the use of antipsychotic medications all effect cognition. Impairment of cognition impacts quality of life and the patient's ability to live alone**.** Some antipsychotic medications exert more influence over the negative symptoms of schizophrenia while other medications induce cognitive blunting. Studies indicate chronically institutionalized patients have a greater than average cognitive decline and conversion to dementia (Jeste et al., 2011). Practitioners should be aware that efforts to help the patient maintain a community-based existence might counter cognitive decline.

Cardiovascular Disease

Cardiovascular disease (CVD) and increased risk of MI are found in the older population as well as the patients with schizophrenia. According to Hennekens, Hennekens, Hollar, and Casey (2005), CVD was the explanation for excess mortality among people with schizophrenia. Aging, antipsychotic medications, and disease all have major influence on the condition of the heart and cardiovascular system. Lifestyle factors also influence those predisposed towards CVD. Substance abuse, diets high in fats and of low nutritional quality, and non-compliance with prescribed medications for treating dyslipidemia and hyperglycemia can all impact cardiovascular health in this patient population.

Summary

The older patient with schizophrenia experiences challenges associated with the cumulative effects of an aging body, the disorder and medication use. As the demographic shift occurs along with the increasing concern about comorbidity, and mortality associated with antipsychotic use, a need to understand and maintain wellness becomes evident. To minimize drug exposure while balancing the positive and negative symptoms with least side effects is a major goal. Keeping a careful eye on the aging body, with all the alterations of the many years of living, becomes a complicated task. Health problems pinpointed in this chapter's tables were target specific for this population based on age, schizophrenia, and exposure to antipsychotic medications.

Awareness of the major health problems identified in this population provides insight for practitioners regarding areas needing attention. Issues related to metabolic syndrome (MetS), immune system depression, increased risk of respiratory disease, cognitive impairment, and cardiovascular disease will be examined in detail using evidence-based tables for graded research in these areas to determine best practice recommendations for optimum care.

Chapter 3 provides the results of a literature search of these areas as they apply to the treatment of older adults with schizophrenia. The focus will be medication and changes in medication management because of drug actions and side effects, comorbidities, and physiological changes due to disease and age.

Chapter 3 Search Process

With the number of older adults schizophrenia increasing, practitioners face a very complex situation for the context of care and action and side effects of drugs. This evidence-based project's focus is safe and effective medication management for the aging population with schizophrenia.

Methodology

An evidence review was completed to address the PICOT question, "In community dwelling older adults with schizophrenia, what is the best practice for antipsychotic medication management?" The following sections describe the components of the evidence review approach including: (a) description of evidence sources; (b) search terms; (c) inclusion/exclusion criteria, and (d) search process.

Description of Evidence Source

A total of eight sources was searched: Cochrane Database of Systematic Reviews (CDSR), National Guideline Clearinghouse (NGC) through the Agency for Healthcare Research and Quality (AHRQ), U.S. National Library of Medicine via National Institute of Health, Public Medicine (PUBMED), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Joanna Briggs Institute, Dissertations & Thesis: Full Text database, PsycARTICLES, PsycINFO, and MedlinePlus (OVID). The current analytical framework began with identification of the systematic reviews on the topics in

current research. The search was then narrowed to focus more specifically on the articles examining the select topics.

The search began with CDSR because it offers systematic reviews including medical and pharmacological data on many relevant healthcare issues (Melnyk & Fineout-Overholt, 2005). A systemic review is a high-level overview of primary research on a specific question that seeks to answer that question by identifying, selecting, synthesizing, and appraising quality research evidence relevant to the question ("Evidence-based," 2013). The key characteristics of the Cochrane review are (a) utilization of clearly stated objectives with pre-defined eligibility criteria for studies; (b) methodology that is explicit and reproducible; (c) search criteria that attempts to identify all eligible criteria; (d) findings assessed for validity including bias, and (e) synthesis and systematic presentation of the characteristics and findings of the included studies (Higgins & Green, 2011). Systematic reviews of randomized clinical trials (RCTs) are considered Level I evidence and are found at the top of the hierarchy of evidence with the most rigorous approach to the minimization of bias (Melnyk & Fine-Overholt, 2005). Focusing on the current PICOT question, this exploration process began with a search for a systematic review of RCTs in medication management for older populations with schizophrenia.

The second database searched was NGC via AHRQ. This is an evidence-based guideline clearinghouse for clinical practice with quality measures. The mission of the AHRQ is to improve the quality, safety, efficiency, and effectiveness of health care for all Americans ("Mission," 2014). The agency is a division of the U.S. Department of Health and Human Services. The NGC supports a clearinghouse for links to full

guidelines on specific health subjects ("About," n.d.). This database offered superior evidence-based guidelines to provide quality outcomes for medication management for the treatment of older patients with schizophrenia when searched utilizing the PICOT criteria.

The third search was of PUBMED because of the large, electronic biomedical bibliographical records this site offers. PUBMED comprises more than 22 million citations for biological and medical literature for MedlinePlus, life science journals, and online books ("PubMed help," n.d.). The United States National Library of Medicine (NLM) at the National Institutes of Health maintains the database with the latest information from the world of public medicine ("Fact Sheet," n.d.). The PICOT question prompted search of this site for peer reviewed, scholarly journals providing a valid, unbiased meta-analysis or research, giving insight to medication management for the older schizophrenic population to provide best-practice clinical care.

The fourth database in the search process was CINAHL, a large database for nursing and allied health information. Records include comprehensive research indexes with documents dating back to 1937 including 1,637 peer-reviewed journals in the CINAHL database ("Full text," n.d.). Melnyk and Fineout-Overholt (2005) consider CINAHL a renowned source of comprehensive healthcare and scientific data. CINAHL's focus is nursing and allied health including overviews of diseases and conditions with outlines of the most effective options for treatment relevant to the older patients with schizophrenia.

The fifth source searched was the Joanna Briggs Institute, Dissertations & Theses: Full Text database. This is a non-profit, international research and development

organization that collaborates with over 70 entities across the world to promote and support the synthesis, transfer, and utilization of evidence to improve healthcare throughout the world ("About us," n.d.). The site was searched to locate research into schizophrenia in older adults and related focal areas of concern related to medication management.

The sixth and seventh sources of data searched were PsychINFO and PsycARTICLES. These bibliographic databases index scholarly literature in behavioral sciences and mental health with a psychiatric, neuroscience, and nursing focus (Melnyk & Fineout-Overholt, 2005). The American Psychological Association supports both sites. PsycINFO has more than 3.4 million records for peer-reviewed journals, books, and dissertations (PsycINFO, n.d.). PsycARTICLES is a database of full text articles from 90 landmark journals in behavioral science as well as nursing and neuroscience. All are peer-reviewed, top psychology and social science journals ("PsycARTICLES," n.d.). Both sites offered timely research on the older population with schizophrenia including medication management, drug studies, and recommendations for clinical practice.

The eighth database searched was MedlinePlus using OVID search technology. MedlinePlus is the National Institutes of Health web site, produced by the National Library of Medicine, the world's largest medical library ("About MedlinePlus," 2013). OVID offers journal articles in life sciences with a concentration on biomedicine. Tailoring the OVID search criteria facilitated a focused search for schizophrenia in the older population with six selected journals using the medical subject headings (MeSH) ("Overview," n.d.). The goal was to target any relevant articles that enhanced the biological and medical knowledge base of the project.

Search Terms

Key terms used in the search were *schizophrenia, older adult, antipsychotic medication, side effects, comorbidities*, and *community dwelling*. These were important because of their link to the PICOT question. Older adults with schizophrenia living in their communities were the specific population of interest. Records were further grouped by searching via intervention, specifically medication management for schizophrenia, as identified in the PICOT. Changes in medication management because of drug actions and side effects, comorbidities, and physiological changes dues to disease and age were identified while reviewing the articles of interest. Additionally, metabolic syndrome, cardiovascular disease, cognitive impairment, immune system depression, and increased risk of respiratory disease as they related to medication management were added to further narrow the focus. The outcome of this thorough search of the available research provides practitioners with evidence-based recommendations for the safe and effective medication management of this specific population of interest.

Inclusion/Exclusion Criteria

The inclusion/exclusion criteria (see Table 3.1) were based on the PICOT question for the evidence-based project. The terms used in the search included *antipsychotic medications, pharmacotherapy, side effects, elderly*, and *physiological complications*. *Physiological complications* included metabolic syndrome, cardiovascular disease, cognitive impairment, increased risk of respiratory diseases, and immune system depression. Evidence that qualified for inclusion targeted these criteria for clinical

Table 3.1

Inclusion/Exclusion Criteria

Inclusions	Exclusions
adult population 65 years + elderly and older (aging) male and female chronic schizophrenia peer review journals scholarly journals antipsychotic medications side effects pharmacotherapy 1999 to 2013 (except landmark) comorbid disease occurrences physiological implications metabolic syndrome cardiovascular disease cognitive impairment respiratory diseases immune system depression	schizotypal diagnostic interventions non-English language acute schizophrenia ECT children adolescent early adulthood middle adulthood (considered)

practice. Inclusion focused on the older population (65 years and older). Individuals with chronic schizophrenia were the target population as they had the most exposure over time to the medications and accumulation of comorbidities. Acute schizophrenia was therefore eliminated. Institutionalized patients were excluded, as the focus is on those living within the community not in nursing homes. The search was limited to peer-reviewed publications. A ten-year period of time was selected for the most up-to-date information with exceptions made for landmark or classic data. An exclusion for schizotypal was related to the disorder's classification as a personality disorder that may be treated with therapy or other means. Diagnostic interventions and electroconvulsive

therapy (ECT) were also excluded, as those topics were not a focus of this project. Finally, children, adolescent, and early adulthood were also barred from the search as the focus was on the older population. However, records that directly addressed the PICOT terms that provided quality data and interventions for recommendations using a middle adulthood group were considered for inclusion. Although these studies were not exclusively focused on the elderly population, the data could be extrapolated to draw inferential conclusions potentially applicable to the target population.

Search Process Description

In identifying relevant research studies unrelated documents were eliminated using a Boolean search strategy, which combines terms together in a logical, concise manner using inclusion or exclusion. The initial search utilized the most expansive term — schizophrenia —combined with PICOT terminology of older adult, community dwelling, and medication management.

Once the initial search was completed, the inclusion/exclusion criteria were utilized to focus the search for a more targeted list of record results. Each topic was searched separately as a subheading with the main topics remaining schizophrenia, older community dwelling, and antipsychotic medication management. The additional comorbid disease occurrences were added to the database of search criteria. The summary from evidence sources is summarized in Table 3.2.

Table 3.2

Search Process Summary

Evidence	Search Terms	Results	Number Retained
Cochrane	Schizophrenia + antipsychotic medications + older adult	47 records: Records for this search addressed multiple drug studies that were inconclusive, short term and not robust for recommendations. Subjects were young adults, or subject matter was excluded topics of this project.	2
National Guideline Clearinghouse (NGC) via Agency for Healthcare Research and Quality (AHRQ)	Schizophrenia + older adults + antipsychotic medication management + Schizophrenia	20 records: Records excluded: occupational therapy, substance abuse, depression, hepatitis, autism, pathways to care, health lifestyle for young adults, and Veterans guides.	0
PUBMED	Schizophrenia + older adult + antipsychotic medication (Table 3.1 criteria applied)	334 records found: Exclusions: drug comparatives, poorly designed research, pregnancy, autism, glutamate studies, genetics, animal studies, editorial, depression, quality of life, alcohol and drug abuse, social rehabilitation, suicide, first psychotic break, global representation and perspective.	7

CINAHL	Schizophrenia + older adult + antipsychotic medication (Table 3.1 criteria applied)	618 records found: Exclusions: depression, acute psychosis, poorly designed research, clinical attitudes, animal studies, stigma, substance abuse in younger age, psychosocial and quality of life issues, negative and positive symptoms, religion, editorials, nursing home residents and financial aspects of schizophrenia. 29 duplicate or repeat articles	1
Joanna Briggs Institute	Schizophrenia + older adult + antipsychotic medication (Table 3.1 criteria applied)	11 records found: Exclusions: hospitalization, younger adult articles, clinic attendance and alternative therapies	0
PsycARTICLES	Schizophrenia + older adult + antipsychotic medication (Table 3.1 criteria applied)	65 records found: Exclusions: counseling technique (CBT, DBT), religion, family therapy, coping, school-based issues.	0
PsycINFO	Schizophrenia + older adult + antipsychotic medication (Table 3.1 criteria applied)	44 records: Exclusions: social rehabilitation, family therapy, perceptions of illness, concepts, cost comparisons, coping.	0
MedlinePlus (OVID) Specific journals chosen: *Acta Psychiatrica Scandinavica, American Journal of Nursing, British Medical Journal, Journal of Clinical Psychopharmacology, Journal of Nervous and Mental Disease, Schizophrenia Bulletin*	Schizophrenia + older adult + antipsychotic medication (Table 3.1 criteria applied)	213 records: Exclusions: psychosocial and quality of life issues, editorials, poorly designed studies, rapid switching of drugs, alcohol and drug abuse with treatment recommendations, animal studies, stigma, first psychotic break, family counseling. Duplicates of / or repeat articles – 32.	6

Summary

A systematic method was utilized to identify and retrieve evidence relevant to clinical practice to provide best practice care for medication management of community dwelling older adults with schizophrenia. After applying the inclusion/exclusion criteria, the process initially involved searching through the listing of articles one by one for the specific information desired. The availability of the electronic databases, full text article downloads, and the consolidation of multi-journal sites of OVID helped to focus the search. The evidence search resulted in a total of 16 articles and records being retained. The findings identified in the search will be discussed in Chapter Four.

Chapter 4 Evidence Synthesis

Focusing on safe and effective medication management for the aging population with schizophrenia, this project's aim was to develop an evidence table drawing on quality evidence and presenting conclusions for medication management. This chapter is divided into four sections: Evidence Table Development, Evaluation of the Evidence, Analysis of Findings and Recommendations for Practice.

Evidence Findings and Analysis

Evidence Table Development

The search for articles appropriate for the EBP question and PICOT question identified 16 articles related to medication used with elderly patients with schizophrenia. The articles were entered into an evidence table using the headings: brief citations, level, aim, design/setting/sample, intervention, outcome, and limitations. Mean age of the population was noted where possible as the target age of interest for this evidence-based project was 65 years and older.

Evaluation of the Evidence

The articles were analyzed using the hierarchal method proposed by Melnyk and Fineout-Overholt (2010). The hierarchy contains seven levels with I being highest quality and VII lowest quality. The levels are based on the ability of the design to protect against threats to internal and external validity.

Table 4.1

Evidence Table

Aim	Design/sample/ setting/number	Outcome	Limitations
Level I			
Marriott, Neil & Waddingham (2006)/ Cochrane Collaborative			
To estimate the effects of anti-psychotic medication for treatment of SZ in people over 65.	Systematic review/ Three randomized clinical trials (RCT) evaluating antipsychotic drugs for SZ in older people 2003-2010/ N=252.	Little robust data available to guide clinicians to most appropriate drug to prescribe for elderly. Clinicians must weighing risks and benefits.	Small sample size in one study; short duration of all 3 studies (6-8 weeks) limited results; some data did not define how randomization occurred; no data collected on global or social functioning or quality of life; Western bias to data noted in 2 studies.

Aim	Design/sample/ setting/number	Outcome	Limitations
Level II			
Essali, A, Ali, G. (2013)/ Cochrane Collaborative			
To assess the effects of antipsychotic drugs for elderly people with late onset Schizo-phrenia (SZ).	Systematic review/ 38 studies identified in the original Cochrane SZ Group with no study meeting criteria retained; updated 1/2/13 with 88 studies identified with one meeting inclusion criteria, 48 are awaiting further classification. that compared antipsychotic drugs for the 65 years + diagnosed with SZ.	Treatment will be by providers using good clinical judgment and habit to guide prescribing.	Limited data because only one study met inclusion criteria for the review to date.

Aim	Design/sample/ setting/number	Outcome	Limitations
Level II			
Harvey, Napolitano, Mao, & Gharabawi (2003)/CINAHL			
To compare effects of Risperidone and Olanzapine on cognition in elderly patients with SZ or Schizo Affective (SZ AFF).	RCT / Double blind, randomized, parallel 8-week study. (Mean age: 71 yrs.) Random assignment to 1 to 3 mg/day of Risperidone or 5 to 20mg of Olanzapine /Recruited in and out patients / Diagnosed with Sz or SZ AFF. /N=176.	Low doses of Risperidone and Olanzapine improved cognitive function in elderly patients with SZ or SZ AFF. The improvements occur in aspects of cognitive function related to functional outcome.	Results may be influenced by patients' prior higher-dose First generation antipsychotics (FGA), which may affect the tested second-generation antipsychotics (SGAs) ability to enhance cognitive function. Educational levels of recruited by vary in multinational trials.

Aim	Design/sample/ setting/number	Outcome	Limitations
Level II			
Maixnew, Mellow, & Tandon, (1999)/ PUBMED			
To assess the efficacy, safety and tolerability of antipsychotics in the elderly.	Literature review of pharmacologic, clinical and regulatory issues involving antipsychotic use in elderly patients, compares FGA and SGA, and make some general recommendations/ 140 citations and references from 1955 to 1999.	FGA: Chlorpromazine - modest efficacy, side effects limit use. Thioridazine- moderate efficacy, side effects limit use, low EPS, high sedation, anticholinergic. Haloperidol- moderate efficacy, moderate side effects limit use, High EPS, low sedation. Thiothixene- insufficient, conflicting data. Fluphenazine- insufficient data SGA: Clozapine - Moderate to good efficacy, very low EPS, significant side effects, Dose low and slowly titrate 6.25-12.5mg/day. Risperidone- Moderate-good efficacy, greatest symptom reduction at 2mg (increased side effects). Begin 0.25– 0.5mg /day to 1-2 mg/day. Olanzapine - Moderate efficacy, more data needed. 5 to 10 mg best dose. Quetiapine - Moderate efficacy, more data needed. Low EPS. Begin 25mg daily. Average dose 100-150mg/day. Range 25-800mg /day. Summary- SGA preferred due to better tolerability. Elderly dose at 25% that of young adult. Go slow, start low, ongoing monitoring.	Study limited by the absence of data after 1999.

Aim	Design/sample/ setting/number	Outcome	Limitations
Level II			
Ritchie et al. (2006)/ OVID			
To compare the efficacy and safety of Olanzapine and Risperidone in the treatment of elderly patients with SZ.	Quantitative comparative design/Recruited 60 yrs. + of outpatients in Australia between 1998 and 2001). Patients switched from FGA to SGA. FGA had inadequate symptom management or side effects issues. Patients monitored every 6 weeks with battery of testing to measure efficacy and safety. (Mean age 69.5 yrs.) /N=61.	Both drugs were well tolerated, and their use was associated with fewer symptoms of SZ and less adverse effects. Olanzapine had a higher score on quality of life. Olanzapine (mean dose 12.4mg/day)/ Risperidone (mean dose 1.97mg/day).	Difficulty with recruitment limited the sample size and diminished power.

Aim	Design/sample/ setting/number	Outcome	Limitations
LEVEL II			
Suzuki et al. (2011)/ PUBMED			
To examine management of SZ in late life with antipsychotic medications and evaluated treatment resistance.	Qualitative review/23 studies included (8 double blind, 15 prospective/) 65 yrs. + population with SZ/1980 thru 4/2011/ N=23.	Dosing: (average) Olanzapine- 11.7mg/day. Risperidone- 2.4-3.7 mg/day, (both preferred for treatment resistance). Clozapine - 53.2 mg/day. Fluphenazine- was well-tolerated. Mixed results on aripiprazole and quetiapine. Threshold for extra pyramidal symptoms (EPS) lower in elderly. High vulnerability for metabolic issues due to smoking and lifestyle issues. Excess mortality due to cardiovascular, respiratory as well as suicide. Caution with Clozapine and anticholinergic burden. Little difference in efficacy exists between FGA and SGA.	None.

Aim	Design/sample/ setting/number	Outcome	Limitations
LEVEL II			
Tzimos et al. (2008)/ PUBMED			
To evaluate safety and tolerability of Paliperidone extended release (ER) tablets in elderly with SZ.	RCT/ Recruited outpatients sample were screened to meet criteria (Mean age 70 yrs.)/Multi-center international 6 week, double blind prospective study, with open label extension to 30 weeks/N=114.	Treatment over 30 days was generally well tolerated and may improve severity of symptoms of SZ. Elevated prolactin level in one-half patients. Paliperidone ER 3-12mg/day.	This study was primarily designed to obtain safety and tolerability data in an elderly population for special populations' guidelines and was not powered for statistical significance. The data was consistent with efficacy results for similar study in younger age group and was generalized by this study utilizing the flexible dosing design for this population.

Aim	Design/sample/ setting/number	Outcome	Limitations
LEVEL III			
Ciudad, Montes, Olivares, & Gomez (2004)/ PUBMED			
To evaluate the safety and tolerability of Olanzapine in an open comparison in parallel groups that compared other SGA in treatment with outpatients in the treatment of elderly patients with SZ.	Observational prospective, pharmaco-epidemiologic naturalistic study/ SZ outpatients. ≥60 yrs. of age (Mean age 65.8 ±5.9 yrs.)/from EFESO study in Spain/ /N=135.	Olanzapine has a favorable patient profile in treatment-emergent adverse in elderly, less probability of resistance to treatment, increase global functioning and improved clinical severity. Mean dose of Olanzapine was 11.7mg/day. The combined use of two or more antipsychotic drugs to maximize treatment response is frequent in daily practice. Less anticholinergic drugs were used as an adjunctive medication. Somnolence and weight gain were the top two side effects found exceeding 10%.	Small size of the control group, no randomization, post hoc sample from parent study, concomitant medications may have affected outcomes. Statistical significance was not achieved due to small size of the control group.

Aim	Design/sample/ setting/number	Outcome	Limitations
LEVEL III			
Davidson et al. (2000)/ PUBMED			
To assess the effects of Risperidone in elderly, chronically psychotic patients for 12 months.	Quasi-experimental /Multicenter, open label of elderly patients (65yrs +), median age: 72 yrs.,with SZ or other psychotic disorder (0.5mg 2 times a day, beginning dose titration, could be increased to 1.5mg to 4 mg 2 times a day) /N=180	Long-term treatment was found to continue both positive and negative symptom improvement, decrease in the severity of pre-existing symptoms of EPS, improved Cognitive Global Impression (CGI), and a low incidence tardive dyskinesia. Average dose 3.7mg/day.	Lack of randomization decreased the power of the results.

Aim	Design/sample/ setting/number	Outcome	Limitations
LEVEL III			
Jaskiw, Thyrum, Fuller, Arvamitis, & Yeh (2004)/PUBMED			
To assess the pharmacokinetics and tolerability of quetiapine in elderly patients with selected psychotic disorder.	Quasi-experimental /Patients recruited from multicenter in four states age > 65 yrs. of age (Mean age 71.8 yrs.)./an open label Diagnosis of Sz, SZ AFF, or Bipolar, rising multiple dose trial. Increased dosing in fixed step-wise progression reaching max of 250mg, 3 times on day 21. Total days of testing 27. Investigators could halt progression for 2 days if intolerant./ /N=12	Pharmacokinetics of quetiapine were identified as linear. Side effects included postural hypotension, tachycardia and dizziness. No QT changes observed. The effective dose should be introduced at a lower dose and titrated at a relatively slower rate in patients >65 yrs. old.	Trial limited by the small number of patients, lack of a control group, the open label design.

Aim	Design/sample/ setting/number	Outcome	Limitations
LEVEL VI			
Barak & Aizenberg (2003)/ OVID			
To assess the effects of Olanzapine on lipid abnormalities in elderly psychotic patients.	Prospective quantitative / elderly inpatients (Mean age 71.7 ± 8.2 yrs.), SZ AFF or SZ exposed to Olanzapine (mean dosage 12.9mg/day)/6 month (minimum) Mean duration of treatment, 289 days, with follow up / Israel/N=21	No significant change from baseline serum lipid levels was found for triglycerides or cholesterol. No weight gain was recorded. The association of olanzapine exposure and lipid abnormalities may not hold true for older patients.	Small size may have decreased the power of the results.

Aim	Design/sample/ setting/number	Outcome	Limitations
LEVEL VI			
Barak, Shamir, & Weizman (2002)/OVID			
To assess if switching from a typical antipsychotic to Risperidone would be beneficial for elderly SZ patients	Naturalistic retrospective study/ elderly inpatients (Mean age 72.7 yrs.), followed for 18 months with SZ or SZ AFF in Israel. Treated with either Risperidone or FGA (haloperidol, chlorpromazine, perphernazine, or 4 other FGA not used in the US) /Low doses of Risperidone were used (mean 2.3mg) /N=51	Patients in both groups had improved Positive and Negative Symptom Scale (PANSS) scores. Risperidone - CGI scores reached significance at 18 months of the test and antiparkinsonian meds were used less frequently. Fewer side effects. Basal Metabolic Index was higher, but did not reach statistical significance. Side effects causing discontinuation-FGA - EPS (1) -Needed more anticholinergics. SGA- Lack of efficacy (2) Needed more sedatives to sleep.	Naturalistic setting of the study including non-random distribution, pre-selection of patients and non-uniform treatment conditions may affect the outcome. There was no washout period, high use of concurrent medications and possible inclusion of treatment resistant patients.

Aim	Design/sample/ setting/number	Outcome	Limitations
LEVEL VI			
Finkel et al. (2009)/ PUBMED			
To examine metabolic side effects of yearlong treatment with Clozapine, Risperi-done, Quetiapine or Olanzapine in comparison to treatment with Haloperidol or Perphenazine among elderly individuals with SZ.	A retrospective chart review/ clinical records of psychiatric inpatients with chronic SZ, (Mean age:FGA-74.5yrs.SGA-73.8.yrs.) /Duration of 12 months/ in Israel /N=228	Elderly patients may be less susceptible to the MetS side effects associated with SGA agents than younger patient's populations.	Broad exclusion criteria limited generalization of results. Combinations of drug classes were not screened. Questionable too old for study sample at 74 yrs. old. Bias results.

Aim	Design/sample/ setting/number	Outcome	Limitations
LEVEL VII			
Alexopoulos, Streim, Carpenter, & Docherty (2004)/ OVID			
To examine an expert opinion survey on antipsychotic use in older patients with psychiatric disorders (SZ, delirium, dementia, psychosis mood disorder)	Literature review and expert opinion with guidelines for recommendations/survey sent to geriatric psychiatrists, geriatric internists/47 question survey with 1411 options / N=48.	Consensus reached in 78% with 92% completion of survey. SZ-recommendations: Preferred Risperidone- 1.25-3.5mg/day or Quetiapine-100 to 300mg/day or Olanzapine -7.5 to 15mg/day or Aripiprazole -15 to 30 mg. /day. If the patient with SZ has responded well to treatment, the experts recommend reducing to the lowest effective dose and continuing treatment indefinitely. For cognitive impairment- preferred Risperidone. For diabetes, prefer Quetiapine or Aripiprazole.	None.

Aim	Design/sample/ setting/number	Outcome	Limitations
LEVEL VII			
Kohen, Lester, & Lam (2010)/ OVID			
To explore Aripiprazole treatments for the elderly: efficacy and safety.	Expert opinion/ /Neuropsychiatric Disease and Treatment/ SZ or SZ Aff/ 62 to 85yrs. old/ N=10	7 of 10 responded, 4 with positive symptoms, 3 with positive and negative symptoms. Less EPS and pre-existing EPS decreased. With less antiparkinsonian meds. Less sedation, weight gain, anticholinergic effects, and no QT prolongation. Improved CGI scales at discharge.	None.

Aim	Design/sample/ setting/number	Outcome	Limitations
LEVEL VII			
Rado & Janicak (2012)/ OVID			
To examine the pharmacological and clinical profile of new SGA antipsychotic, Paliperidone, Iloperidone Asenapine, Lurasidone for older patients.	Case report /A review of current data of new SGA /Examines current trials involving these new drugs/ 65 yr. + patients with schizophrenia	In younger adults: Paliperidone - useful in hepatic failure. Major Side effects: Iloperidone - hypotension, QT prolongation, Asenapine– orthostatic hypotension. Somnolence, improve cognition, Lurasidone - hypotension, QT prolongation, cognitive improvement. Drugs in study are less likely to have metabolic or EKG changes.	Limited data available at this time on these new SGAs use in this age group to recommend in this population.

Level I evidence is from a systematic review or meta-analysis of all relevant randomized controlled trials (RCT) or evidence based clinical practice guidelines based on systematic reviews of RCTs. Level II is evidence obtained from at least one well-designed RCT. Level III is evidence from well-designed controlled trials without randomization, and Level IV is evidence from well designed case-controlled and cohort studies. Level V is evidence from systematic reviews of descriptive and qualitative studies; Level VI is evidence from a single descriptive and qualitative studies; Level VII is evidence from the opinions of authorities and/or reports of expert committees (Melnyk & Fineout-Overholt, 2005, p. 10). The articles were organized from highest to lowest level. The evidence table (see Table 4.1) displays one Level I studies, six level II studies, three level III studies, three level VI studies, and three level VII studies. No studies fell into the categories of Level IV or V evidence.

Analysis of Findings

Level I studies. The one Level I study was a systematic review of medications best suited for elderly patients with schizophrenia. Marriott, Neil, and Waddingham (2006) reviewed three randomized controlled trials comparing thioridazine with remoxipride, risperidone with olanzapine, and olanzapine with haloperidol. They concluded that there was no robust data to support the preferential selection of any of the antipsychotic medications examined. The Level I study clearly indicated that there is little scientific evidence to guide the selection of antipsychotics, with the exception of olanzapine and risperidone.

Level II studies. Expanding on Marriott et al.'s (2006) systematic review, Suzuki et al. (2011) reviewed 23 studies, including eight RCTs, in an effort to synthesize evidence related to management of late-life schizophrenia using antipsychotic medications. They noted that over half of the studies were limited by small sample sizes, and there is little robust data available to support any medications with the exception of olanzapine and risperidone (which was supported for use in non-treatment resistant late-life schizophrenia). Similarly, Essali and Ali (2013) identified 88 studies pertaining to use of antipsychotics for elderly patients with late-onset schizophrenia. Only one RCT, comparing the effects of risperidone and olanzapine, met inclusion criteria. The authors concluded that there is no convincing evidence to support the use of any specific antipsychotic drug with this population. Suzuki et al. (2011) remarked on the lack of evidence related to treatment resistance, antipsychotic polypharmacy, and medication augmentation for older patients with schizophrenia.

More broadly, Maixner, Mellow, and Tandon (1999) conducted an extensive review of the existing literature concerning pharmacologic, clinical, and regulatory issues related to the use of antipsychotic medications in elderly patients. They concluded that second generation antipsychotics (SGA), in general, had a favorable side effect profile compared to first generation antipsychotics (FGA) because of the lower association with extrapyramidal symptoms (EPS), but noted the paucity of scientific data to document the efficacy and safety of antipsychotic medications for older adults, despite the frequency of their use. The authors reviewed literature dating from 1955 through 1999, which is a limitation in that more recent literature is not included.

Ritchie et al. (2006) examined the efficacy and safety of olanzapine and risperidone utilizing a sample size of 61 elderly patients with schizophrenia. Criteria for inclusion included having completed a previous crossover study in which patients switched from FGA to a SGA, and having experienced imperfect symptom control or troublesome side effects while prescribed the FGA. During the comparative six-month study, patients in the olanzapine and risperidone groups were assessed every six weeks. The following rating instruments were used for monitoring: the Brief Psychiatric Rating Scale; The Scale for the Assessment of Negative Symptoms; the Montgomery Asberg Depression Rating Scale; the Mini-Mental State Examination; the Abnormal Involuntary Movement Scale; the Barnes Akathisia Rating Scale; the Simpson Angus Scale; World Health Organization Quality of Life instrument-brief. The study was limited by the difficulty with recruitment, as many of the potential participants were already on risperidone or olanzapine, and clinicians were reluctant to change patients' current medications. This reduced the available participant pool to less than 80 patient subjects, decreasing the statistical power of the study. Additionally, cost concerns prevented the use of a double blind study design. Results indicated that both drugs were well tolerated and effective in reducing symptoms of schizophrenia with few side effects as compared to FGA. Participants on olanzapine scored higher on a quality of life measure than participants on risperidone. Patients switched to risperidone or olanzapine from FGA improvements cannot exclude that the change in class of drugs and a reduction in dose over time were the causative factors of improvement. The authors also noted a lack of high quality evidence regarding use of antipsychotic medication in elderly patients with schizophrenia.

Harvey, Napolitano, Mao, and Gharabawi (2003) also examined the effects of risperidone and olanzapine on cognition in a RCT involving 176 elderly patients with schizophrenia or schizoaffective disorder over an eight-week period. Participants on both drugs showed significant improvement in cognitive functioning at low doses. This study concluded with the recommendation of longer studies for future research.

Tzimos et al. (2008) conducted a six-week RCT that examined the safety and tolerability of oral paliperidone extended release (ER) in 114 elderly patients with schizophrenia. A screening phase consisting of up to a five-day washout period proceeded the six-week double blind phase. To ensure patient safety during this study, patients were hospitalized from the first day of the double blind phase for at least 14 days for monitoring. The eligible patients were then randomized 2:1 to receive a flexibly dosed paliperidone ER or placebo once daily. Starting dose was 6mg a day. Doses adjustments were increased weekly by 3mg increments, but decreased dosing could be made at any time. Safeties of adverse events were measured using The Medical Dictionary for Regulatory Activities Terminology Version 8.1, IFMPA, and Geneva, Switzerland. Movement disorders rating scales, Simpson Angus Scale, Barnes Akathisia Rating Scale and Abnormal Involuntary Movement Scale were used throughout the double blind and open label phases of the study. The efficacy of paliperidone was measured with Positive and Negative Symptom Scale, Clinical Global Impressions Scale Severity Score. Personal and Social Performance Scale, and Schizophrenia Quality of Life Scale were used in examining the efficacy of paliperidone on the patients' perception of function, mood, and life. Clinical laboratory collection to monitor metabolic data and body parameters included routine tests, plus serum prolactin, C-

peptide and insulin, vital signs, body measurement, body weight, and 12-lead EKG. Of the 38 patients in the original placebo group, 26 (68%) completed the six-week double blind phase trial, and 64 of 76 (84%) of the paliperidone patients completed the study. The study further offered an optional 24-week open-label extension in which 88 patients continued. Paliperidone ER treatment was found to be well tolerated and may improve symptom severity in elderly patients with schizophrenia. Prolactin levels were elevated in one-half of patients. No adverse events were reported of any cardiovascular or QT prolongation. Two patients with glucose-related issues and three patients with significant weight increase were reported as experiencing adverse events. The authors further noted the scarcity of data for treatment of schizophrenia in the elderly population, commenting that only a handful of published studies have assessed tolerability of an SGA longer than three months in duration. At least two design flaws must be considered in interpreting and generalizing the results of this study. Due to small sample size, the study may not have had enough power to determine significant group differences, and the short time frame (six weeks) may also not be enough time for differences to manifest themselves.

In summary, Level II criteria provided five FGA and six SGA for examination within six studies. Level II studies favored SGA for the elderly population for positive and negative symptom management as well as positive effects on cognitive, and quality of life outcomes. Compared to the safety profile of FGA, these medications were less likely to be associated with the occurrence of EPS. Risperidone and olanzapine were the most frequently examined medications, which could be due to their longevity on the market. Prolactin level elevation was observed in patients medicated with paliperidone.

A lack of high quality studies in the elderly patient population that meet level II criteria especially any of long duration was notable.

Level III studies. Three Level III studies were identified. Each well-designed, controlled trial examined a different SGA in elderly patients with a psychotic disorder. Ciudad, Montes, Olivares, and Gomez (2004) compared the safety and tolerability of olanzapine to other antipsychotics with 135 elderly outpatients over 60 years of age. Participants were non-randomly assigned to two groups. One hundred and five patients were assigned to the olanzapine group and 30 to the comparison group. Half of those in the control group received risperidone, and the remaining fifteen received medication defined as high potency or low potency FGA. Assessment times included baseline, three month, and six-month assessments, as well as spontaneous assessments as deemed necessary by the provider during the treatment. Assessments included screening for EPS using the Udvalg for Kliniske Undersøgelser side effect rating scale, Clinical Global Impressions –Severity and Global Assessment of Function scales to assess patients clinical status and effectiveness of medications. The Awad scale assessed the patients' attitude regarding medications. Quality of life was measured using the EuroQol that assess health state in five dimensions: mobility, personal care, daily activities, pain/discomfort and anxiety. No significant group differences were found which could be related to the small size of the control group. Participants in the olanzapine group had lower akathisia, tremor, hypertonia, and higher incidence in insomnia, malaise, diarrhea as compared to the control group. However, 10% had somnolence and weight gain. Additionally, there was a lower use of anticholinergic drugs in patients taking olanzapine. Olanzapine was effective in reducing the severity of symptoms and increasing global

function at the end of the six-month follow-up as compared to treatment with other antipsychotic medications, as reflected by an increase in the Global Assessment of Function scores and a decrease in the Clinical Global Impression-Severity scale (Ciudad, Montes, Olivares, & Gomez, 2007).

Davidson et al. (2000) conducted a yearlong study of risperidone enrolling 180 elderly patients with schizophrenia or schizoaffective disorder. The trial focused on the effects of long term use of risperidone in the older population as measured by changes in the Positive and Negative Symptom Scale (PANSS), EPS assessment including the Extrapyramidal Symptom Rating Scale, and Clinical Global Scales, which were assessed at one, two, three, six, nine, and 12 months during the study. A historical comparison group was utilized to improve the validity of the interpretation of the results. This comparison group with similar demographics and diagnoses of chronic schizophrenia was treated with FGA for one year (Davidson et al., 1995). Greater than 50% of the patients had both positive and negative symptom improvement at the endpoint. Risperidone was well tolerated with lower incidence of tardive dyskinesia compared to participants in the 1995 study group. A decrease in the severity of the pre-existing EPS was observed with a concomitant decrease in the use of anticholinergic medications. Cognitive improvements were also noted, but could not be clearly attributed to treatment with risperidone. Other factors affecting cognitive outcomes may have been a reduction in use of anticholinergic medications, or the discontinuation of the previous antipsychotic medication that may have caused the decline of cognition.

Jaskiw, Thryum, Fuller, Arvanitis, and Yeh (2004) assessed in a 27-day study the tolerability of quetiapine in 12 elderly patients: eight with schizophrenia, two with

schizoaffective disorder, and two with bipolar disorder. A more rapid titration of the medication was chosen for this study to allow a longer pharmacokinetic testing time at the desired dose range. This resulted in higher incident of adverse reactions including postural hypotension and dizziness with a 30-50% reduction in the drug's clearance from the body. Prolactin was unaffected. The authors found quetiapine had favorable efficacy and adverse effects profile in the 65 years and older population, with doses up to 250mg given three times a day. This study was limited by its small sample size, uneven distribution of male (nine total) and female (three total) participants, and a rapid titration of medication. Future recommendation for replicating this study would suggest a slower titration as a means of minimizing the negative side effects found in this study. Considering the reduction of overall hepatic and renal clearance in the elderly population that occurs with aging, a slower titration would be prudent.

In summary, Level III articles noted each of the three drugs — risperidone, olanzapine and quetiapine — were effective in reducing symptoms of psychosis in elderly patients with schizophrenia or other chronic psychotic disorder. Side effects included somnolence and weight gain with olanzapine, and postural hypotension or dizziness with quetiapine. Researchers recommended that medications be initiated at low doses and titrated slowly in order to minimize side effects, keeping in mind potential interactions and effects of concurrent medications. Improvement of psychosis may also improve cognitive and global functioning. Caution was offered to monitor anticholinergic medication suggesting less use for a more positive cognitive outcome.

Level VI studies. Three single descriptive or qualitative studies met criteria for Level VI. Barak, Shamir and Weizman (2002) questioned whether switching from a

FGA to risperidone would be beneficial. Fifty-one elderly subjects, age 65 to 88 years, were chosen for this study. Twenty-five patients were treated with a FGA, including haloperidol, perphernazine, chlorpromazine and four other FGA not FDA approved for use in the US, and 25 patients were switched to risperidone with both groups monitored for 18 months. Both classes of medications improved Positive and Negative Symptom Scale scores. The results indicated switching was effective and well tolerated. Patients switched to risperidone experienced improved Cognitive Global Impression Scale scores and a reduction in side effects from the FGA including hypersalivation, sedation, and apathy. The authors noted the Basal Metabolic Index was higher in the risperidone group, but the difference was not statistically significant with patients noted to return to near baseline at the testing's endpoint. The incidence of EPS was higher in the FGA group, which resulted in a greater need for anticholinergic medications. The risperidone group used more concomitant sleep aids. This was thought to be due to the less sedating quality of the risperidone as compared to the FGA. Limitations that may have affected outcomes included a naturalistic setting, pre-selection of patients, non-uniform treatment conditions, non-random assignment, no medication wash out period, high use of concurrent medications, and inclusion of treatment resistant patients (Barak, Shamir, & Weizman, 2002).

Barak and Aizenberg (2003) studied 21 elderly patients with schizophrenia or schizoaffective disorder to assess the effects of first time exposure of olanzapine on lipid abnormalities. The mean duration of olanzapine treatment was 289 days (SD± 139 days. At the end of this prospective study, no significant changes from baseline lipid levels or weight gain were found. Finkel et al. (2009), in a one-year retrospective study examining

the metabolic side effects of clozapine, risperidone, quetiapine, olanzapine compared to perphernazine and haloperidol in 228 elderly patients with schizophrenia, similarly found no significant differences with respect to triglycerides or cholesterol levels. Additionally, in examining the metabolic effects of FGA and SGA, the elderly patients' Basal Metabolic Index, body weight, blood glucose, B12 and folic acid levels remained unaffected. The SGA carry a class warning for weight gain, lipid abnormalities, and are associated with inducing the metabolic syndrome. Elderly patients may be less susceptible to the metabolic side effects associated with antipsychotic medications than younger populations. The elderly population as a group has a higher rate of chronic conditions including cardiovascular disease and diabetes. Finkel et al. (2009) suggested the mean age of this study, 74 years, was too old to represent the elderly population with schizophrenia whose average lifespan is typically 65 years. Both studies suggested further trials with larger, younger samples.

In summary, Level VI evidence suggested the elderly population might be less susceptible to the metabolic challenges of the SGA. These would include cholesterol, triglycerides and weight gain. Both FGA and SGA are effective in reducing Positive and Negative Symptoms Scale scores. More EPS occurs with use of the FGA requiring more anticholinergic medications. Studies that are more extensive are needed to explore the metabolic and lipid changes in the elderly patients prescribed antipsychotic medication.

Level VII studies. Evidence from the reports of expert committees and/or opinion of authorities comprises Level VII, the last level of the rating system. Three reports qualified for Level VII. Alexopoulos, Streim, Carpenter, and Docherty (2004) developed a 47-question survey based on a literature review to assess expert opinion on

antipsychotic use in elderly patients with schizophrenia, delirium, dementia, delusional disorder, and psychotic mood disorder. Fifty-two American experts in geriatric psychiatry and medicine responded to the survey. The responses were used to write guidelines for use of antipsychotics in older patients. Experts treating elderly patients with a diagnosis of schizophrenia preferred risperidone 1.23-3.5mg/day, quetiapine 100mg-300mg/day, or aripiprazole 15mg -30mg/day. If the patient response was successful, the expert panel recommended reducing the medication to the lowest effective dose and continuing indefinitely. The experts preferred risperidone for use in their elderly patients with a cognitive impairment when diagnosed with schizophrenia and quetiapine or aripiprazole for prescribing for patients with co-occurring diabetes.

Kohen, Lester, and Lam (2010) published a clinical article focusing on the safety and efficacy of aripiprazole to treat schizophrenia in patients over 60 years of age. The authors reviewed clinical trials with aripiprazole and elderly patients with schizophrenia, as well as clinical studies involving psychosis in Alzheimer's and Parkinson's disease, agitation associated with schizophrenia and bipolar disorder and the use of aripiprazole in the older population group. Few studies were found completed to date on this topic and population. Only one study within the article addressed the target population. Ten elderly patients, age 62 to 85 years of age, with schizophrenia or schizoaffective disorder were treated with aripiprazole. Seven responded to the treatment noting improved Positive and Negative Symptom Scale and Clinical Global Impression score, less EPS from prior medications, and less anticholinergic medications required to treat side effects. Less weight gain and sedation were also observed. Improvements were based on prior use of FGA and other SGA medications and clinical observations of patients' behavior

and Clinical Global Impression Scale assigned retrospectively. Based on prior reports, clinical reviews and clinical practice experience, the effective dose range utilized for safety and tolerability was 2 - 15mg/day for the elderly population. The authors further suggested 20 minutes of exercise a day to reduce metabolic syndrome or providing healthy food choices if patients were unable to exercise.

Rado and Janicak (2012) examined case reports describing the use of the new SGAs for treatment of schizophrenia in elderly patients. The authors' goal was to examine these SGA because of the adverse effects profile of the FGA and the potential alternatives offered by the new SGA in the elderly population. The case reports were obtained from an extensive internet search of MedlinePlus, references from relevant articles and abstracts from professional meetings. This report offered no new evidence beyond that already reported concerning the use of paliperidone (Tzimos et al., 2008). The author found no studies examining the use of luradone or iloperidone in elderly patients and reported one study involving asenapine (Dubovsky, Frobose, Phiri, Greef & Panagides, 2012). Prior research involving non-elderly populations has indicated that patients treated with iloperidone, paliperidone, asenapine, and lurasidone are less likely to have metabolic alterations than older SGA. Prolonged QT intervals and orthostatic hypotension are side effects observed with iloperidone, asenapine and paliperidone. Paliperidone, like risperidone, increased prolactin levels. The authors suggested paliperidone for patients with hepatic impairment because of the drugs predominant renal excretion. Asenapine and lurasidone were noted to improve cognition as measured by improved Clinical Global Impression scores. These drugs need to be adjusted for renal

and/or hepatic impairments. All of the new SGA have minimal research in the elderly population. Further studies with adequately designed and powered studies are needed.

In summary, The Level VII evidence added the dimension of the newest atypical antipsychotic medications on the market. Although not supported by scientific evidence, clinical experts noted that these newer medications may have fewer metabolic issues, and relatively low risk of prolactin elevations and EPS, while being effective at reducing psychotic symptoms. Lurasidone's low risk for hypotension and QT prolongation with the potential of cognitive improvement may make it a useful agent in older people. Cautions regarding risks of cardiovascular side effects were drug specific. Further research will be needed to validate the Level VII evidence.

Recommendations for Practice

Relatively few robust studies have been conducted involving antipsychotic treatment in elderly patients with schizophrenia. Unfortunately, there has been little accumulation of new knowledge since 1999, despite the introduction of several SGA with unique side effect and risk profiles. The limited research has left providers with little guidance as to how to proceed with psychopharmacologic treatment in this population. Reduced incidences of EPS and TD in SGAs have supported SGA use over FGA in all age groups. There is some very preliminary evidence to suggest that SGAs are effective for treating symptoms of schizophrenia in older patients and may be better tolerated than in younger patients, with a lower incidence of metabolic issues. Researchers and clinical experts recommend relying on the clinicians' assessment and clinical reasoning skills until more evidence becomes available.

General Clinical Practice Recommendations

In general, providers are advised to identify the target symptoms to be treated, weigh the risks and benefits of all potentially appropriate medications, and use best clinical judgment to choose a medication based on the individual patient's needs and psychological/physiological status. Adherence is critical to successful treatment and positive outcomes, therefore patients and families should be included in the decision-making process to simplify the protocol and maximize compliance.

The following recommendations are drawn from individual studies and expert opinion and may only be used as data in the clinical reasoning process.

Recommendation 1. Perform a thorough diagnostic evaluation to include review of systems, physical assessment, and laboratory analysis of cardiac, hepatic, and renal functions prior to prescribing medications (Maixner, Mellow, & Tandon, 1999).

Recommendation 2. Second-generation antipsychotics are preferred over FGA when choosing the best antipsychotic drug for the elderly patient (Alexopolos, Streim, Carpenter, & Docherty, 2004; Finkel et al., 2009).

Specific medication recommendations based on safety and efficacy include:

Risperidone is identified as the number one choice (based on safety and efficacy) (Alexopoulos et al., 2004; Barak, Shamir & Weizmann, 2002; Davidson et al., 2000; Finkel et al., 2009; Harvey, Napolitano, Mao, & Gharabawi, 2003; Maixnew et al., 1999; Marriott, Neil, & Waddingham, 2006; Ritchie, et al., 2006; Suzuki et al., 2011)

Olanzapine is the second choice (based on safety and efficacy) (Alexopolos et al., 2004; Barak & Aizenberg, 2003; Ciudad et al., 2004; Harvey et al., 2003; Maixnew et al., 1999; Ritchie et al., 2006; Suzuki et al., 2011).

Quetiapine is the third choice (based on safety and efficacy) (Alexopolos et al. 2004; Jaskiw, Thyrum, Fuller, Arvamitis and Yeh, 2004).

Aripiprazole is the fourth choice (based on safety and efficacy) (Alexopolos et al., 2004; Kohen, Lester & Lam, 2010).

Recommendation 3. The dosing range suggestion is to start low (25% of young adult dose) and to titrate slowly with careful monitoring of side effects (Maixner et al., 1999).

Recommendation 4. Avoid the use of anticholinergic medications when possible because of negative effects to cognition (Ciudad et al., 2004; Kohen et al., 2010; Suzuki et al., 2010).

Recommendation 5. The recommended frequency of follow-up monitoring to evaluate antipsychotic treatment protocol is based on patient status.

- Upon initiation of antipsychotic: Every one to two weeks until symptomatically stable for one month on the same dose of antipsychotic medication.
- Early in treatment monitor tolerability and therapeutic benefit every two to three months until the patient has been stable for six months on the same medication and dose.
- Routine follow-up every three to six months if patient is stable and there have been no medication adjustments.
- Monitor 10 days to four weeks following an antipsychotic dose change (Alexopoulos et al., 2004).

Recommendation 6. Allow two weeks to assess whether symptoms are adequately controlled before changing the antipsychotic dose or type of antipsychotic medication, as long as the patient is tolerating the medication (Alexopoulos et al., 2004).

Recommendation 7. Continue antipsychotic treatment indefinitely at lowest effective dose necessary to control symptoms of schizophrenia (Alexopoulos et al., 2004).

The findings of this project will be reviewed and discussed in Chapter Five. Clinical implications of the evidence and recommendations for future research will also be addressed.

Chapter 5 Outcome and Implications

Patients dealing with mental illness encounter many lifetime hurdles within the mental health system. One challenge is to find the appropriate medication to help manage symptoms. Advances in psychopharmacology include the frequent introduction of new drugs to treat schizophrenia. Unfortunately, the older population is not included in any significant trials of these new drugs. This follows the historical pattern of minimal representation of older patients with schizophrenia in high quality drug studies of second generation antipsychotic (SGA) medication. Despite an exhaustive literature search, only 16 articles were found that met inclusion criteria for this project. The majority of these studies examined the older drugs, especially the first few SGA medications on the market in the United States, in comparison with each other or with first generation antipsychotic (FGA) medications. The newer drugs were mentioned as promising, but no viable studies to date have been conducted. These studies provided little new insight into best practice for the use of antipsychotics to treat older adults with schizophrenia beyond the already known prescribing practices for this population.

There are many possible reasons for this absence of data. Recruitment of a sufficient number of elderly subjects to participate and follow up may be difficult. The researchers may want to avoid the confounding effects of other medical conditions and medications. Reluctance to involve this more delicate population may also be a concern.

Unfortunately, RCTs are not the ideal nor preferred method to study medication actions for this more sensitive population. The pharmacokinetic and pharmacodynamic response to medications in the elderly population is unique and best monitored in a more naturalistic setting over longer time spans. These conditions are not easily managed within the pharmaceutical six or eight week trial protocols preferred in most drug studies. There is limited access to this population as well, as community dwelling elderly people with schizophrenia are dependent on community resources for transportation and coordination of care, which results in missed medications, lab work, and appointments. During the search process, more studies were available examining the use of antipsychotic medications in the elderly with dementia. This trend may be attributed to better accessibility of the elderly population with dementia for participation and monitoring in research, as they are more likely to reside in assisted living facilities or nursing homes. There is also a larger pool of patients in the dementia population versus the elderly population with schizophrenia from which to draw the study group.

To provide context for the evaluation of evidence, this project examined the complex intersection of normal aging processes, physiological changes associated with schizophrenia, and the action of antipsychotic medications to provide an overview of the factors providers must consider in order to safely prescribe antipsychotic medications for older adults with schizophrenia. The expected cognitive and physiological changes associated with aging combined with comorbid conditions and polypharmacy can further complicate the symptom management by affecting the tolerance and efficacy of antipsychotics in aging patients. Unfortunately, for the reasons noted above, although

the older population with schizophrenia is increasing, it is likely that high-level evidence to guide prescriptive practice will continue to be lacking.

Nevertheless, awareness of the considerations outlined in the project can help providers evaluate the potential for newly marketed drugs to be incorporated safely into patients' treatment regimens. Further, the information presented emphasizes the importance of ongoing monitoring to determine the need for medication adjustment as individuals age and their care becomes more complex. Proactively identifying the risks to health in this fragile patient population will help prevent exacerbation of comorbid health problems or the occurrence of complications requiring more medications and increasing the potential for hospitalizations. Better overall health will allow older patients with schizophrenia to live independently in the community for a longer period of time and attain a higher quality of life.

Healthcare System and Community Resources

Providers' knowledge and skills become even more critical because of the barriers within the healthcare system to providing efficient care to this older population with chronic, severe mental illness. From 2005 to 2010, 14% of psychiatric hospital beds nationwide were closed, with four states closing an estimated 50% of their inpatient psychiatric beds and another 13 states closing 25% of their total inpatient psychiatric beds ("New Treatment," n.d.). More and more, patients must depend on community mental health providers for their psychiatric care. Due to the increasing life expectancy and the aging of the baby boomer generation, there will be a greater number of older patients with mental health disorders, including schizophrenia. Once an elderly patient is established within the system, complicated insurance protocols, prior authorizations, and

regulatory restrictions on prescribing can make offering a medication for symptom management for elderly patients a daunting task. The Affordable Care Act (ACA) mandates parity for treatment of mental health and physical illness. Unfortunately, this comes at a time of decreased mental health funding and fewer medical students choosing to enter psychiatry as a career, resulting in a lack of qualified mental health professionals in a time of peak need (Thomas, Ellis, Konrad, Holzer, & Morrissey, 2009). Psychiatric mental health nurse practitioners (PMH-NP), as the only other mental health provider with prescriptive authority, have the opportunity to fill some of these gaps and make a powerful impact in the lives of older patients with schizophrenia for whom medication is an integral part of symptom management.

The system does try to optimize health for elderly patients with schizophrenia enabling them to follow through with acquiring necessary care. Medical expenses are an ongoing issue. Medicare is available to this population, as are the insurance benefits of Medicare A and B. Choice for Medicare D coverage for medication coverage is the choice of the individual, which leaves many patients questioning which plan to choose. Co-payments for the patients are widely variable. Medicaid is available in some limited financial circumstances for additional coverage to help defray the monetary burden of medical care. Some areas offer a base form of case management, but with funding cuts for mental health services, these are limited. Accessing care can also be problematic. Transportation services are offered in some areas to help individuals with special needs, whether physical or psychological, but the trend has been to begin charging a fee for each way or per mile, which is difficult for those patients on limited income to afford.

Community mental health facilities are available as well but typically in larger cities and communities.

Regrettably, the weaknesses within the system for elderly patients with schizophrenia outweigh the strengths in meeting their needs for services and care. Limited access to mental health care remains a problem due to a shortage of qualified providers and overcrowding of the existing mental health clinics. Funding cutbacks in mental health services have reduced case management to almost non-existent except for the most severely impaired patients. The logistics for the patient to maneuver the mental health system, obtain lab work as requested, and fill out forms for insurance coverage as requested become overwhelming. This population is more likely to be unmarried and without children, requiring more independent functioning within the community. With less support to draw upon in stressful times, the elderly population with schizophrenia is more likely to be in need of an inpatient respite. However, with fewer hospital beds available and poor individual support systems, the options are limited.

Limitations of the Project

This project was limited by the paucity of available quality research that included older adults with schizophrenia. Ultimately, it was disheartening to learn that there is not a lot of high-level research data available on the 65-year and older population with schizophrenia. The majority of information available was anecdotal, not empirical. Most empirical studies were descriptive and had limitations that resulted in few findings to guide practice. Recommendations were broad and focused primarily on use of clinical judgment. In order for clinical judgment to be useful, clinicians must have a clear understanding of the type of medications available and associated actions, risks, and side

effects. Further, the clinician needs a strong awareness of each patient's baseline status and health factors that might affect his or her response to antipsychotic therapy. Almost every publication reviewed since 1999 concluded by calling for future research utilizing the older population in high quality studies. This, however, did not occur.

Research Implications

Out of the frustrations of finding so few reliable studies investigating the older population with schizophrenia arises opportunity. An intriguing possibility is that the older population might be less susceptible to metabolic side effects than younger patients with schizophrenia. Two studies indicated a lack of dyslipidemia in elderly patients when similar studies indicated an increase in dyslipidemia in younger patients with schizophrenia (Barak & Aizenberg, 2013; Finkel et al., 2009). Additional quality research concerning safety profiles is needed in light of the high-risk potential of the metabolic syndrome and cardiovascular disease currently associated with the elderly population with schizophrenia.

Second, research noted elevated prolactin levels with FGA, as well as risperidone and paliperidone (Tzimos et al., 2008; Table 2.2; Table 2.3). Younger patients manifest breast tenderness, gynecomastia, and libido issues signaling elevated prolactin. However, in elderly patients these cues are muted or nonexistent. With aging, a lower libido may be considered normal and not questioned. The standard protocol for monitoring prolactin is to assess "for cause" when symptoms are present. Without symptoms, these warning signs would go unnoticed when levels are elevated. Hyperprolactinemia may initiate calcium loss. With the higher prevalence of osteoporosis and hypocalcemia in the older

population, a better understanding of the impact of elevated prolactin in older age is important from both safety and good health standpoints.

Third, two studies examining sleep apnea and aging (Winkelman, 2001) and severe obstructive sleep apnea and psychiatric patients (Martinez-Garcia et al., 2012) indicated a high probability of increased cardiovascular death in the target patient population. Although there are no studies that measure the relationship of sleep apnea to antipsychotic medications, it is a potential concern because adding psychotropic medication can impact the depth of sleep. Studies focusing on problem areas of obstructive sleep apnea, respiratory issues, pneumonia, and cardiovascular issues are critical as respiratory issues were a high-risk area identified in the correlation Table 2.3.

Fourth, the research most urgently needed would be pharmacology-based to explore safety, tolerability, and efficacy of the newest second-generation antipsychotics (SGA) such as iloperidone, lurasidone, asenapine, and paliperidone. The newest SGA appear to have a promising profile, especially with the low affinity antagonism for histaminic and muscarinic receptors reducing side effects to which elderly individuals are particularly sensitive, including anticholinergic effects (Rado & Janicak, 2012).

Finally, more research funding for investigation of promising new antipsychotic medications would be potentially beneficial. Some medications are not yet available in the USA because they have not met criteria for FDA approval. Other medications may have a broader research base because of the willingness of pharmaceutical companies to fund the studies necessary to gain approval for specific medications. More independent research about the multiple types of medications available is needed to help prescribers

be as knowledgeable about the choices as possible to better guide decision-making for each individual older patient with schizophrenia.

Practice Implications

With the increased knowledge base required for practice decisions, PMH-NPs have a major role to play in treating patients with chronic severe mental illnesses that persist into older age. Keeping abreast of new treatment, medications, and treatment protocols with continuing education will continue to be a part of best practice expectations. Maintaining records of patients' lab work, current medications, and other medical conditions at each visit is a cornerstone to quality care. Checking for TD and EPS as well as side effects of the antipsychotic medications at each visit must be included. Coordination with other disciplines that provide case management or providing a holistic approach is ideal, but with funding often a problem for these services, PMH-NPs can continue to advocate for patients as part of the best practice approach regardless of the circumstances. Becoming aware of the lifestyle choices of each patient and guiding them towards the healthiest options will be invaluable. Careful monitoring for drug-to-drug interactions or symptoms of alcohol or substance abuse to minimize harm is critical. Teaching and giving feedback for concerns of the patient and challenging individuals to take their medication every day are important goals in helping patients remain out of the hospital. Celebrating goals and achievements with the patient, as well as mourning losses and failures, are ways of acknowledging the patient as a person. All important parts of treating the whole patient, gaining trust, making a bond, and treating the person must be included in care. The patients' families should be incorporated as partners in care and decision-making if possible and permitted by the patient. With the

skills, training, and caring of the PMH-NP, the older patient with severe mental health issues can find a competent professional for one-to-one treatment.

Policy Implications

The examination of literature for this project brought to light several policy implications related to mental health care in the US. Foremost is the need for funding to improve access to care. The Affordable Care Act (ACA) opened the door to many people by offering healthcare to those who were previously uninsured. While still in the early stages of implementation, the process was intended to be affordable and easier to navigate with a greater transparency of services offered. Although Medicare covers elderly adults with schizophrenia, changes to required insurance coverage may affect access to mental health care in general. Several benefits afforded by the ACA have significant implications for patients with chronic severe mental illnesses including coverage for mental health, substance abuse, and pre-existing conditions. The ACA requires that these benefits not be subject to greater restrictions or limitations than the plan's medical/surgical benefits ("Do marketplace," n.d.). Closing the Medicare D "donut hole" for medications have left some with even higher copayments. While problems remain, PMH-NPs can use their influence to support policies that increase access to affordable mental health care as well as to increase state and federal appropriations for community mental health to permit case management, more clinics, and more services for those who desperately need this assistance.

Second, the majority of funding for medication research comes from pharmaceutical companies. Many of the studies are completed in fulfillment of FDA requirements of trials required for protocols, with the goal of final drug approval for use

in the US. These studies are usually 6 to 8 weeks, and rarely include the elderly population. The newer drugs are also not included in the comparison studies. Financial limitations drive the study designs, as the longer, RCT double blind placebo-controlled studies are more costly. More funding must be allocated to independent researchers to encourage more, less biased studies to explore the full range of drugs available to the mental health population.

Finally, in order to best meet the expanding need for mental health care in the US, PMH-NPs should be able to work within their full scope of practice. Removal of restrictions on practice in all states would provide a bounty of highly skilled professionals to care for the burgeoning older population, as well as the newly insured, to provide competent care for all. Active participation in professional organizations at state and national levels, and taking leadership roles within the community and healthcare organizations, can help remove barriers to practice and raise awareness of the ways in which PMH-NPs can impact the healthcare system.

Conclusion

The key points of this project will help psychiatric practitioners be successful in understanding the challenges and limitations of antipsychotic prescribing for older people with schizophrenia, and offers recommendations for medication management of patients who are living in the community. The goal of treatment with antipsychotic medication is to achieve remission with fewer positive symptoms, reduced comorbid involvement, better self-esteem, and the ability to remain independent. Dosage should be adjusted with the individual patient's profile, preference, response, and history in mind. By careful monitoring of the metabolic indices, and maintaining a dialogue with the patient's

primary care provider or an independent practitioner, an active approach will minimize side effect potentials of comorbid complications.

Primarily, practitioners must understand that regarding antipsychotic medications, there is no right answer for what and how much to prescribe. While the recommendations provided are a starting point, the best evidence to date involves utilization of the provider's best judgment on a case-by-case basis. Understanding the patient as a person with unique preferences, personality, capabilities, and qualities is a prime component in this process, as important as expertise in medical treatment and psychopharmacology. When reaching a clinical decision, practitioners can use guidelines but must generate a list of options based on best-practice choices distinct to each individual. As new medication becomes available, the need for continuing education and reassessment of knowledge and assumptions remains an ongoing process for all mental health providers.

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Appendix A

Physiological Changes of Normal Aging by Body System

Cardiovascular
• A thickening of the interior lining of the heart muscle due to hypertrophy of muscle fibers and narrowing of blood vessels causing arteriosclerotic streaks and fibrous tissue to develop
• Loss of contractile efficiency due to muscle fibers replacement with collagen or connective tissue calcium and decreased levels of circulating catecholamines
• Decreased maximum heart rate and increased stroke volume with stress
• Peripheral vascular resistance increased 1% per year after age 60
• Cardiac output decreased one % a year
• Failed valves in legs and varicose veins result in venous stasis
• Higher blood pressure with longer time needed to return to baseline due to decreased diameter of arteries and diminished stretch ability
• Decreased blood flow to the kidneys by 50% and 15-20% less to the brain
Hematologic
• Less sensitive baroreceptors
• Decreased serum albumin concentration
• Cell density of bone marrow decreased and cell proliferation diminished
Respiratory
• Loss of elasticity due to increased cross-linkage in collagen and elastin fibers around alveolar sacs, causing decreased vital capacity
• Diminished chest wall compliance due to deformities of thorax, postural changes, decreased strength of muscular skeletal system to assist in respiration, degeneration of intervertebral disks, and increased anterior posterior diameter of the chest
• Alveolar surface area collapse sooner on expiration, decreased by 20%, which reduces O2 uptake by as much as 60% at age 85

• Lung bases are less ventilated resulting in ineffective redistribution of blood to compensate
• Oxygen levels fall and become worse when lying down resulting in nocturnal hypoxemia (may cause confusion)
• Decreased number of cilia with an increase of mucous producing cells
• Less efficient in monitoring and controlling breathing
• Less sensitive to hypoxia
• History of smoking increased risks due to an increase in obstructive components of lung function and decreased compliance of lung tissue through deposits of foreign material
Gastrointestinal: Stomach
• Shrinking and inflammation of the inner lining of the stomach from prolonged infection common in older adults
• Insufficient production of stomach acid
• Long-term use of pain medications causes stomach lining damage or H. pylori
• Reduced colonic muscle tone and decreased colonic motor function
• Degeneration of smooth muscle lining the lower two thirds of the esophagus resulting in delay in esophageal emptying, dilation of the esophagus, and increased nonproductive contractions
• Oral issues include: loss of teeth, tongue papilla, reduced salivary ptyalin and reduced or irregular esophageal peristalsis contributing to poor intake, weight loss, and delayed emptying
Gastrointestinal: Liver
• Decreased ability of the liver to store Vitamin B12
• Reduced size and blood flow, with restricted oxygen diffusion
• Decreased ability to regenerate damaged liver cells
Gastrointestinal: Intestines
• Altered ability to absorb calcium, iron and lactose
• Weakness of intestinal wall and impaired intestinal muscle function
• Reduced peristalsis in the large intestine
Urinary: Renal
• Kidney mass is decreased by 25-30% with a decrease by 30-40% in glomeruli by age 80, with an additional 30% sclerotic or nonfunctional
• Decrease in creatine clearance
• Total body water and lean body mass decrease
• Difficulty maintaining acid/base balance
• Hormones that regulate dehydration/hydration and the ability to conserve sodium decline
• Decreased bladder capacity and residual urine

• Nocturnal frequency of micturition and urinary incontinence due to: loss of muscle tone that result in relaxation of perineal muscles (female); prostatic hypertrophy, bladder diverticula and sphincter relaxation (male) may increase UTI in both male and female
• In the elderly: low fluid intake, fluid loss from diarrhea, vomiting, shock due to hemorrhage, acute or chronic cardiac failure, septicemia, toxicity from antibiotics or injudicious use of diuretics can lead to renal ischemia and acute renal failure
Endocrine
• Decreased insulin secretion and increased insulin resistance with decrease in insulin receptor sites in the cell walls (Normal FBS levels rise 6-14mg per deciliter every 10 yrs.)
• Decrease in aldosterone (30%) by age 70-80
• Cortisol decreased by 25% effecting anti-inflammatory and anti-allergy effects
Neurological
• Decline in homeostatic mechanisms
• Intelligence remains unchanged
• Nerve impulses decrease conduction rate by 10% with decreasing neurons and degenerating myelin sheath causing blurred signal and altered threshold of organ response after a stress response
• Reduction in brain size by 20% with decrease in white matter by 11% between 70 to 90 yrs. old and decrease in the number of synapses
• Decrease in dopamine content and receptor abundance
• Brain loses 100 gm. resulting in reduced oxygen consumption, less intracellular energy produced, and glucose and cerebral blood flow reduced
• Depression is associated with declining levels of norepinephrine
• Declining dexterity and agility, difficulties with association, recall, and retrieval, with decreased memory and cognitive abilities
•Decline in visual spatial abilities, both in perception and reproduction
•Problem-solving skills decline after 70+ yrs.
• Slowed processing reaction time
Immune
• Decreased production of thymic hormones
• Decreased levels of antibody response
• Diminished response to antigens
Musculoskeletal
• Loss of bone density: osteoblasts<osteoclasts
• Loss of muscle mass with decrease in amount and size of muscle fibers (23% by age 80)

• Peripheral motor neurons: decreased protein synthesis with thickening at the myoneural junction and decreased acetylcholine level causing a general decreased in movement, muscle stiffness, and slowness in initiation of movement
• Joint changes include: erosion of the cartilaginous surface, degenerative changes of soft tissue, calcification and ossification of ligaments, loss of cartilage elasticity, and development of fibroblasts
• Increase in body fat
Reproductive: Female
• Decrease by 95% of levels of circulating estrogen with menopause
• Follicle stimulating hormone (FSH) and luteinizing hormone (LH) increase
• Atrophic changes in uterus and vagina, thinning uterine lining, decreased elasticity and vaginal secretions with decreased libido and reduced or anorgasmic
Reproductive: Male
• Decreased sperm production, by age 85, a 35% reduction of testosterone and reduction in the size of the testes
• Increased irregular thickening with fibrous tissue causes enlarged prostate
• Decreasing testosterone levels may decrease libido, with a less intense orgasm to erectile dysfunction
Sensory: Vision
• Corneal flattening reduces light admitted into the eye by one third. Pupil size decreases by one third
• Transparency of the lens decreases with a yellowing occurs that alters colors (Blue become more green, reds and oranges become more vivid)
• Diminished sensitivity of the retina reduces spatial discrimination, white/black contrast, and flicker sensitivity. More time required to adapt from dark to light
• The lens becomes less elastic decreasing focus and reducing visual acuity
• Arcussenilis may develop and lenses may cloud as a result of soluble proteins forming cataracts
• Eyelids become thinner and wrinkled and skin folds from a loss of orbital fat leading to ptosis; inversion or eversions of the lids are common as the conjunctivae are thinner and more fragile
Sensory: Hearing
• Reduction in auditory acuity with 10dB sensitivity loss for each decade beginning at age 60, male>female
• Degeneration of the vestibular apparatus
• Stiffness and less sensitive middle ear and tympanic membrane

• Reduction in hearing acuity of one-third the older population related to cerumen, antibiotics, or diuretics
Sensory: Olfactory, Taste, and Touch
• Decrease in receptors beginning at age 50. By age 80, smell reduced 50%
• Atrophy of tongue and sensory receptors diminish taste
• Decrease in touch receptors and response to painful stimuli
Skin & Hair
• Thinning of the area between the dermis and epidermis by two %, decrease in elastin and collagen with a reduction in the size of skin cells and a decreased ability to retain moisture
• Thinning of the subcutaneous layer of fat under skin
• Decrease in melanin and number of hair follicles with loss of pigment and slower growth
• More facial hair with decreasing estrogen levels (female)
• Increased hair growth in nose, ears, and eyebrows (male)
• Less active sebaceous and sweat glands

Note. Adapted from *Pathophysiology: Adaptions and alterations in function* (3rd ed.) by G. McDaniel, pp. 156-173. Copyright 1992 by Courier Book Company.