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# META-ANALYSIS OF THE COST-EFFECTIVENESS OF CLOZAPINE

By

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## ABSTRACT

META-ANALYSIS OF THE COST-EFFECTIVENESS OF CLOZAPINE

By

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This meta-analysis demonstrates that clozapine is more cost-effective than conventional antipsychotics in terms of decreasing psychiatric inpatient hospital costs and utilization and decreasing total levels of psychopathology. When clozapine was compared to conventional antipsychotics, inpatient psychiatric hospital costs decreased by an average of $19,200 annually; when clozapine was examined using quasi-experimental single group designs, inpatient psychiatric hospital costs decreased by an average $17,865 annually. Regarding psychopathology, symptoms decreased by an average of 9 points when clozapine was compared to conventional antipsychotics and by an average of 12 points when clozapine was examined using quasi-experimental single group designs; symptoms were assessed using the Brief Psychiatric Rating Scale.

This thesis is dedicated to three people. It is first dedicated to my husband and best friend Robert Jean-Jacques. I thank you for always being in my corner....I love you and don't know where I would be without you!

This thesis is also dedicated to my parents, Errol and Eva Kelly. Where would the child be without the parent? Rob and I love you both and thank you for all of your unending support.

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# INTRODUCTION

While schizophrenia affects only approximately 1% of the US population, the cost of treating people with schizophrenia is greater than all of the other mental illnesses combined. Schizophrenia not only affects the person who has it, but also the person's loved ones and the society in which the person lives. People with schizophrenia have to live with the spectrum of symptoms that define schizophrenia such as hallucinations, cognitive impairments, social isolation, and stigma. The loved ones of people with schizophrenia, specifically family members, are most often affected emotionally and financially such as when they lose time at work as a result of caring for their ill family member. The society in which people with schizophrenia live is impacted via loss of a productive member and the cost of caring for the person in terms of using public funds to pay for direct costs associated with schizophrenia. The US spends approximately $32 billion annually providing treatment for people with schizophrenia.

Various modalities are available to treat people with schizophrenia. The two broad categories of treatments are psychosocial and psychopharmacologic. Psychosocial treatments, while helpful, have not had the impact that psychopharmacologic interventions have had in terms of symptom reduction. Psychiatric drugs used in the treatment of schizophrenia were introduced in the 1950s and their introduction marked a shift in the way mental health professionals care for people with schizophrenia. The older psychiatric drugs, currently referred to as typical antipsychotics, used to treat schizophrenia are effective in decreasing positive symptoms; however, their aversive side effects often negate the benefits of reduced

positive symptoms. Newer antipsychotic drugs, called atypical antipsychotics, were FDA approved for use in the US in 1990. Although atypical antipsychotics are effective and do not produce the dramatic negative side effects associated with typical antipsychotics, their use has been limited as a result of their exorbitant cost.

Atypical antipsychotics designed to treat people with schizophrenia cost nearly 100 times more than typical antipsychotics and funders of mental health services are reluctant to approve the funds needed for their use despite the numerous studies that demonstrate their effectiveness. In comparison to the other atypical antipsychotics, clozapine is the oldest and has been studied the most. Clozapine helps people whose symptoms of schizophrenia do not respond to typical antipsychotic drugs (i.e., their symptoms are treatment-resistant or treatment-refractory); additionally, clozapine reverses the negative side effects (e.g., tardive dyskinesia) that occur with typical antipsychotic drugs.

The proposed study focused on the use of the atypical clozapine. The initial purpose of this study was to aggregate the results of cost-effectiveness studies that compared clozapine to typicals using meta-analytic techniques; this however was not possible for two reasons. First, there was a dearth of cost-effectiveness studies available and second available studies were found to be missing too much data to be properly meta-analyzed. The proposed meta-analysis was re-conceptualized and sought to demonstrate the cost-effectiveness of clozapine over typical antipsychotics.

## Background Literature

Multiple aspects of schizophrenia will be discussed. A detailed definition of schizophrenia, including the course and prevalence of schizophrenia, will be

discussed first. Pharmacologic treatment of people with schizophrenia will be presented second. Third, will be the definition of treatment resistant schizophrenia, followed by a detailed discussion of the atypical clozapine, including its benefits and limitations. Costs related to schizophrenia will follow and be presented from the perspectives of people with schizophrenia (hereafter also referred to as consumers), their care-takers, private insurers, and the society in which people with schizophrenia reside. The significance of this study will be discussed last.

*Definition of Schizophrenia*

Schizophrenia is a debilitating and chronic psychiatric illness (Awad, Lapierre, Angus, Rylander, & The Canadian Remoxipride Group, 1997; Rosenheck et al., 1997). Historically schizophrenia has been regarded as a disorder that is functional in nature (i.e., does not have an organic cause), more recently it is being defined as an organic brain disease (Buckley, 1998; National Alliance of the Mentally Ill, 1997). Symptoms of schizophrenia are classified into positive and negative categories. People with schizophrenia also contend with cognitive impairments that are not classified as fitting into the positive or negative categories (Bond & Meyer, 1999; American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders-IV, 1994).

*Symptoms and Cognitive Impairments*

The *DSM-IV* (p. 275) categorizes positive symptoms along the "psychotic dimension" and the "disorganization dimension". The "psychotic dimension" consists of delusions and hallucinations. The "disorganization dimension" consists of disorganized speech and behavior, suspiciousness, agitation, and hostility. Negative

symptoms typically consist of affective flattening, alogia, and avolition. See Table 1 for definitions of positive and negative symptoms. Cognitive impairments typically involve impairments in mental functioning including difficulties with memory, decreases in attention span and concentration, and impairments in judgment and decision making (Bond & Meyer, 1999; Meltzer, 1997).

Table 1 Symptom Definitions

| Symptom | Definition |
|---|---|
| Delusion | False belief, often bizarre and firmly held, despite evidence to the contrary |
| Hallucination | Sensory experiences in the absence of environmental stimuli |
| Affective Flattening | Restrictions in the range and intensity of emotional expression |
| Alogia | Restrictions in the fluency and productivity of speech |
| Avolition | Restrictions in the initiation of goal directed behavior |

*Course*

Symptoms of schizophrenia typically develop between the ages of 18 to 24 in men and 25 to 34 in women (Rasmussen, 1997; Rice, 1999); symptoms rarely occur prior to adolescence (*DSM-IV*, 1994). Prognostic indicators that are suggestive of the course of schizophrenia include: age at onset; level of premorbid adjustment and education; timing of antipsychotic medication intervention; and presence of structural brain abnormalities and negative symptoms, such as withdrawal. The course of schizophrenia improves as the age of onset increases. Higher levels of premorbid adjustment and education, as well as early intervention with antipsychotic drugs, are suggestive of a better prognosis (*DSM-IV*; Wyatt, 1995). The presence of structural brain abnormalities and negative symptoms are suggestive of a poor course.

While the prognostic indicators listed above assist in predicting the course of schizophrenia, the exact course of the illness varies widely, with some people being affected only mildly while others are severely affected (Watt, Katz, & Shepherd, 1983). Davies and Drummond (1990) reported that while some people with schizophrenia have a single episode and recover, approximately 80% of people with schizophrenia remain ill for the rest of their lives. Within the population of people with schizophrenia, 9% experience lasting impairment and of this number, 43% suffer further increases in impairment with each episode of schizophrenia (Watt et al.). These rates are linked to mortality and morbidity rates of people with schizophrenia.

Mortality is higher in psychiatric populations than in the general public (Osborn, 2001). Rice and Miller (1996) define mortality as premature death related to illness and state that the overall mortality rate in people with schizophrenia is 3 to 4

times higher than in the general population (Black & Fisher, 1992; Ciapparelli et al., 2000). Morbidity is defined as lost productivity secondary to illness (Rice, Kelman & Miller, 1991). Mortality and morbidity often act together causing people with schizophrenia to lose time and "effectiveness at work and other productive activities, forcing them out of the labor force completely, or bringing about premature death" (Rice & Miller, p. 322).

*Prevalence*

Approximately 1% of adults over the age of 18 in the United States have schizophrenia (Meltzer, 1997; Rupp & Keith, 1993). Buckley (1998) puts this prevalence rate into perspective by noting that rates of schizophrenia exceed more commonly thought of illnesses such as Alzheimer's disease and multiple sclerosis. Alzheimer's disease affects approximately 15% of adults over the age of 65 (www.emindhealth.com) and multiple sclerosis affects approximately 250,000 to 350,000 people in the United States (http://encarta.msn.com). Even though schizophrenia composes a relatively small proportion of the total number of mental illnesses affecting people in the United States (e.g., 12.6% have anxiety disorders and 9.5% have affective disorders), people with schizophrenia consume a disproportionate amount of the resources set aside to treat mental illness (Buckley, 1999; Rice, 1999). One percent of adults in the US have schizophrenia, yet they occupy 25% of hospital beds (Davies & Drummond, 1990) and consume 22% of the total dollars available to treat mental illness (Rice & Miller, 1996). Rupp and Keith report that schizophrenia accounts for 2.5% of all healthcare expenditures and 10% of

all permanent disability cases in the US. Several interventions are available to treat people with schizophrenia.

*Pharmacologic Treatment of Schizophrenia*

Schizophrenia is an illness that requires multiple intervention regimens such as psychotherapy and psychosocial treatment (e.g., counseling, education, and family intervention), rehabilitative efforts, and pharmacotherapy (Awad, Voruganti & Heslegrave, 1997; Campbell, Young, Bateman, Smith & Thomas, 1999). While all of these interventions are beneficial, this study will focus on pharmacotherapy as it is the primary modality used to treat people with schizophrenia (Buckley, 1998; Campbell et al.).

As a class, drugs used to treat people with schizophrenia are referred to as antipsychotics and they are classified into two categories: typical and atypical. All of the atypicals are at least as effective as typicals, however, only clozapine will be discussed as it is the only atypical to date that is effective in consumers whose symptoms of schizophrenia do not respond to other pharmacologic interventions (Essock, Hargreaves, Covell & Goethe, 1996; Flynn et al. 1997; Kane, Honigfeld, Singer & Meltzer, 1998). A complete list of typical and atypical antipsychotics is provided in Table 2.

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Table 2 Typical and Atypical Antipsychotics

| Generic Name | Trade Name | FDA Approval |
|---|---|---|
| Typicals | | |
| Haloperidol | Haldol | 1950s |
| Chlorpromazine | Thorazine | 1950s |
| Atypicals | | |
| Clozapine | Clozaril | 1990 |
| Risperidone | Risperidal | 1993 |
| Olanzapine | Zyprexa | 1996 |
| Quetiapine | Seroquel | 1997 |
| Ziprasidone | Zeldox | 2001 |
| Sertindole | Serlect | Not Available in US |
| Amisulpiride | Solion | 1998 |
| Zotepine | Zoleptil | 1998 |

*Treatment with Typical Antipsychotics*

The typical antipsychotics, haldol (Haloperidol) and thorazine (Chlorpromazine), were introduced in the 1950s (Campbell et al., 1999; Rosenheck et al., 1997). Haldol and thorazine decrease positive symptoms, but have no reported effect on negative symptoms short of worsening them (Breier et al., 1994; Rasmussen, 1997). While typicals are effective in decreasing positive symptoms, they do not do so in all people with schizophrenia; 25% to 33% of people with schizophrenia fail to obtain symptom relief from taking typical antipsychotics (Campbell et al.). Approximately 70% of people taking typicals experience decreases in positive symptoms, yet they often continue to experience clinically significant levels of negative symptoms, lowered levels of quality of life in comparison to non clinical populations, poor social and work functioning, and they continue to be at higher risk to commit suicide than people who do not have schizophrenia.

Other effects of typical antipsychotics are their dramatic physical side effects. Rasmussen (1997) provides a list of short and long term physical side effects of typical antipsychotics. Short-term side effects are listed and described in Table 3. The primary long-term side effect of typical antipsychotics is tardive dyskinesia (TD), which is a movement disorder typically involving the lips, tongue, jaw and upper parts of the body (Larsen, 1997; Spiegel, 1997). TD can take years to develop and when it does there is an overall incidence rate of 15% with 8% of cases being moderate to severe and less than 1% of cases being severe and irreversible. Side effects of typicals are often intolerable and, as a result, people often stop taking them (Palmer, Revicki, Genduso, Hamilton, & Brown, 1998). While typical antipsychotics

often result in drug noncompliance, use of atypical antipsychotics does not (Rasmussen).

Table 3 Short Term Side Effects of Typicals

| Side Effect | Description |
|---|---|
| Hypotension | Low blood pressure |
| Anticholinergic Effects | Dry mouth and blurred vision |
| Increases in Prolactin | In women may be associated with amenorrhea and in men may be associated with reduced sexual potency |
| QT prolongation | Increase between the Q and T waves on an electrocardiogram |
| Risk of Arrhythmias | Change in the regular beat of the heart (heart may skip a beat or beat irregularly fast or slow) |
| Extrapyramidal Side Effects (EPS) | |
| Parkinsonism | Slowing of voluntary movements, lack of facial expression, trembling in arms and head |
| Dystonia | Neurological disorder characterized by involuntary and excessive muscle contractions throughout the body resulting in abnormal postures |
| Akathisia | Movement disorder characterized by restlessness in the legs |

*Treatment with Atypical Antipsychotics*

Atypical antipsychotics were accepted into clinical practice in the United States in 1990 (Buckley, 1999; Campbell et al., 1999). There are several benefits and few aversive side effects associated with atypical antipsychotics. The benefits of taking atypical antipsychotics include fewer requests for changes in medication, reduced risk of developing TD, and decreases in TD when switching from typical antipsychotics to atypical antipsychotics (Rasmussen et al., 1997). Atypical antipsychotics are also beneficial in comparison to typicals because they decrease positive symptoms and cognitive impairments, produce fewer side effects, increase quality of life (QOL) and possess antidepressant properties which may be useful in alleviating negative symptoms (Buckley, 1999; Ciapparelli et al., 2000).

Side effects associated with atypical antipsychotics vary depending on the one that is being used. In general, side effects of atypicals include agitation, anxiety, EPS (when prescribed at higher than recommended doses), headaches, insomnia, postural hypotension, rhinitis, constipation, dose dependent increases in liver enzymes, nervousness, somnolence, and weight gain (Bennett, 1999; Larsen, 1997; Rasmussen, 1997). Larsen notes that most of these can be effectively managed without the use of additional medications. For instance, insomnia may be alleviated by taking the prescribed dose in the morning as opposed to in the evening or before bed. Postural hypotension can be dealt with by instructing the consumer to rise slowly from the sitting position. Weight gain can be managed with dietary counseling and exercise. Psychoeducation, adequate rest, and exercise are beneficial in helping consumers who experience nervousness or agitation.

*Treatment Refractory Schizophrenia*

Rosenheck et al. (1997) and Meltzer (1997) describe a person with treatment resistant schizophrenia as someone who, despite adequate trials of typical antipsychotics, continues to experience moderate to severe positive and negative symptoms accompanied by deficits in social and work functioning over long periods of time. There are different definitions of treatment resistant schizophrenia; it is generally agreed though, that certain criteria must be met before a person is described as being treatment resistant. Kane et al. (1988) specify:

1. At least three periods of treatment in the preceding five years with neuroleptic agents (from at least two chemical classes) at dosages equivalent to or greater than 1000 mg/d of chlorpromazine for a period of six weeks, each without significant symptomatic relief.
2. No period of good functioning within the preceding five years.
3. Total Brief Psychiatric Rating Scale (BPRS) score of at least 45 plus a minimum Clinical Global Impressions (CGI) Scale rating of 4 (moderately ill). In addition, item scores of at least 4 (moderate) were required on two of the following four BPRS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content (p. 790).

Although approximately 30% (range 10-45%) of people with schizophrenia fit the description of treatment resistant (Ciapparelli et al., 2000; Meltzer, 1999), the criteria given by Kane et al. tend to exclude all but those with the most severe symptoms. These criteria exclude people who respond to typicals, but still experience difficulties

with negative symptoms and social functioning. In response to this, Meltzer (1997) suggests that treatment resistance should be evaluated along a continuum that includes relevant outcome criteria. Relevant outcome criteria include psychopathologic symptoms, cognitive and affective functioning, mortality in terms of suicide, extrapyramidal symptoms and tardive dyskinesia, rates of hospitalization, quality of life, and work and social functioning.

Realization that not all people with schizophrenia respond to treatment with antipsychotics has prompted research along two fronts. The first is to identify phenomenologic, demographic, and/or biologic factors that contribute to poor treatment response (Kane et al., 1988). Despite numerous studies that have sought to understand why some people with schizophrenia are refractory to treatment with antipsychotics, while some respond to them, Kane et al. stated that consistent differences have not been identified. Although consistent differences do not exist between people with schizophrenia who respond to antipsychotics and those who do not respond to them (Edwards, McGory, Harrigan, & Cocks, 1998), people identified as treatment resistant tend to experience longer periods of psychosis during their first hospitalization, greater levels of depressive symptoms 12 months after stabilization, and poorer psychosocial functioning 12 months after stabilization than people who respond to antipsychotic medications.

The second of line of research has explored alternative treatments that might be beneficial to people with schizophrenia who do not respond to treatment with antipsychotics (Kane et al., 1988). This research has yielded the development of the drug class atypical antipsychotics, clozapine being the first.

Clozapine is currently the drug of choice for people with treatment resistant schizophrenia. Approximately 60% of people with treatment resistant schizophrenia have a better response to clozapine than to typical antipsychotics (Buckley, 1998; Meltzer, 1997).

*Treatment with Clozapine*

Introduced in the United States in the 1970s, clozapine's use was discontinued when eight patients in Finland developed agranulocytosis (acute disease marked by a deficit or absolute lack of white blood cells) and died (Buckley, 1998; Thomas, 1997). Clozapine's use began again on a restricted basis when it was found that people who had been taking it not only experienced a return of their symptoms, the symptoms were worse than before clozapine use began. In addition to experiencing a worsening of symptomatology, people who had been taking clozapine failed to achieve at least adequate responses to other available antipsychotics following clozapine's discontinuation (Meltzer, 1997). Clozapine was reintroduced in the United States in 1990 following a large multicenter clinical drug trial by Kane et al. (1988), who sought to evaluate its effectiveness in people with treatment resistant schizophrenia. Kane et al.'s sample included data on 319 inpatients, all of whom had a *DSM-III* diagnosis of schizophrenia and met the aforementioned criteria for treatment resistance. All patients entered into the study were treated with haldol and benztropine mesylate for six weeks to confirm the presence of treatment resistance. Improvement in response to the haldol was defined as a 20% decrease in the total BPRS score as well as either a posttreatment CGI scale rating of less than or equal to 3 (mildly ill). Participants who responded to haldol (33) were dropped from the study.

Patients who continued in the study (286) were randomly assigned to a six-week double blind treatment with clozapine or thorazine plus benztropine mesylate. To maintain blinding, patients in the clozapine group were given placebos that were identical to benztropine mesylate in appearance and patients in the haldol group were subjected to blood monitoring similar to patients in the clozapine group. Patients in the clozapine group (30% classified as responders) demonstrated statistically greater improvements in BPRS and CGI scores than patients in the thorazine group (4% classified as responders) after 6 weeks of treatment. This finding is strengthened by Meltzer et al. (1989) who report that by 12 months 60% of people using clozapine experience a decrease in psychopathology. Honigfeld and Patin (1990) report that clozapine's broad spectrum of action make it effective in alleviating positive symptoms, such as hallucinations and delusions, and negative symptoms, such as apathy and blunted affect. Clozapine's ability to reduce psychopathology is directly related to its broad spectrum of action (Honigfeld and Patin).

Common side effects associated with clozapine include postural hypotension, sedation, weight gain, seizures, and agranulocytosis (Honigfeld & Patin, 1990; Larsen, 1997). Postural hypotension is best managed by having the person rise slowly from sitting to standing; sedation is best managed by taking clozapine at bed time (Larsen). Weight gain is difficult to manage and tends to be a chronic problem for people taking clozapine (Larsen). There is a 1-2% chance of having seizures while taking clozapine; this risk increases as dose levels increase beyond 600-900mg per day. Average daily doses of clozapine, however, do not typically exceed 300-400mg (Honigfeld & Patin, 1990). Agranulocytosis is the most severe side effect of

clozapine; if left untreated, agranulocytosis can be fatal (Honigfeld & Patin). Agranulocytosis can only be managed by discontinuing clozapine. Agranulocytosis is detected via blood monitoring that must be conducted weekly during the first 6 months of use and then biweekly for as long as the person is taking clozapine.

*Costs of Schizophrenia*

According to Andreasen (1991), evaluating the costs of schizophrenia is difficult because of the multifaceted nature of the illness. Specifically, costs of schizophrenia are monetary and non-monetary. Additionally, multiple parties are affected by the illness. As a consequence of the multifaceted nature of schizophrenia and the manner in which it impacts multiple parties, costs related to schizophrenia will be discussed from the perspectives of the consumer (personal perspective), the consumer's care takers (care taker perspective), health insurance providers (private payers), and the society in which the consumer lives (societal perspective). The societal perspective will be discussed in greater detail than the personal, care taker, and private insurer perspectives because it is the perspective from which costs related to this study will be evaluated.

*Personal Perspective*

There are many personal costs related to having schizophrenia. Prominent among these are cognitive impairments and positive and negative symptoms. Costs considered to be primary or direct in nature include impairments and symptoms directly associated with schizophrenia such as impaired cognition and positive and negative symptoms. Costs considered to be secondary or indirect include emotional suffering and stigma.

As an example of problems related to cognitive impairments, Andreasen (1991) notes that schizophrenia typically develops at a point where people are just beginning to pursue skills that will provide them with lifetime employment opportunities. Cognitive impairments related to schizophrenia interfere with completion of this typical early adult task and potentially set the person up for a lifetime of dependence on family, friends, and society. Meltzer, Thompson, and Lee (1996) provide further support of the relationship between cognitive impairments and employment difficulties in their study where they used the Wisconsin Card Sorting Task (test designed to evaluate one's ability to switch mental sets) to examine the relationship between cognitive impairments and work functioning in people with schizophrenia. They found that people who scored higher on this measure were more likely to have full time employment; higher scores on the Wisconsin Card Sorting Task are presumed to be indicative of higher levels of cognitive functioning. People who are less cognitively impaired can be expected to have fewer employment difficulties.

Indirect costs related to schizophrenia include emotional suffering, stigma, social isolation, and feelings of hopelessness. Meltzer (1997) states that people with schizophrenia are prone to experience depression and anxiety. People who have insight into the severity of their illness may be depressed by the realization that they are not likely to be able to resume premorbid levels of functioning in terms of intelligence, work, and social interactions (Meltzer, 1997; Meltzer & Okayli, 1995).

*Care Taker Perspective*

Family members usually act as care givers to people with schizophrenia who are unable to care for themselves or need assistance. The burden of having a family member with schizophrenia often takes an emotional and financial toll on the members caring for the person with schizophrenia (Novartis, 1998). The mental health of family members is often impacted in terms of reduced coping abilities and decreased time available for social and leisure activities (Fadden, Bebbington, & Kuipers, 1987; Noh & Turner, 1987). Family members of people with schizophrenia often complain that the member with schizophrenia is disoriented, does not care for him/herself properly, and/or is aggressive (Fadden et al.). Additionally, Torrey (1995) notes that 38% of families of people with schizophrenia report that the ill member is violent and destructive in the home; this behavior has the potential to impose an economic burden as well as an emotional one.

Families of people with schizophrenia endure an economic burden as a result of caring for their ill member. The inability of the person with schizophrenia to work can drain household resources in a short period of time (Allenbeck, 1989). This strain on household resources is magnified when the person with schizophrenia is the primary provider in the home and can no longer serve this function as a consequence of the illness (Fadden et al., 1987; Novartis, 1998). Rupp and Keith (1993) estimate that the cost to families to care for their ill member, not including pain, suffering, stigma, and disruption of the family, is $2 billion annually. This cost cannot be covered by families alone and as such insurance is necessary.

*Private Payers*

Like any chronic and debilitating illness, costs related to schizophrenia are often too large to be paid without some form of insurance. Private insurance, however, is often not available to people with schizophrenia due to their inability to work full time. People with schizophrenia are most often dependent on public health insurance in the forms of Medicaid and Medicare (American Psychiatric Association, 1996; Ciapparelli et al., 2000).

*Societal Perspective*

This perspective focuses on what it costs society to support a person with schizophrenia and is the focus of the current study. Although schizophrenia affects only 1% of the US population, people with it consume approximately 2.5% of health dollars and account for 10% of all people in the US who are totally and permanently disabled (Rupp and Keith, 1993). Rice and Miller (1996) state that in 1985, schizophrenia cost the US economy $22.8 billion and this number increased to $32.5 billion by 1990. If the value reported for 1990 were adjusted for inflation, schizophrenia cost the US economy $45.3 billion in 2002 (The Inflation Calculator, n.d.). Costs from this perspective will be briefly discussed in terms of the impact schizophrenia has on Medicaid and Medicare and the indirect costs associated with schizophrenia. A more detailed discussion of the direct costs of schizophrenia will follow.

*Medicaid and Medicare*

Since people with schizophrenia are often unable to work, public services such as Medicaid and Medicare (Social Security) bear the cost of providing services

to them (American Psychiatric Association, 1996; Ciapparelli et al., 2000). Medicaid is a jointly funded federal and state government health insurance program for low income people; whereas, Medicare is a heath insurance program for people age 65 and older, some people with disabilities under the age of 65, and for people with end stage renal disease (Centers for Medicare and Medicaid Services, n.d.). As of July, 2001, 40,025,724 people in the US were enrolled in Medicare and of these 5,563,269 were classified as disabled. In 1999, inpatient mental health care costs to Medicaid were $1,758,000 (Centers for Medicare and Medicaid Services). According to Rupp and Keith (1993), people with schizophrenia consume approximately 24% of federal funds available for health care and approximately 40% of state funds available for health care. Rupp and Keith state that people with schizophrenia rely on public assistance, not just for income and health care, but also for other welfare resources such as food stamps and housing.

*Indirect Costs of Schizophrenia*

Rice et al. (1991) define indirect costs as costs that result from a loss of resources. Approximately 70% of costs related to schizophrenia go toward indirect expenses resulting from lost members of the workforce, suicide, substance use, use of criminal justice resources, homelessness, and lack of proper care for illnesses that are common in the general population (American Psychiatric Association, 1996). A key component underlying these indirect costs is the psychopathology, manifested as positive, negative, and cognitive symptoms, experienced by nearly every person with schizophrenia.

Schizophrenia often develops at a point when most people are just beginning to pursue educational and vocational skills that will later provide them with employment opportunities (Andreasen, 1991). Impairments associated with the illness often prevent consumers from completing this training and as such the ability to obtain gainful employment decreases (Andreasen). Bond and Meyer (1999) note that negative symptoms and cognitive impairments associated with schizophrenia interfere with their ability to establish potential employment contacts as well as respond appropriately during interviews. In instances where people with schizophrenia gain employment, cognitive impairments may cause them to have difficulty remembering work related tasks and as such cause them to have difficulty maintaining employment (Bond & Meyer; Torrey, 1995). Torrey states that 80%-94% of people with schizophrenia are not capable of maintaining full-time employment. Unemployment is higher within the population of people with schizophrenia than it is in the general population of all people (Allenbeck, 1989; Andreasen). Just as impairments related to schizophrenia decrease the person's ability to gain and maintain employment, so also does suicide in the sense that society permanently loses a potential member of the work force.

Approximately 10% of people with schizophrenia commit suicide within the first ten years of being ill (Ciapparelli et al., 2000). Meltzer and Okayli (1995) report that 20%-40% of people with schizophrenia attempt suicide and that 9%-13% succeed over the course of their lifetime. The risk of suicide among people with schizophrenia is 20 to 50 times greater than in the general population. It is thought that the primary reason people with schizophrenia commit suicide is they become

hopeless when they realize that the prospect of returning to their premorbid level of functioning is poor and for those who suffer them, severe drug side effects (e.g., TD) are most likely permanent (Meltzer & Okayli).

Additional indirect costs associated with schizophrenia include problems with chronic psychopathology, substance abuse, increased rates of homelessness, and failure to receive proper care for common health conditions such as diabetes and heart disease (Ciapparelli et al., 2000). Substance abuse occurs in approximately 40% to 70% of people with schizophrenia. Approximately 10% to 15% of people with schizophrenia are incarcerated. Torrey (1995) estimates that approximately 100,000 people with schizophrenia in the US are homeless.

*Direct Costs of Schizophrenia*

Direct costs associated with schizophrenia are most often those that are readily monetized and frequently include hospitalization and pharmaceuticals (Knapp, 1997; Rice et al., 1991; Rupp and Keith, 1993). In 1975, direct costs of schizophrenia were estimated at 2 to 4 billion dollars (Wasylenki, 1994); more recently, it is estimated that nearly 30% of the annually estimated $65 billion cost of caring for people with schizophrenia goes to direct costs (American Psychiatric Association, 1996). Knapp notes that the direct costs of schizophrenia are large because of its chronic nature and disabling effects. The current study focuses on direct costs of schizophrenia with regard to the effect clozapine has on decreasing the number and length (in terms of days) of psychiatric hospitalizations and indirect costs with regard to clozapine's ability to decrease overall levels of psychopathology.

According to Rosenheck et al. (1999) and Awad, Lakshmi, and Voruganti (1999), hospitalization contributes the most to direct care expenses. Muller and Caton (1983) provide an extension of this stating that direct costs of schizophrenia are most affected by occurrences of re-hospitalization. Buckley (1998) states that short stay hospitalizations are estimated to cost 9 billion dollars annually or 28% of schizophrenia's total cost of care.

Although pharmacotherapy represents only a small portion of the total cost of care of people with schizophrenia (Muller and Caton, 1983), it is often discussed in the economic literature of schizophrenia as health care policy makers are increasingly asking drug manufacturers to demonstrate the cost-effectiveness in addition to the clinical effectiveness of newer and more expensive drugs (e.g., Neuman, 1999; Reid, 1999; Revicki, 1999). Pharmacoeconomic studies assist clinicians and health care policy makers to select treatments that provide the most benefit at the most acceptable cost (Revicki). Buckley (1998) estimates that prior to the introduction of atypical antipsychotics, pharmacotherapy for people with schizophrenia cost 397 million dollars annually. This figure represents 5% of the total cost of care for people with schizophrenia and 18% of the cost of medications for all mental illnesses. Since the introduction of atypical antipsychotics, pharmacotherapy costs have increased by at least 400 times (Docherty, 1999).

*Cost Analyses*

Broadly defined, the term cost analysis reflects all types of analyses that evaluate costs. The four types of analyses: cost-benefit, cost-utility, cost-feasibility and cost-effectiveness are briefly presented below. The current study utilizes a cost-

effectiveness framework; the rationale for this decision is presented at the end of the discussion on cost-effectiveness analysis.

Cost-benefit analysis (CBA) asks the question: are the benefits of a single intervention greater than its costs. Costs and outcomes are strictly measured in pecuniary terms. The advantages of CBA are it can be used to judge the absolute worth of a project and it can be used to compare cost-benefit results across diverse settings (i.e., education vs. health care). The disadvantage of CBA is it is often difficult to monetize particular outcomes, such as decrements in quality of life for the person withy schizophrenia and emotional stress for that person's family (Levin & McEwan, 2001). Muller and Caton (1983) support this, stating that many psychosocial outcomes cannot be monetized. Cost-utility analyses and cost-effectiveness analyses are employed when outcomes are difficult to impossible to monetize (Levin & McEwan).

Cost-utility analysis (CUA) asks the question which alternative yields a given level of utility at a particular cost. Specifically, CUA asks people with particular illnesses what they would be willing to pay to avert their illness (Muller & Caton, 1983). According to Awad et al. (1999) treatments examined in this framework may be more expensive in the short term, but become the most economical alternative in the long term. Savings potentially result from reduced relapses. CUA costs are measured in terms of the monetary values of resources and outcomes are measured in terms of utility. The strengths of using the CUA framework are it incorporates individual preferences for units of effectiveness, it can incorporate multiple measures of effectiveness into a single measure of utility, and it promotes consumer

participation in decision making. There are multiple disadvantages of using this framework. First, it is occasionally difficult to arrive at consistent and accurate measures of individual preferences and the overall worth of single alternatives cannot be judged (Levin & McEwan, 2001). Second, results are often expressed in a manner that impedes communication and understanding between clinicians and health economists (Awad et al., 1999). Third, CUA may not work well with people who have more severe and chronic forms of schizophrenia due to the interference of hallucinations and delusions, as well as cognitive impairments, that may make it difficult for them to complete cost-utility tests (Awad et al., 1999).

Cost-feasibility analyses ask if a single alternative can be carried out within an existing budget. Costs are monetized and outcomes are not examined. Outcomes are not examined because as the name suggests, this type of analysis seeks to determine if a particular alternative is possible in a particular budget, if it is not outcomes are not examined. The strength of this approach is alternatives that are not feasible are immediately ruled out and resources are not wasted evaluating potential outcomes. While not evaluating outcomes is considered to be an advantage of this type of analysis, it is also a disadvantage because it prevents a judgment of the overall worth of the project from being made (Levin & McEwan, 2001).

Cost-effectiveness analysis (CEA) asks the question which alternative yields a given level of effectiveness for the lowest cost or which alternative yields the highest level of effectiveness for a given cost. Ideally, the most preferable alternative is the one that yields the greatest level of efficacy for the least amount of money. As will be demonstrated in this study, the most efficacious alternative is not always the one that

costs the least. In fact, sometimes the most efficacious alternative costs more than all other alternatives and it is in such a situation that the CEA is necessary to determine if this additional cost is worthwhile in terms of making resources available to other areas. In the case of the proposed study, other areas could possibly be increasing funds available to outpatient and community based treatment programs. Within a CEA framework, costs are measured in terms of the monetary value of resources and outcomes are measured in units of effectiveness.

While there are disadvantages that are inherent to CEA (e.g., it can only compare alternatives with similar goals), the ability to compute cost-effectiveness ratios without being required to monetize all alternatives and outcomes makes its use more advantageous than CBA. Although CUA has often been used in health-related research, it is not being employed here because the results it produces are often difficult to reproduce among different evaluators because of the numerous and sometimes conflicting methodologies that are used to estimate the importance of weights (Levin & McEwan, 2001).

*Current Study*

The current study focused on clozapine because it is the subject of the most research on atypical antipsychotics and is also the only atypical antipsychotic to date that is effective for people with treatment resistant schizophrenia (Essock et al., 1996; Flynn et al., 1997; Kane et al., 1988). This study employed meta-analytic techniques as a means of compiling the results of published studies that specifically address the cost-effectiveness and/or efficacy of clozapine using quasi-experimental single group pretest/posttest designs and clozapine in comparison to typicals by using controlled

experimental designs. Use of this technique was important because purchasers of health care demand cost-effectiveness evaluations for newer and more expensive treatments (Davies et al., 1998). Meta-analytic techniques offer the opportunity to compile available literature on the cost-effectiveness and/or efficacy of clozapine in one place that can be conveniently accessed by those who determine what modalities can and should be used in the care of people with treatment refractory schizophrenia. Meta-analytic techniques also offer the opportunity to combine studies with small sample sizes that may not have detected significant effects. By pooling studies with small sample sizes, meta-analysis provides an increase in power, thereby increasing the potential to find a statistically significant overall effect (Lipsey & Wilson, 2000).

Lipsey and Wilson (2000) describe meta-analysis as a form of survey research in which research reports are examined as opposed to people. In meta-analysis, a coding scheme is developed, a population of literature is targeted, and each study from that population is examined by a coder who reads it carefully and records information about its attributes and quantitative findings (Lipsey & Wilson). The results of a meta-analysis are examined using "adaptations of conventional statistical techniques to investigate and describe the pattern of findings in the selected set of studies" (Lipsey & Wilson, p.2).

*Hypotheses*

Meta-analytic techniques were used to test the following hypotheses:

1. Clozapine is more cost-effective than haldol/thorazine for people with treatment resistant schizophrenia in terms of decreasing psychiatric inpatient hospitalization costs.

2. Clozapine is more cost-effective than haldol/thorazine for people with treatment resistant schizophrenia in terms of decreasing the number of days they spend in inpatient psychiatric settings.
3. Clozapine is more cost-effective than haldol/thorazine for people with treatment resistant schizophrenia in terms of decreasing the number of times they are hospitalized for psychiatric reasons.
4. Clozapine is more cost-effective than haldol/thorazine for people with treatment resistant schizophrenia in terms decreasing overall levels of psychopathology as measured by the BPRS.
5. Clozapine, when examined using quasi-experimental single group pretest/posttest procedures, is cost-effective in terms of decreasing psychiatric inpatient hospitalization costs.
6. Clozapine, when examined using quasi-experimental single group pretest/posttest procedures, is cost-effective in terms of decreasing the number of days people with treatment resistant schizophrenia spend in psychiatric inpatient settings.
7. Clozapine, when examined using quasi-experimental single group pretest/posttest procedures, is cost-effective in terms of decreasing the number of times people with treatment resistant schizophrenia are hospitalized for psychiatric reasons.
8. Clozapine, when examined using quasi-experimental single group pretest/posttest procedures, is cost-effective for people with treatment resistant

schizophrenia in terms of decreasing overall levels of psychopathology as measured by the Brief Psychiatric Rating Scale.

# METHOD

The cost effectiveness of clozapine was investigated using meta-analytic techniques. This section discusses the specific meta-analytic technique used as well as the procedures used in the identification of studies.

*Meta-analytic technique*

The results of the meta-analysis were examined using unstandardized mean differences between the target group means to calculate effect sizes. The unstandardized mean difference is a type of effect size that applies to research findings where "the same operationalization of a variable of interest is used in all the group-contrast research findings to be meta-analyzed, i.e., using the same measurement procedures and numerical scale, and the variable is continuous" (Lipsey & Wilson, 2000, p. 47). The decision to use this technique was based on a preliminary examination of the studies included in the sample pool. Selected studies examined total cost of inpatient psychiatric care, number of days people with treatment refractory schizophrenia spent in inpatient psychiatric settings, number of times people with treatment refractory schizophrenia were hospitalized for psychiatric reasons, and overall psychopathology as assessed using the BPRS. Selected studies examined these variables by 1) comparing mean outcome scores for haldol/thorazine against clozapine and 2) comparing mean outcome scores for clozapine against itself over time using quasi-experimental pretest/posttest designs.

*Selection of Studies*

*Literature Search*

Multiple key word searches were conducted in the database Silver Platter to obtain the initial pool of literature for this meta-analysis. The first search utilized the keywords "BPRS and clozapine"; this search yielded 75 studies, of which 27 were accepted into the meta-analysis. The second search utilized the keywords "cost and clozapine and schizophrenia"; this search yielded 84 studies of which 14 were accepted into the meta-analysis. The third search utilized the keywords "clozapine and hospital and schizophrenia"; this search yielded 164 studies of which 12 were accepted into the meta-analysis. Additional literature was searched for using the bibliographies of studies obtained through Silver Platter; this search yielded 3 additional studies, which were accepted into the meta-analysis. A final search was conducted in the web browser Google; this search did not yield any additional studies.

A total of 326 studies were reviewed for this meta-analysis; 35 were excluded because they were letters to the journal's editor, comments on previous studies, or replies to comments; 29 studies were excluded because they had appeared in multiple searches (specifically, the first time studies appeared, they were either accepted into the meta-analysis if they fit a priori criteria or rejected from it if they did not); 43 studies did not report baseline and/or follow-up data; 32 studies were literature reviews; clozapine was not the primary drug examined in 23 studies (i.e., the study focused on risperidone and though clozapine was mentioned, data were not reported on it); 89 studies fell outside the scope of the meta-analysis; 1 study reported data from a study the investigators had previously done; 2 studies reported data that could

not be coded because it encompassed the entire examination period (when the examination period exceeded a year) as opposed to the end of specific time points between the time clozapine was initiated and the end of the study; and 16 studies were rejected because they were not translated into English.

*Inclusion Criteria*

The primary inclusion criteria for perspective studies were participants had to be defined as treatment resistant to conventional antipsychotic medications as defined by Kane et al. (1998) and they had to be taking clozapine. Selected studies had to either 1) report data related to cost of inpatient psychiatric care, 2) examine the number of times study participants had been hospitalized for psychiatric reasons, 3) examine the number of days study participants spent in psychiatric inpatient settings, or 4) examine overall level of psychopathology as measured by the BPRS. Studies were not excluded if they addressed more than one of these selection criteria. Selected studies also had to either 1) compare clozapine to haldol/thorazine with regard to the aforementioned variables or 2) compare clozapine to itself in a pretest/posttest manner with regard to the aforementioned variables.

*Measures*

Studies included in this meta-analysis utilized one or more of the following outcome measures to assess the cost effectiveness of clozapine as it was examined in controlled randomized experiments, where it was compared to typicals, and as it was examined in quasi-experimental single group pretest/posttest designs.

*Measurement of Total Cost of Time Spent in Psychiatric Inpatient Settings*

Total cost of time spent in psychiatric inpatient settings was assessed by calculating the average costs related to inpatient care in psychiatric settings (e.g., cost of psychopharmacology and staff time) before and after the introduction of clozapine.

*Measurement of Number of Days Spent in Psychiatric Settings*

Number of days spent in psychiatric inpatient settings was assessed by tallying the mean number of days the sample participants spent in inpatient psychiatric settings before and after the introduction of clozapine.

*Measurement of Number of Psychiatric Inpatient Hospitalizations*

Numbers of psychiatric inpatient hospitalizations were assessed by tallying the mean number of times the sample participants had been hospitalized for psychiatric reasons before and after the introduction of clozapine.

*Measurement of Psychopathology*

Psychopathology, in terms of positive and negative symptoms, is commonly assessed using the Brief Psychiatric Rating Scale (BPRS) (e.g., Aitchison & Kerwin, 1997; Breier et al., 1994; Ciapparelli et al., 2000). Published in 1962 by Overall and Gorham, the BPRS is based on a structured clinical interview designed to assess the person's positive and negative symptoms. It is specifically designed to detect patient change, while yielding a comprehensive description of the patient's major symptoms. The BPRS is most often given just before the start of psychopharmacologic treatment and again over fixed intervals set by the person administering the treatment. The scale consists of 18 symptom areas that are rated on a 7-point continuum where 1= symptom not present, 2= symptom very mild, 3= symptom mild, 4= symptom

moderate, 5= symptom is moderate-severe, 6= symptom is severe, 7= symptom is extremely severe. Symptom areas are clearly defined, while anchoring criteria are not. Total scores on the BPRS range from 18–126. Overall and Gorham indicate that the interview portion of the BPRS, along with completion of the rating scale, take approximately 20-25 minutes for raters who are familiar with the instrument. High scores on the BPRS indicate worsening of symptoms; a 20% reduction in the person's score following intervention is considered to represent clinically significant improvement in symptoms (Rosenheck et al., 1997). Interrater reliabilities for the BPRS range from r = .56 to r = .86. Though not specified by Overall and Gorham, Halpin and Carr (2000) indicate that the BPRS has good concurrent validity. The BPRS is strongly correlated with equivalent items from Andreasen's (1984) Scale for the Assessment of Positive Symptoms (SAPS, r>.88) and her Scale for the Assessment of Negative Symptoms (SANS, r>.84).

*Data Collection and Analysis*

Data were collected on psychiatric inpatient hospitalization costs, number of days participants spent in inpatient psychiatric settings, number of times study participants had been hospitalized for psychiatric reasons, and total psychopathology as measured by the BPRS. These criteria were guided by characteristics of the literature that comprise the sample of studies accepted into this meta-analysis. Additional data were collected on study participant's mean age, gender, duration of illness, dose of clozapine received, and length of time on clozapine. These additional data were collected in an attempt to explain variance unaccounted for by study level sampling error.

The following were used to analyze the data collected across studies. Cost data, when reported in foreign currencies, were converted to US dollars using the website the Currency Converter (n.d.). Once all costs were coded as US dollars, they were adjusted for inflation to the year 2002 using the Inflation Calculator (n.d.). Effect sizes and their associated confidence intervals were calculated and adjusted using Microsoft Excel 2002. Additional analyses (e.g., correlations between variables) were conducted using Statistical Package for the Social Sciences (SPSS), Version 11.0.

# RESULTS

*Treatment of the Data*

Since chosen variables were all operationalized in the same manner and the raw data were thus reported in the same metric (e.g., psychopathology was always assessed using the BPRS), all effect sizes were calculated using Lipsey and Wilson's (2001) unstandardized mean difference. The unstandardized mean difference is determined as

$$ES_{um} = \overline{X}_{G1} - \overline{X}_{G2}$$

where $\overline{X}_{G1}$ is the mean outcome value for participants taking clozapine and $\overline{X}_{G2}$ is the mean outcome value for participants taking haldol/thorazine (number of comparison group studies = 7). Among studies that utilized a quasi-experimental pretest posttest design (n= 49), where clozapine was the only drug examined, $\overline{X}_{G1}$ is the mean baseline outcome value taken just before participants began taking clozapine and $\overline{X}_{G2}$ is the mean outcome value after participants had been on clozapine for a specified period of time. Because effect sizes tend to be upwardly biased when they are based small sample sizes, all effect sizes were adjusted using Hedges' (as cited in Lipsey and Wilson) formula for determining the unbiased effect size, which is

$$ES'_{um} = [1 - (3/(4n-9)]\ ES_{um}$$

where n is the total number of participants in the study. All subsequent computations are based on this unbiased effect size.

Once all effect sizes and their associated confidence intervals were determined for each hypothesis, a separate analysis of homogeneity of the variance across each set of studies associated with each hypothesis was conducted. This analysis was conducted to determine if the error of the effect sizes was above what would be expected from the subject samples upon which the effect sizes were based. The statistic associated with this analysis, Q, is "distributed as a chi-square with k-1 degree of freedom where k is the number of effect sizes" (Hedges & Olkin as cited in Lipsey & Wilson, p.115). Lipsey and Wilson define Q as

$$Q = \Sigma w_i (ES_i - \overline{ES})^2$$

where "$ES_i$ is the individual effect size for i = 1 to k (the number of effect sizes), $\overline{ES}$ is the weighted mean effect size over the k effect sizes, $w_i$ is the individual weight for $ES_i$" (Lipsey & Wilson, p. 116). In the instance that Q, with its associated degrees of freedom, exceeds the critical value of chi-square, set at $\alpha = .05$, the hypothesis that the sampling errors are homogenous is rejected. Examination of Q, associated with a priori hypotheses, revealed that it exceeded the preset critical value in all instances, except two. In the instances where the dispersion around the effect size mean was found to exceed that which would be expected by sampling error alone, correlations were run in an attempt to identify the additional sources of variance. Q will be discussed in greater detail as it applies to each hypothesis. Following is a brief discussion of how studies were coded, overall study characteristics, and the findings associated with each hypothesis.

*Coding of the Studies*

This brief discussion of how studies were coded focuses on how data for the effect sizes and length of time participants had been taking clozapine were coded for the primary variables associated with this meta-analysis, which were: average inpatient psychiatric hospitalization costs, average number of days spent in inpatient psychiatric settings, average number of psychiatric inpatient hospitalizations, and average level of psychopathology as assessed using the total BPRS score. This discussion will begin with the first four hypotheses where clozapine was compared to haldol/thorazine and follow with a discussion of the last 4 hypotheses where clozapine was examined in quasi-experimental pretest/posttest designs. Other coded variables (e.g., age and duration of illness) are detailed in Appendix A.

Regarding the first four hypotheses, that compared clozapine to haldol/thorazine, effect sizes were calculated using reported follow-up values. The decision to use follow-up values was based on the assumption that these groups were equivalent at the beginning of the studies, when clozapine was initiated. Concerning the length of time participants had been taking clozapine, in all studies accepted into this meta-analysis, participants began taking clozapine at the beginnings of respective studies; therefore, length of time on clozapine refers to the length of respective studies. Specifically, if a study reported to have occurred over a period of 4 years (e.g., 2 years prior to the initiation of clozapine and 2 years after the initiation of clozapine), length of time on clozapine was the period that began when clozapine was initiated and ended when the study was terminated.

In the last four hypotheses, which utilized quasi-experimental pretest/posttest designs, effect sizes were determined based on differences between the values reported when study participants began clozapine and when respective studies were concluded. As with studies that utilized comparison groups, length of time on clozapine for studies that utilized pretest/posttest designs was defined as the period of time between when clozapine was initiated and the end of the study.

*Study Characteristics*

A total of 56 studies were entered into this meta-analysis. Accepted studies were examined together to obtain basic demographic data. Overall, participants had been taking an average of 459.49 ± 141.32mg/day of clozapine with a range of 215-900mg/day ($n_{studies}$ = 46). Participants had been taking clozapine for an average of 53.35 ± 65.20 weeks, with a range of 6-348 weeks ($n_{studies}$ = 56). Prior to beginning to use clozapine, participants had been ill for an average of 14.30 ± 6.17 years, with a range of 6-37.60 years ($n_{studies}$ = 25). Participants were an average of 36.15 ± 9.49 years of age, with a range of 11.63-70.60 ($n_{studies}$ = 48). There were a total of 4,601 participants across all studies and among those studies that reported gender, were 1,726 males ($n_{studies}$ = 43) and 720 females ($n_{studies}$ = 43). Selected studies were obtained from journals and were published between 1987 and 2002. All other findings are presented in terms of their respective hypotheses.

*Findings*

*Hypothesis 1: Clozapine, when compared to haldol/thorazine, significantly reduces psychiatric inpatient hospitalization costs.*

Three of the studies (51, 57, 58)[1], accepted into this meta-analysis, reported comparison group data on psychiatric inpatient costs. These data were reported as they were assessed between participants who had been taking clozapine and participants who had been taking haldol/thorazine. Participants in these studies had, on average, been taking 552 mg/day (sd = 229)of clozapine, for 69.33 weeks (sd = 30), and had been ill for 15.50 years (sd = 7.70). The weighted mean effect size between the groups was -19.22 and significant at $\alpha = .05$, indicating that inpatient psychiatric hospitalization costs were $19,220 lower among participants who had been taking clozapine than they were among participants who had been taking haldol/thorazine. There is a 95% probability that the true decrease in inpatient psychiatric costs lies between $18,368 and $20,081.

Analysis of homogeneity variance across the studies associated with this hypothesis yielded a Q value of 5402.68 with 2 degrees of freedom. This value is greater than the $\alpha = .05$ critical value of 5.99, indicating that the variance across this sample of studies is greater than what would be expected from sampling error alone. The variance, unaccounted for by sampling error, was explored using Pearson correlations. Non-significant relationships were found when the unbiased effect size was correlated with the average age of study participants ($n_{studies} = 3$, $r = .96$), the total sample size ($n_{studies} = 3$, $r = .61$), and the length of time participants had been taking clozapine ($n_{studies} = 3$, $r = -.99$). Correlations could not be examined between the

[1] These numbers are study id numbers. The references for these study ids are presented in Appendix A.

unbiased effect size and the average number of year's participants had been ill or the average dose of clozapine participants had been taking. These correlations could not be conducted because, collectively, the studies that went into this hypothesis yielded fewer than 3 effect sizes for each of these variables.

*Hypothesis 2: Clozapine, when compared to haldol/thorazine, significantly reduces the number of days participants spent in inpatient psychiatric settings.*

Three of the studies (49, 51, 57), accepted into this meta-analysis, reported comparison group data on the number of days participants spent in inpatient psychiatric settings. These data were reported as they were assessed between participants who had been taking clozapine and participants who had been taking haldol/thorazine. Participants in these studies had, on average, been taking 522 mg/day (sd = 229) of clozapine, for 65 weeks (sd = 18.38), and had been ill for 11.90 years (sd = 2.3). The weighted mean effect size between the groups was -24.27 and significant at $\alpha = .05$, indicating that participants who had been taking clozapine spent, on average, 24 fewer days in inpatient psychiatric settings than participants who had been taking haldol/thorazine. There is a 95% probability that the true decrease in days spent in inpatient psychiatric settings lies between -26.73 and -21.80.

Analysis of homogeneity of the variance across the studies associated with this hypothesis revealed a Q value of 49.16 with 2 degrees of freedom. This value is greater than the $\alpha = .05$ critical value of 5.99, indicating that the variance across this sample of studies is greater than what would be expected from sampling error alone. The variance, unaccounted for by sampling error, was explored using Pearson

correlations. Non-significant relationships were found when the unbiased effect size was correlated with the total sample size ($n_{studies}$ = 3, r = -.50) and the length of time participants had been taking clozapine ($n_{studies}$ = 3, r = -.96). Correlations could not be examined between the unbiased effect size and the average age of study participants, the average number of years participants had been ill, or the average dose of clozapine participants had been taking. These correlations could not be conducted because, collectively, the studies that went into this hypothesis yielded fewer than 3 effect sizes for each of these variables.

*Hypothesis 3: Clozapine, when compared to haldol/thorazine, significantly reduces psychiatric inpatient hospitalizations.*

Two of the studies (49, 57), accepted into this meta-analysis, reported comparison group data on the number times participants had been hospitalized in inpatient psychiatric settings. These data were reported as they were assessed between participants who had been taking clozapine and participants who had been taking haldol/thorazine. Participants in these studies had, on average, been taking 522 mg/day (sd = 229) of clozapine, for 65 weeks (sd = 18.38), and had been ill for 11.90years (sd = 0). The weighted mean effect size between the groups was 0.20 and significant at $\alpha$ = .05, indicating that participants who had been taking clozapine had been hospitalized for psychiatric reasons, on average, 0.20 times more than participants who had been taking haldol/thorazine. There is a 95% probability that the true decrease in psychiatric inpatient hospitalizations lies between 0.13 and 0.26. This finding, that participants taking haldol/thorazine had fewer inpatient psychiatric hospitalizations than participants taking clozapine, was unexpected and likely

occurred as a result of the paucity of existing literature that examines this variable. Specifically, it is likely that if the number of studies that compared the number of psychiatric inpatient hospitalizations experienced by participants taking clozapine and participants taking haldol/thorazine were greater, the results would have favored clozapine.

Analysis of homogeneity of the variance across studies associated with this hypothesis revealed a Q value of 0.001 with 1 degree of freedom. This value is less than the $\alpha = .05$ critical value of 3.84, indicating that the variance across this sample of studies is what would be expected from sampling error alone. No further analysis of this hypothesis is necessary, since the variance in the effect sizes is not greater than what would be expected from sampling error alone (Lipsey & Wilson, 2000).

*Hypothesis 4: Clozapine, when compared to haldol/thorazine, significantly reduces overall psychopathology as it is measured by the BPRS.*

Three of the studies (8, 23, 25), accepted into this meta-analysis, reported comparison group data on total BPRS scores as they were assessed between participants who had been taking clozapine and participants who had been taking haldol/thorazine. Participants in these studies had, on average, been taking 470.39 mg/day (sd = 67.16) of clozapine, for 9.33 weeks (sd = 3.06), and had been ill for 14 years (sd = 0). The weighted mean effect size between the groups was -8.88 and significant at $\alpha = .05$, indicating that participants who had been taking clozapine for an average of 9.33 weeks (sd = 3.06), experienced, on average, 8.88 fewer symptoms than participants who had been taking haldol/thorazine. There is 95% probability that the true decrease in BPRS total scores lies between -11.32 and -6.45.

Analysis of homogeneity of the variance across studies associated with this hypothesis revealed a Q value of 5.75 with 2 degrees of freedom. This value is less than the $\alpha = .05$ critical value of 5.99, indicating that the variance across this sample of studies is what would be expected from sampling error alone. No further analysis of this hypothesis is necessary, since the variance in the effect sizes is not greater than what would be expected from sampling error alone (Lipsey & Wilson, 2000).

*Hypothesis 5: Clozapine, when examined using single group quasi-experimental pretest/posttest designs, results in a significant decrease in psychiatric inpatient hospitalization costs.*

Seven of the studies (3, 6, 32, 46, 50, 52, 56) accepted into this meta-analysis, reported quasi-experimental pretest/posttest single group comparison data on accumulated psychiatric inpatient costs. Participants in these studies had, on average, been taking 430.68 mg/day (sd = 109.88) of clozapine, for 92.86 weeks (sd = 51.69), and had been ill for 10.95 years (sd = .35). The weighted mean effect size between the time participants began taking clozapine and the time follow-up data was taken was 35.73 and significant at $\alpha = .05$, indicating that inpatient psychiatric hospitalization costs were $35,730 lower after participants had been taking clozapine for an average of 92.86 weeks (sd = 51.69). There is a 95% probability that the true decrease in psychiatric inpatient hospitalization costs lies between $27,941 and $43,571.

Analysis of homogeneity of the variance across the studies associated with this hypothesis revealed a Q value of 178.21 with 6 degrees of freedom. This value is greater than the $\alpha = .05$ critical value of 12.59, indicating that the variance across this

sample of studies is greater than what would be expected from sampling error alone. The variance, unaccounted for by sampling error, was explored using Pearson correlations. Non-significant relationships were found when the unbiased effect size was correlated with the total sample size ($n_{studies}$ = 7, r = .36), the mean dose of clozapine ($n_{studies}$ = 5, r = .65), the length of time participants had been taking clozapine ($n_{studies}$ = 7, r =-.30) and the mean age of participants ($n_{studies}$ = 5, r = -.53). A correlation could not be examined between the unbiased effect size and the average number of years participants had been ill because, collectively, the studies that went into this hypothesis yielded fewer than 3 effect sizes for each of these variables.

*Hypothesis 6: Clozapine, when examined using single group quasi-experimental pretest/posttest designs, results in a significant decrease in the number of days participants spent in inpatient psychiatric settings.*

Ten of the studies (3, 7, 32, 46, 50, 52-56) accepted into this meta-analysis, reported quasi-experimental pretest/posttest single group comparison data on the number of days participants spent in inpatient psychiatric settings. Participants in these studies had, on average, been taking 406.6 mg/day (sd = 96.63) of clozapine, for 103.13 weeks (sd = 77.47), and had been ill for 10.53 years (sd = 3.39). The weighted mean effect size between the time when participants began taking clozapine and the time at which follow-up data was taken was 40.43 and significant at $\alpha$ = .05, indicating that participants spent 40 fewer days in psychiatric inpatient settings after they had been taking clozapine for an average of 103.13 weeks. There is a 95% probability that the true decrease in the number of days participants spent is inpatient psychiatric settings lies between 35.38 and 45.48.

Analysis of homogeneity of the variance across the studies associated with this hypothesis revealed a Q value of 72.53 with 9 degrees of freedom. This value, greater than the $\alpha = .05$ critical value of 16.92, indicates that the variance across this sample of studies is greater than what would be expected from sampling error alone. The variance, unaccounted for by sampling error, was explored using Pearson correlations. Non-significant relationships were found between the unbiased effect size and the total sample size ($n_{studies} = 10$, $r = .11$), the average age of study participants ($n_{studies} = 6$, $r = -.34$), the length of time participants had been taking clozapine ($n_{studies} = 10$, $r = -.11$), and the average dose of clozapine participants had been taking ($n_{studies} = 8$, $r = .58$).

*Hypothesis 7: Clozapine, when examined using single group quasi-experimental pretest/posttest designs, results in a significant decrease in the number times participants were hospitalized for psychiatric reasons.*

Six of the studies (4, 7, 32, 46, 50, 54) accepted into this meta-analysis, reported quasi-experimental pretest/posttest single group comparison data on the number of times participants had been hospitalized for psychiatric reasons. Participants in these studies had, on average, been taking 398.14 mg/day (sd = 115.37) of clozapine, for 104.28 weeks (sd = 126.98), and had been ill for 9.63 years (sd = 4.18). The weighted mean effect size between the time when participants began taking clozapine and the time at which follow-up data were taken was 0.82 and significant at $\alpha = .05$, indicating that participants had been hospitalized for psychiatric reasons 0.82 fewer days after they had been taking clozapine for an average of 104.28 weeks. There is a 95% probability that the true decrease in the

number of times participants had been hospitalized for psychiatric reasons lies between 0.70 and .93.

Analysis of homogeneity of the variance across the studies associated with this hypothesis revealed a Q value of 106.88 with 5 degrees of freedom. This values is greater than the $\alpha = .05$ critical value of 11.07, indicating that the variance across this sample of studies is greater than what would be expected from sampling error alone. The variance, unaccounted for by sampling error, was explored using Pearson correlations. A significant relationship was found when the unbiased effect size correlated with the length of time participants had been taking clozapine ($n_{studies} = 6$, r = .83), suggesting that larger effect sizes are associated with increased time on clozapine. Non-significant relationships were obtained when the unbiased effect size was correlated with the total sample size ($n_{studies} = 6$, r = -.37), the mean dose of clozapine ($n_{studies} = 5$, r = .73), the length of time participants had been ill ($n_{studies} = 3$, r = .10), and the mean age of study participants ($n_{studies} = 5$, r = -.58).

*Hypothesis 8: Clozapine, when examined using single group quasi-experimental pretest/posttest designs, results in a significant decrease in the total level of psychopathology reported on the BPRS.*

Forty-two (1-7, 9-22, 24, 26-45) of the studies, accepted into this meta-analysis, reported quasi-experimental pretest/posttest single group comparison data on the participant's total level of psychopathology as measured by the BPRS. Participants in these studies had, on average, been taking 471.28 mg/day (sd = 149.20) of clozapine, for 45.54 weeks (sd = 62.17), and had been ill for 22.19 years (sd = 29.75). The weighted mean effect size between the time when participants

began taking clozapine and the time at which follow-up data was taken was 12 and significant at $\alpha = .05$, indicating that participants had experienced a decrease of 12 symptoms, as measured by the BPRS, after they had been taking clozapine for an average of 45.54 weeks. There is a 95% probability that the true decrease in the total level of psychopathology lies between 11.55 and 12.45.

Analysis of homogeneity of the variance across the studies associated with this hypothesis revealed a Q value of 1446.17 with 41 degrees of freedom. This value is greater than the $\alpha = .05$ critical value of 56.94, indicating that the variance across this sample of studies is greater than what would be expected from sampling error alone. The variance, unaccounted for by sampling error, was explored using Pearson correlations. A significant relationship was obtained when the unbiased effect size was correlated with the mean age of study participants ($n_{studies} = 39$, $r = -.37$), indicating that larger effect sizes are associated with younger consumers of clozapine. Non-significant relationships were obtained when clozapine was correlated with the mean dose of clozapine ($n_{studies} = 37$, $r = -.30$), the length of time participants had been taking clozapine ($n_{studies} = 42$, $r = .24$), the number of years participants had been ill ($n_{studies} = 19$, $r = -.31$), and the total sample size ($n_{studies} = 42$, $r = -.15$).

*Summary of Results*

Table 4 provides an overview of the weighted mean effect sizes and their associated Q values for each hypothesis. Table 5 provides an overview of analysis of homogeneity variance across studies. Table 6 lists study availability by variable.

Table 4 Weighted Mean Effect Sizes[a] and Q Values

| Hypothesis | $n_{studies}$ | $ES_{um}$ | Q | df | Crit Val |
|---|---|---|---|---|---|
| 1 | 3 | -$19,220[b] | 5402.68 | 2 | 5.99 |
| 2 | 3 | -24.27 | 49.16 | 2 | 5.99 |
| 3 | 2 | 0.20 | .001 | 1 | 3.84 |
| 4 | 3 | -8.88 | 5.75 | 2 | 5.99 |
| 5 | 7 | -$35,730[b] | 178.21 | 6 | 12.59 |
| 6 | 10 | 40.43 | 72.53 | 9 | 16.92 |
| 7 | 6 | .82 | 106.88 | 5 | 11.07 |
| 8 | 42 | 12 | 1446.17 | 41 | 56.94 |

a. All effect sizes significant at $\alpha = .05$

b. Adjusted for inflation to the year 2002.

Table 5 Exploration of Analysis of Homogeneity Variance Across Studies Using Pearson Correlations

| | Variable | r | $n_{studies}$ |
|---|---|---|---|
| Hypothesis 1 | Mean Age | .96 | 3 |
| | Total Sample Size | .63 | 3 |
| | Time on Clozapine | -.99 | 3 |
| Hypothesis 2 | Total Sample Size | -.50 | 3 |
| | Time on Clozapine | -.96 | 3 |
| Hypothesis 6 | Mean Age | -.34 | 6 |
| | Total Sample Size | -.11 | 10 |
| | Mean Dose Clz | .58 | 8 |
| | Time on Clozapine | -.11 | 10 |
| Hypothesis 7 | Mean Age | -.58 | 5 |
| | Total Sample Size | -.37 | 6 |
| | Mean Dose Clz | -.73 | 5 |
| | Time on Clozapine | **.82 | 6 |
| | Duration of Illness | .10 | 3 |
| Hypothesis 8 | Mean Age | **-.37 | 39 |
| | Total Sample Size | -.15 | 42 |
| | Mean Dose Clz | -.30 | 37 |
| | Duration of Illness | -.31 | 19 |

** Correlation is significant at the .01 level (2-tailed).

Note: Correlations could not be done for hypotheses 3 and due to lack of data from studies associated with these hypotheses. Correlations were not necessary for hypothesis 4 because the variance was not greater than what would be expected from sampling error alone.

Table 6 Study Availability By Variable

| | Study ID Numbers |
|---|---|
| Studies Using Comparison Groups | |
| Inpatient Psychiatric Hospitalization Costs | 51, 57-58 |
| Number Days Spent In Inpatient Psychiatric Settings | 49, 51, 57 |
| Number of Inpatient Psychiatric Hospitalizations | 49, 57 |
| BPRS Total Score | 8, 23, 25 |
| Studies Using Pretest/ Posttest Design | |
| Inpatient Psychiatric Hospitalization Costs | 3, 6, 32, 46, 50, 52, 56 |
| Number Days Spent In Inpatient Psychiatric Settings | 3, 7, 32, 46, 50, 52-56 |
| Number of Inpatient Psychiatric Hospitalizations | 4, 7, 32, 46, 50, 54 |
| BPRS Total Score | 1-7, 9-22, 24, 26-45 |

Overall, the findings of this meta-analysis are promising, despite the paucity of literature comprising it. All findings were initially presented in terms of how many weeks study participants had been taking clozapine; this metric will now be converted to years. Converting weeks on clozapine to years, will hopefully increase the meaningfulness of the findings.

Regarding cost savings, participants taking clozapine experienced significant decreases in inpatient psychiatric hospitalization costs. These costs were $19,225 lower among participants who had been taking clozapine than they were among participants who had been taking haldol/thorazine. This change occurred after participants had been taking clozapine for just over a year. Among studies that examined this variable without the benefit of a comparison group, participants taking clozapine experienced a decrease in psychiatric inpatient costs of $35,726 after a period of nearly two years (this value, if averaged out becomes $17,865 after a period of a year).

Analysis of the number of days people with treatment refractory schizophrenia spent in psychiatric inpatient settings revealed significant decreases. Among participants taking clozapine, who were compared to participants taking haldol/thorazine, participants taking clozapine spent 24 fewer days in inpatient psychiatric settings than participants taking haldol/thorazine. This decrease in number of days spent in inpatient psychiatric settings occurred after participants taking clozapine had been on it for just over a year. With regard to studies that examined participants taking clozapine, in the absence of a comparison group, days spent in psychiatric inpatient settings decreased by an average of 40 days after an average

period of nearly 2 years (this value, if averaged out becomes 20 days after a period of a year).

Concerning the number of times participants had been hospitalized for psychiatric reasons, participants taking haldol/thorazine experienced 0.20 fewer hospitalizations than participants taking clozapine. This unexpected change occurred after participants had been taking clozapine for a period of just over a year. When number of inpatient psychiatric hospitalizations were examined in studies that did not use a comparison group, number of psychiatric inpatient hospitalizations decreased by 0.82 after an average period of nearly two years (this value, if averaged out becomes .41 after a period of a year). Although the number of psychiatric inpatient hospitalizations decreased, the change is not particularly striking. These small decreases are best understood as a factor of the lack of studies that examined this variable.

Psychopathology, as assessed using the BPRS, was the last variable examined in this meta-analysis. In studies where participants taking clozapine were compared to participants taking haldol/thorazine, participants taking clozapine experienced 9 fewer symptoms after an average period of two months. Among studies that did not use a comparison group, participants taking clozapine experienced 12 fewer symptoms after an average period of nearly a year.

# DISCUSSION

Not only is schizophrenia an expensive illness in terms of multiple domains (i.e., inpatient hospitalization costs, outpatient drug costs, and psychopathology), it is likely one of the most expensive mental illnesses in the United States (Andreasen, 1991). This study sought to meta-analyze the available literature on the cost-effectiveness of the atypical clozapine. This, however, was not possible due to 1) the lack of studies that specifically addressed this construct as it pertained to clozapine and 2) the pervasive problem of missing data that occurred across the studies available to address it. Although studies that specifically addressed the cost-effectiveness of clozapine were scarce, the current study was still carried out. This meta-analysis was re-conceptualized as a meta-analysis of studies that contribute to the construct of cost-effectiveness as it was defined in the studies that addressed it directly. Selected studies thus examined direct costs defined as costs of inpatient psychiatric hospitalizations, number of days spent in inpatient psychiatric settings, number of psychiatric hospitalizations; indirect costs were defined as ratings of psychopathology as it was assessed using the BPRS. Although problems with missing data across studies continued to pose difficulties (primarily in terms of conducting necessary analyses beyond calculating the effect sizes), these difficulties were significantly lessened by the increase in available studies from 9 (when focusing exclusively on cost-effectiveness studies) to 56 (when broadening the entrance criteria to include studies that reported data on the variables that define cost-effectiveness). Following are discussions of the direct and indirect costs related to

clozapine use that were explored in this meta-analysis. Also included in these discussions are thoughts about why these findings are important to policy makers.

Regarding direct costs, this meta-analysis is of use to policy makers primarily because it creates a central place where information is available not just on hospitalization costs associated with clozapine, but also on the number of days people taking clozapine spend in inpatient psychiatric settings and the number of times people taking clozapine are hospitalized for psychiatric reasons. This information is important because it assists policy makers to make informed decisions about the drugs they approve for the care of people with treatment-resistant schizophrenia. At present, clozapine is not often prescribed because of its exorbitant cost. Specifically, whereas 100mg/day of clozapine cost at minimum $7,761.50 annually (including monitoring costs), typical antipsychotics such as haldol cost $14.90 per 100mg/day annually(Quarterly Drug Costs for Schizophrenic Medications, 2001). At a glance, this cost difference causes clozapine to appear unreasonably expensive, however, its high cost is more than offset by the money saved from its use in terms of decreased psychiatric hospital utilization.

The finding that hospital utilization decreases and thus produces cost savings is striking. Focusing on dollars saved, use of clozapine produced an annual savings of $19,225, when it was examined using controlled randomized designs, and $17,863 when it was examined using quasi-experimental single group designs. The value of $19,225 is more informative than the $17,863 because it represents a more accurate estimate of cost savings. This more representative estimate is important because, while psychiatric hospital utilization costs decreased when clozapine was examined in

isolation, it is more meaningful to know that these costs continued to decrease even when a comparison group was used.

Regarding indirect costs in terms of psychopathology, this meta-analysis demonstrated that clozapine decreases overall levels of psychopathology under experimental randomized comparison group conditions and under single group quasi-experimental conditions. The importance of this finding to policy makers, however, is somewhat unclear because of the small number of studies that were available to conduct a secondary analysis of the relationships between psychopathology and number of days spent in psychiatric inpatient settings and between psychopathology and the number of times participants had been hospitalized for psychiatric reasons. Intuitively one should expect that as levels of psychopathology decrease (secondary to using clozapine), inpatient psychiatric hospital utilization should also decrease; this, however, was not the case when clozapine was examined using quasi-experimental pretest/posttest designs. When clozapine was examined in this manner, correlations between psychopathology and hospital utilization were non-significant and negative. Specifically, the correlation between psychopathology and number of days spent in inpatient psychiatric settings was $r = -.04$ ($n_{studies} = 10$); the correlation between psychopathology and number of times participants were hospitalized for psychiatric reasons was $r = -.52$( $n_{studies} = 6$). Both of these correlations suggest that as symptoms decrease, psychiatric hospital utilization increases. It is possible that these unexpected correlations occurred because they were based on a small number of studies that did not utilize comparison groups. When clozapine was examined using randomized controlled experimental designs, a positive, though non-significant,

correlation was obtained when psychopathology was correlated with days spent in inpatient psychiatric settings ($r = .63$, $n_{studies} = 3$), suggesting that as symptoms decreased number of days spent in inpatient psychiatric settings also decreased; the relationship between psychopathology and number of psychiatric inpatient hospitalizations could not be explored using randomized designs as a consequence of too few studies.

While the major benefit of this meta-analysis is it met its primary goal of demonstrating that the use of clozapine produces greater dollar savings than haldol/thorazine in terms of inpatient psychiatric hospital utilization, it has three limitations. These limitations are 1) it does not assess outpatient costs related to the use of clozapine, 2) very few studies were used to support the hypotheses underlying this meta-analysis, and 3) satisfactory explanations could not be ascertained to explain variance across studies that was greater than what would be expected from sampling error alone.

The lack of outpatient data is problematic because it creates an unbalanced portrayal of the findings presented thus far. Specifically, it is not enough to know that money is saved secondary to reduced psychiatric hospital utilization; one must also demonstrate that this saving is not negated by a surge in outpatient costs that surpass any money saved from reduced psychiatric inpatient costs. Given that the failure to assess rises in outpatient costs produces a source of weakness in the argument for clozapine's cost-effectiveness, a brief examination of these costs follows.

The first step taken to address outpatient costs related to clozapine involved revisiting the studies accepted into this meta-analysis. Seven of the 58 studies (8, 23,

25, 49, 51, and 57-58) accepted into this meta-analysis utilized comparison group designs where some participants took haldol/thorazine while others took clozapine. Unfortunately, of these seven studies, only study number 57 provided data on outpatient costs in relation to inpatient costs and clozapine use. Although outpatient costs did rise, they did not do so to such an extent as to negate the dollars saved secondary to decreased psychiatric hospital utilization. Specifically, psychiatric hospitalization costs were $54,109 among clozapine users and $64,494 among haldol users after a period of one year. The difference between these two groups was $10,385 in favor of clozapine. Regarding outpatient costs, clozapine costs were $10,132 and haldol costs were $4,154, creating a difference of $5,978 in favor of haldol. Although clozapine outpatient costs were higher than haldol outpatient costs, they were more than offset by the decreased psychiatric hospital utilization costs. Specifically, the $5,978 increase in outpatient costs was subtracted from the $10,385 saved in inpatient psychiatric hospital utilization costs to bring about a total savings of $4,407 in favor of clozapine.

The second step taken to address outpatient costs involved examining the studies accepted into this meta-analysis that reported data using quasi-experimental pretest/posttest designs. Five of these studies provided data on outpatient costs in relation to inpatient psychiatric hospital utilization and clozapine (3, 6, 32, 50, and 52). Outpatient costs focused on increased medication costs; however, one study (id number 32) also included physician, case management, and group therapy costs under the umbrella of outpatient costs. Savings gained secondary to reduced psychiatric hospital utilization were observed in 4 of the 5 studies discussed here. Rising

outpatient costs negated psychiatric inpatient savings in study number 50. In study 50, outpatient costs exceeded gained savings by $752 annually. The total spectrum of savings, above increased outpatient costs, ranged from $2,280 to $52,595. Specific dollar values are reported in Table 7. Despite the finding of study 50, the overall result is use of clozapine not only produces dollar savings secondary to reduced psychiatric hospital utilization, it produces these savings over and above rising outpatient costs, and it produces these savings in as little as 6 months (see Table 7).

The second and third limitations, paucity of studies supporting the hypotheses and failure to satisfactorily explain variance across studies, are addressed concurrently. Although all of the weighted mean effect sizes were statistically significant, it is likely that they would have been even stronger had more studies been available. Although dearth of available studies did not negate the significance of obtained effect sizes, it did interfere with the ability to explain across study variance that exceeded what one would expect from sampling error alone. Specifically, when conducting correlations to explain this variance, the correlations were often either insignificant or impossible to run as a consequence of having too few studies available to correlate. Additionally, non-significant relationships were moderate to strong and might have reached significance had more studies been available to test the hypotheses. The scarcity of cost-effectiveness studies on clozapine in comparison to conventional (typical) antipsychotics is an area of concern that warrants attention.

Table 7 Pretest/ Posttest Comparisons of Inpatient Psychiatric Hospitalization Costs and Outpatient Costs[a]

| Study ID | Pre-Hosp. Costs | Post-Hosp. Costs | Diff. | Pre-Outpatient Costs | Post-Outpatient Costs | Diff. | Total Savings |
|---|---|---|---|---|---|---|---|
| 3[e] | $51,412 | $34,908 | $16,504 | $5,728 | $9,803 | -$4,075 | $12,429 |
| 6[b] | $51,413 | $48,590 | $2,823 | $1,638 | $2,181 | -$543 | $2,280 |
| 32[d] | $70,569 | $4,082 | $66,487 | $12,683 | $26,573 | -$13,892 | $52,595 |
| 50[c] | $10,945 | $4,746 | $6,199 | $736 | $7,687 | -$6,951 | -$752 |
| 52[c] | $26,548 | $14,484 | $12,064 | $324 | $2,339 | -$2,015 | $10,049 |

a. All dollar values adjusted for inflation to the year 2002.

b. Pre- values assessed immediately after participants started on clozapine; post-values taken 6 months later.

c. Pre-values assessed over the year before clozapine initiated; post-values assessed over the course of first year on clozapine.

d. Pre-values assessed over the two years before clozapine initiated; post-values assessed over the course of the two years after clozapine initiated.

e. Pre-values assessed over the three years before clozapine initiated; post-values assessed over the three years after clozapine initiated.

*Recommendations for Future Research*

Although clozapine significantly decreases the cost of inpatient hospitalization, its effect on outpatient costs needs to be carefully examined. It is evident that outpatient costs do increase, but research needs to be done to determine the level to which the increase occurs. This meta-analysis addressed the issue of outpatient cost increases, however, much still needs to be done. Specifically, the number of studies focusing on clozapine's relationships with psychiatric inpatient hospital utilization and related increases in outpatient service utilization need to increase well beyond what is currently available. In conducting these cost-effectiveness analyses future researchers should strive to meet certain criteria.

Future studies need to address the following issues. A significant problem encountered in this meta-analysis involved deciphering how data were reported. For example, it was often quite difficult to determine what cost entities (e.g., psychiatric care, time in restraints, psychosocial rehabilitation, etc.) went into computing psychiatric inpatient hospital costs. As a consequence of this, standardized measures of costs should be employed to facilitate later comparisons across studies. A second suggestion for future research is that the perspective from which the analyses are being conducted should be clearly defined. If, as in this study, a societal perspective is utilized investigators should strive to include data on costs to such structures as Medicaid and Medicare, as well as rates of jail recidivism by people with schizophrenia, and effects of unemployment among people with schizophrenia. In keeping with clearly identifying perspective, it would also be useful for future researchers to clearly define the costs and benefits of treatments under consideration.

Although this appeared to have been done in the studies included in this meta-analysis, it would be of further use, if when reporting findings researchers included outcomes for all costs and benefits. The final recommendation addresses study designs.

In the past, most studies of cost-effectiveness have utilized retrospective designs. This type of design is most often used by pharmacists who have access to pharmacy and other healthcare databases (Cohen, 1997). Retrospective designs are widely used in managed care settings, in which large patient databases have been compiled and serve as a source of considerable patient information. The advantage of using such a design is it may reveal medicoeconomic trends that are apparent only over a long period of time; such information is useful in estimating the future costs of caring for patients with specific diagnoses. The disadvantages of using retrospective designs are they possess significant potential for selection bias and investigators have little control over the quality of data collection (Cohen). Future research should focus on employing prospective. In prospective studies, participants are followed for the occurrence or nonoccurrence of specified outcomes. Prospective designs allow investigators to establish uniform specifications for observation, as well as, have flexibility in determining which variables will be observed. The disadvantages to using this approach are it tends to be expensive and labor intensive and if the established endpoint rarely occurs, a large number of subjects will be required to obtain statistically significant results. It should be noted that although this is a useful design high numbers of participants are sometimes difficult to obtain without engaging in some type of sample bias. Although this difficulty might be solved by

employing a randomized design, use of such a design is likely to not be ethical with this particular population because they have already demonstrated to be resistant to typicals. In summary, while prospective designs have their limitations, they are more useful than prospective designs.

*Conclusion*

Schizophrenia poses an economic burden to this society in many ways, key among these are high rates of inpatient psychiatric hospital utilization. Although most people with schizophrenia experience inpatient psychiatric hospitalization at some point over their lives, people whose symptoms are refractory to treatment are at greater risk. Clozapine is the only drug to date that offers remediation of the chronic psychopathology (as measured by the BPRS) experienced by people with treatment refractory schizophrenia. The goal of this meta-analysis was to demonstrate clozapine's cost-effectiveness in terms of decreasing inpatient psychiatric hospital utilization over time. Specifically, clozapine's high up front dollar cost may deter healthcare policy decision makers from approving its use for people with treatment refractory schizophrenia. The most salient drawback to withholding clozapine is that people with treatment resistant schizophrenia will likely experience longer and more frequent inpatient psychiatric hospitalizations, which as demonstrated here, are actually more expensive over time than the increased cost of adding clozapine to the person's treatment regimen. As a final comment, it should also be reiterated that although outpatient costs do increase as a result of decreasing inpatient psychiatric hospital utilization, this study also demonstrated that outpatient costs do not negate

savings gained from decreasing inpatient psychiatric hospital utilizations; therefore, clozapine is cost-effective for people with treatment resistant schizophrenia.

# APPENDICES

Appendix A

Studies Entered Into the Meta-Analysis


1. Abraham, G., Nair, C., Tracy, J. I., Simpson, G. M., & Joiassen, R. C. (1997). The effects of clozapine on symptom clusters in treatment-refractory patients. *Journal of Clinical Psychopharmacology, 17*, 49-53.

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## Appendix B

## Coding Scheme

| Name | Type | Width | Decimals | Label | Description |
|---|---|---|---|---|---|
| studyid | Numeric | 2 | 0 | Study ID Number | Enter study id number (1-58) |
| effectsz | Numeric | 3 | 2 | Unstandardized Effect Size | Enter the unstandardized effect size |
| unbiased | Numeric | 3 | 2 | Unbiased Effect Size | Enter the unbiased effect size |
| pubyr | Numeric | 4 | 0 | Publication Year | Enter year, in 4 digits, in which study was published |
| totaln | Numeric | 3 | 0 | Total Sample Size | Total sample size, excluding dropouts |
| nclz | Numeric | 3 | 0 | N Clozapine Group | Number participants in clozapine group, excluding dropouts |

Appendix B (con't)

| Name | Type | Width | Decimals | Label | Description |
|---|---|---|---|---|---|
| ntyp | Numeric | 3 | 0 | N Haldol/ Thorazine Group | Number participants in the haldol/thorazine group, excluding dropouts |
| pmbprscl | Numeric | 6 | 2 | Pre BPRS Mean Clozapine | Average BPRS score (taken just before participants began taking clozapine) |
| psbprscl | Numeric | 5 | 2 | Pre BPRS SD Clozapine | SD of average BPRS value (taken just before participants began taking clozapine) |
| fmbprscl | Numeric | 6 | 2 | Post BPRS Mean Clozapine | Average BPRS value after set period of time on clozapine |

Appendix B (con't)

| Name | Type | Width | Decimals | Label | Description |
|---|---|---|---|---|---|
| fsbprscl | Numeric | 6 | 2 | Post BPRS SD Clozapine | SD of average BPRS value after set period of time on clozapine |
| pmbprsty | Numeric | 6 | 2 | Pre BPRS Mean Typical | Average BPRS value for participants assigned to take haldol/thorazine (taken at same time participants in clozapine group were initiated on clozapine) |

Appendix B (con't)

| Name | Type | Width | Decimals | Label | Description |
|---|---|---|---|---|---|
| psbprsty | Numeric | 6 | 2 | Pre BPRS SD Typical | SD of average BPRS value for participants assigned to take haldol/thorazine (taken at same time participants in clozapine group were initiated on clozapine) |
| fmbprsty | Numeric | 6 | 2 | Post BPRS Mean Typical | Average BPRS value for participants taking haldol/thorazine (taken at same time as participants assigned to take clozapine) |

Appendix B (con't)

| Name | Type | Width | Decimals | Label | Description |
|---|---|---|---|---|---|
| fsbprsty | Numeric | 6 | 2 | Post BPRS SD Typical | SD of average BPRS value for participants taking haldol/thorazine (taken at same time as participants assigned to take clozapine) |
| mdoseclz | Numeric | 6 | 2 | Mean Dose Clozapine | Average dose clozapine participants were taking at the end of respective studies |
| sdoseclz | Numeric | 6 | 2 | SD Dose Clozapine | SD dose clozapine participants were taking at the end of respective studies |

Appendix B (con't)

| Name | Type | Width | Decimals | Label | Description |
|---|---|---|---|---|---|
| lengclz | Numeric | 6 | 2 | Length Time | Length of time between when on Clozapine participants began taking clozapine and the end of the study. (There were no studies where participants had been taking clozapine when the study began.) |
| mdurill | Numeric | 5 | 2 | Mean Duration Ill | Average number of years participants had been ill prior to beginning clozapine |

Appendix B (con't)

| Name | Type | Width | Decimals | Label | Description |
|---|---|---|---|---|---|
| sdurill | Numeric | 5 | 2 | SD Duration Ill | SD of average number of years participants had been ill prior to beginning clozapine |
| mage | Numeric | 5 | 2 | Mean Age | Average age of study participants |
| sdage | Numeric | 5 | 2 | SD Age | SD of average age of study participants |
| nmale | Numeric | 3 | 0 | Total Males | Number males in the study, excluding dropouts (across both groups in the case of comparison group studies) |

Appendix B (con't)

| Name | Type | Width | Decimals | Label | Description |
|---|---|---|---|---|---|
| nfemale | Numeric | 3 | 0 | Total Females | Number of females in the study, excluding dropouts (across both groups in the case of comparison group studies) |

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