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Faculty of Graduate Studies

Prescription Pattern of Antipsychotics in Patients with Schizophrenia in North West-Bank

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Dedication

To my daughters; Mada and Mayar

To my family

Acknowledgment

It is my pleasure to thank the staff members of governmental psychiatric healthcare centers in North West Bank.

الاقرار

أنا الموقع أدناه مقدم الرسالة التي تحمل العنوان :

Prescription Pattern of Antipsychotics in Patients with Schizophrenia in North West-Bank

أقر بأن ما اشتملت عليه هذه الرسالة إنما هي نتاج جهدي الخاص، باستثناء ما تمت الإشارة إليه حيثما ورد، وأن هذه الرسالة ككل، أو أي جزء منها لم يقدم لنيل أية درجة أو لقب علمي أو بحثي لدى أية مؤسسة تعليمية أو بحثية أخرى .

Declaration

The work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name : **اسم الطالب :**

Signature : **التوقيع:**

Date: **التاريخ:**

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List of Abbreviations

Abbreviation	Full Name
APA	American Psychiatric Association
BPRS	Brief Psychiatric Rating Scale
CATIE	Clinical Antipsychotic Trial of Intervention Effectiveness
CPZeq	Chlorpromazine Dose Equivalencies
CUtLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive Therapy
EPS	Extrapyramidal Symptoms
FDA	Food and Drug Administration
FGA	First Generation Antipsychotics
ICD-10	International Classification of Diseases
IPAP	International Psychopharmacology Algorithm Project
MOH	Ministry Of health
NICE	National Institute for Health and Clinical Excellence
PANSS	Positive and Negative Syndrome Scale
PORT	Patient Outcomes Research Team
SGA	Second Generation Antipsychotics
SPSS	Statistical Package for the Social Sciences
SSRIs	Selective Serotonin Reuptake Inhibitors
TMAP	The Texas Medication Algorithm Project
USD	United States dollar
WBC	White Blood Cell
WC	Waist Circumference
5-HT2	5-hydroxytryptamine

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Abstract

Background: Antipsychotic prescription patterns are fundamentally different across countries and even regions due to variations in factors including health care policies, availability and cost of drugs, psychiatric training, and preferred treatment modalities.

Objectives: The objectives of this study were to evaluate the prescribing pattern of antipsychotic drugs and its conformance to international treatment guidelines among patients attending governmental primary healthcare clinics. Furthermore, predictors of antipsychotic prescribing pattern are investigated.

Methods: A cross sectional study at 4 governmental primary psychiatric healthcare centers in northern West-Bank, Palestine was carried out. Patients' medical files were used to obtain demographic, medication and clinical information. International guidelines for schizophrenia were used to create conformance indicators. Descriptive and statistics analysis was conducted using Statistical Package for Social Sciences SPSS 19.

Results: A total of 250 patients were included in the analysis. Mean age of (mean ± SD) the patients was 41.5 ± 10.3 years. A total of 406 antipsychotic agents were used; 348 (85.7%) were form first generation antipsychotics (FGA). The prevalence of antipsychotic combination was 50.4% (n = 126). There was no significant difference in positive (P=0.3), negative (P=0.06) and psychopathology (P=0.5) scores of schizophrenia symptoms among patients on monotherapy versus those on antipsychotic combination. Furthermore, no significant difference was observed in the annual cost of antipsychotic monotherapy versus combination therapy. One hundred and five patients (42%) were using optimum dose (300 – 600 mg CPZeq) while the remaining were using sub or supra therapeutic doses. Regression analysis showed that use of depot, use of anticholinergic agents and use high CPZeq doses were significantly associated with antipsychotic combination.

Discussions and Conclusions: This study indicated that antipsychotic prescribing was not in conformance with international guidelines. Antipsychotic combination was common and has no clinical benefits or economic drawbacks.

Chapter 1

Introduction

1.1 Overview

Schizophrenia is a devastating mental illness that impairs mental and social functioning. In the Arab world and in many other cultures, most people with mental disorders face stigma, discrimination and marginalization **(Kadiri 2005)**. The stigmatization of people who have a mental illness adds to difficulties in their daily life, prevents them from getting access to treatment and care **(Sartorius 2006)**, increases the probability that they will not be offered the treatment they need, or will be offered services that are of inferior quality and insensitive to their needs **(Kadiri 2005)**. Mental health nurse can play an important role in the effective treatment of schizophrenia because they are in a position to recognize the early signs of illness, make referrals to appropriate mental health professionals, help patients and their families cope with the devastating effects of schizophrenia, and encourage a multidisciplinary approach to address all dimensions of the illness.

In the Arab world, mental health services are far away from optimum. There is an urgent need for increased mental health education of the public, psychiatric services, improvement of professional training and the development of mental health services, legislation and policy in all

Arab countries **(Okasha, Karam et al. ; Okasha and Karam 1998; Okasha 2004)**. There is also lack of reliable epidemiological psychiatric data in the Arab world which does not enable rational planning for future psychiatric services, education and research **(Okasha, Karam et al. 2011)** . The Palestinian territories, where this study took place, comprise the West Bank, Gaza Strip and East Jerusalem which are partially governed by the Palestinian National Authority. Since 1967 and until the establishment of the Palestinian National Authority in 1993, the territories were occupied by Israel. In 1993, parts of the Gaza Strip and the West Bank were transferred to the administration of the Palestinian National Authority, becoming Palestinian territories. Palestinian territories are one of the poorest regions in the world. North West-Bank consists of 4 major cities including Nablus, Jenin, Tulkaram, and Qalqilia. Several governmental psychiatric primary health care centers are located throughout West-Bank and Gaza Strip. However, most of these centers are under-staffed and under-resourced **(Afana, Dalgard et al. 2002)**.

To improve psychiatric services, a large number of countries throughout the world have developed their own guidelines for the treatment of schizophrenia **(Gaebel, Weinmann et al. 2005)**. Such guidelines generally acknowledge that there is a lack of evidence to support the routine use of combined antipsychotics except when switching from one antipsychotic to another or augmenting clozapine in treatment-resistant illness **(Buchanan, Kreyenbuhl et al. ; Moore, Buchanan et al. 2007;**

NICE 2011). However, there is an increasing prevalence of antipsychotic drug combination with increased risk of adverse drug reactions **(Botts, Hines et al. 2003; Chong, Tan et al. 2004; Barbui, Nose et al. 2006; Adeponle, Obembe et al. 2007; Barnes and Paton 2011)**.

To identify the status of antipsychotic prescribing in Palestine, prescription pattern of antipsychotics is needed. The need to analyze the prescribing patterns of antipsychotic drugs is not to find blame but to identify areas where regulatory policies can improve prescribing patterns and outcomes. The current study draws a sample of patients with schizophrenia to examine the conformance of antipsychotic drug prescribing in Palestine with international guidelines. Particularly, frequency of antipsychotic combination and maintenance dose will be examined. Furthermore, factors associated with antipsychotic combination, and the clinical and economic impact of antipsychotic combination will be investigated.

1.2 Definition and Epidemiology of Schizophrenia

Psychosis, a disorder characterized by distortion in individual perception of reality and the presence of hallucinations, delusions or disorganized thoughts, is a common disorder with 3 to 5 percent of the general population experiencing related symptoms during their life time

(van Os, Hanssen et al. 2001; Perala, Suvisaari et al. 2007). Psychotic disorders are categorized as schizophrenia, bipolar mania, major depression with psychotic features, schizoaffective disorder, Alzheimer's disease, delirium, brief psychotic disorder, substance induced psychotic disorder, delusional disorder and psychosis secondary to a medical condition **(Jibson and Tandon 1996)**. Schizophrenia is one of the most disabling and challenging psychotic disorders. Schizophrenia affects around 0.3–0.7% of people at some point in their life, or 24 million people worldwide as of 2011 **(WHO)**. The prevalence of schizophrenia varies across the world, within countries, and at the local and neighborhood level **(Jablensky, Sartorius et al. 1992; Kirkbride, Fearon et al. 2006; Kirkbride, Fearon et al. 2007; Kirkbride, Morgan et al. 2007)**. It causes approximately 1% of worldwide disability adjusted life years **(Picchioni and Murray 2007)**. Schizophrenia occurs 1.4 times more frequently in males than females and typically appears earlier in males **(Picchioni and Murray 2007)**. The peak ages of onset of schizophrenia are 20–28 years for males and 26–32 years for females **(Castle, Wessely et al. 1991)**. Onset of schizophrenia in childhood is much rare as is onset in middle- or old age **(Kumra, Shaw et al. 2001; Hassett, Ames et al. 2005)**. The exact cause of Schizophrenia is unknown. It is believed that the risk of schizophrenia is related to genetic and environmental factors **(Mueser and McGurk 2004; Maziade, Rouleau et al. 2009)**. The prevalence of schizophrenia appears to be higher among relatives of people with schizophrenia than among the general

population **(Mueser and McGurk 2004; Drake and Lewis 2005; Maziade, Rouleau et al. 2009)**.

1.3 Diagnosis and Symptoms of Schizophrenia

Schizophrenia is diagnosed based on criteria in either the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, version DSM-IV-TR, or the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, the ICD-10 **(WHO ; APA 2000)**. Both define symptoms and characteristic impairments of schizophrenia in a similar way which improves the inter-rater consistencies of the diagnosis over time **(van Os and Kapur 2009)**.

There are three types of symptoms that help in the definition and diagnosis of schizophrenia. They are: positive symptoms, negative symptoms and cognitive impairment **(Mueser and McGurk 2004; van Os and Kapur 2009)**. Positive symptoms involve a loss of contact with reality, including bizarre behaviors, false beliefs (delusions), or perceptual experiences not shared by others (hallucinations). The presence and severity of these symptoms tends to be episodic over time. Negative symptoms are a lack of or a greatly decreased state of expressing emotions. Examples of negative symptoms could include a lack of facial expression,

pleasure in activities, diminished ability to clearly communicate with others and withdrawal from activities with others. Cognitive impairments can include problems with attention and concentration, learning, memory and executive functions. Impairment in role functioning and/or substantial change in personal behavior are clinical features of schizophrenia. These manifestations may include a reduced ability to work, attend school, have close relations and take care of oneself. Often these symptoms emerge years before the psychotic symptoms **(Mueser and McGurk 2004; van Os and Kapur 2009)**. They can be profound and result in the need for assistance in meeting basic needs, such as: housing, food and medical care. These symptoms can also negatively alter a person's relationship with family and friends. Long-term prognosis for many patients with schizophrenia is poor. It is marked by intermittent acute psychotic episodes and impaired psychosocial functioning between acute episodes, with most of the deterioration in psychosocial functioning occurring within 5 years after the first psychotic episode (Lehman, Lieberman et al. 2004).

1.4 Antipsychotic Agents

Antipsychotic drugs or neuroleptics belong to a larger class of drugs known as psychotropic drugs which consist of antipsychotics, antidepressants, anti-anxiety and hypnotic drugs. Antipsychotic drugs are further subdivided into the conventional or typical antipsychotics and the atypical/ new generation antipsychotic drugs. For the purpose of this thesis, the conventional antipsychotics will be referred to as First

Generation Antipsychotics (FGA) while the newer ones will be referred to as Second Generation Antipsychotics (SGA). Currently, there are six SGA drugs. Clozapine, the first atypical antipsychotic drug, was approved by the Food and Drug Administration (FDA) in 1989. Next was risperidone in 1993, followed by olanzapine and quetiapine in 1996 and 1997 respectively. Ziprasidone was approved in 2001 and finally aripiprazole was approved in November, 2002 **(Firm and Kastrup 2008)**. The following characteristics are generally associated with atypical antipsychotic drugs **(Bunker, Sommi et al. 1996; Markowitz, Brown et al. 1999; Joseph. Dipiro, Robert L. Talbert et al. 2011)**:

1. Less association with extrapyramidal symptoms (EPS) or movement disorders including tardive dyskinesia at doses required to produce an antipsychotic effect.

2. Efficacy against the negative and positive symptoms of schizophrenia.

3. Less effects on elevating prolactin concentration levels.

4. The SGA drugs also have a higher ratio of 5-HT2 to D2 blockade compared to the FGA drugs. Clozapine has all of the attributes of SGA and it is considered the prototype of this group **(Markowitz, Brown et al. 1999)**.

1.5 Safety and Efficacy of Antipsychotic Drugs

Knowledge of the adverse effect profile of antipsychotic drugs is important when treating patients with schizophrenia. Characteristics that differentiate FGA drugs from the SGA drugs lie in the nature and the severity of their adverse effect profile. Conventional FGA drugs have historically been implicated in causing many serious adverse effects that include extrapyramidal symptoms (EPS), and electrocardiogram changes **(Jeste, Linnoila et al. 1982; Firm and Kastrup 2008; Kane and Correll 2010).** The EPS include Parkinsonism, akathesia, acute dystonia and tardive dyskinesia. The first three symptoms occur shortly after treatment while tardive dyskinesia occurs upon chronic use. The EPS which occur in up to 75% of patients treated with conventional antipsychotics (FGA) is believed to be a major cause of non-adherence to medications **(Casey 1995; Barnes and McPhillips 1998)**. The EPS are usually treated with anticholinergic drugs (e.g. trihexyphendyl). However, anticholinergic drugs have misuse potential and can cause delirium **(Buhrich, Weller et al. 2000)**. Other treatment options for EPS include benzodiazepines and propranolol which are associated with adverse effects and contraindication in certain types of patients **(Lewis and Lofthouse 1993; Authier, Balayssac et al. 2009)**.

The SGA drugs provide efficacy with a lower risk of extrapyramidal symptoms and tardive dyskinesia at therapeutic doses **(Jibson and Tandon**

1996; Geddes, Freemantle et al. 2000; Bagnall, Jones et al. 2003; Leucht, Wahlbeck et al. 2003; Lieberman, Stroup et al. 2005; Jones, Barnes et al. 2006). Within the SGA class, the risk of EPS varies. Risepridone show dose-related increase in EPS while Clozapine and Quetiapine show placebo level incidence of EPS across their dosage range **(Peuskens 1995; Gerlach 2002)**.

Conventional FGA drugs and clozapine may cause cardiovascular side effects such as hypotension and orthostasis due to alpha receptor blockade (Haddad and Anderson 2002; Haddad and Sharma 2007). All SGA drugs may cause QTc prolongation especially if they are prescribed above the licensed dosage range **(Dewan and Roth 2004; Lindstrom, Farde et al. 2005; Ozeki, Fujii et al. 2010)**. Atypical antipsychotic drugs, particularly clozapine, may also cause agranulocytosis **(Opgen-Rhein and Dettling 2008)**. Therefore, clozapine is often reserved for treatment of resistant patients because of the risk of agranulocytosis that is associated with its use. The SGA drugs may cause a rare elevation of liver enzymes **(Haddad and Sharma 2007; Hamer and Haddad 2007; Niaz and Haddad 2007)**. Patients on clozapine may experience hyper-salivation particularly at night which is uniquely associated with this antipsychotic **(Perry 2001)**.

There is a growing concern over the metabolic side effects of SGA drugs. Significant weight gain, hyperglycemia, type 2 diabetes and

cardiovascular diseases have been linked with antipsychotic drugs since their introduction **(Casey 1996; Engl, Laimer et al. 2005; Mackin, Watkinson et al. 2005; Correll, Frederickson et al. 2006; Reis 2007; Jufe 2008; Fodor 2011)**. Among SGA drugs, ziprasidone and aripiprazole are the least likely to cause weight gain while clozapine, risperidone and olanzapine have the highest weight gain liability **(Engl, Laimer et al. 2005; Mackin, Watkinson et al. 2005; Correll, Frederickson et al. 2006; Reis 2007; Jufe 2008; Fodor 2011)**. According to a study by Allison et al., clozapine has the highest amount of association with weight gain of the SGA drugs in the United States **(Allison, Mentore et al. 1999)**. The correlation between type 2 diabetes and antipsychotic drugs is well established **(Baptista 2002; Sernyak, Leslie et al. 2002; Lean and Pajonk 2003; Newcomer 2004; Spoelstra, Stolk et al. 2004; Best, Yates et al. 2005; Taylor, Young et al. 2005; Holt and Peveler 2006; Vestri, Maianu et al. 2007; Morrato, Newcomer et al. 2008; Manu, Correll et al. 2012)**. Hyperlipidemia, like type 2 diabetes is another metabolic abnormality associated with SGA drugs **(Meyer 2002; Casey 2004)**. Studies of SGA have shown elevated levels of triglyceride and total cholesterol **(Meyer 2002; Firm and Kastrup 2008)**. All antipsychotic drugs may cause the neuroleptic malignant syndrome **(Pope, Keck et al. 1986; Devinsky, Honigfeld et al. 1991)**. The neuroleptic malignant syndrome could be fatal and it consists of muscle rigidity, hyperthermia, mental status changes, diaphoresis, leukocytosis, tachycardia, and hypertension or hypotension **(Pope, Keck et al. 1986; Devinsky,**

Honigfeld et al. 1991). Antipsychotic drugs, especially clozapine, may increase the risk of seizures and causes more anticholinergic effects such as constipation, urinary retention and blurred vision as well as alpha adrenergic side effects leading to orthostatic hypotension, nasal congestion and sexual dysfunction **(Devinsky, Honigfeld et al. 1991; Firm and Kastrup 2008; Joseph. Dipiro, Robert L. Talbert et al. 2011)**.

1.6 Objectives of the Study

1.6.1 General Objective

1. To investigate and evaluate current prescribing trends of antipsychotic drugs among patients with schizophrenia attending governmental primary psychiatric healthcare centers in Palestine.

1.6.2 Specific Objective

1. To investigate the conformance of prescribing pattern with international guidelines in schizophrenia therapy, particularly the maintenance dose and antipsychotic combination.

2. To investigate the demographic and clinical predictors of antipsychotic drug combination.

3. To assess the severity of symptoms in patients with schizophrenia using PANSS.

1.6.3 Significance of the Study

1. A study of the prescribing pattern of antipsychotic drugs will serve as a baseline data to help policy makers to implement safe and cost effective treatment protocols in Palestinian authority.

2. A review of the literature failed to show studies carried out in Palestine or even in the Arab world regarding antipsychotic drug prescribing in primary care settings. Actually studies and published research in the field of mental health are few in the Arab world. Therefore, a study on the prescribing pattern of antipsychotics will be one of the few in the Arab world.

3. Studies on antipsychotic drug combination have concentrated on institutionalized patient populations where patients are being monitored closely for adverse effects compared to patients in outpatient settings. A study in the primary health care will shed light on the practices made in outpatient basis where monitoring for adverse effects is mostly lacking.

Chapter 2
Literature Review

2.1 Pharmacotherapy of Schizophrenia

There are several guidelines for the treatment of schizophrenia. The most comprehensive review to date examining schizophrenia guidelines was conducted by Moore, 2011 **(Moore 2011).** There are several major and well known guidelines/algorithms for the treatment of schizophrenia: the American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Schizophrenia **(APA 1997)**; the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations **(Lehman, Kreyenbuhl et al. 2004)**; the TMAP antipsychotic algorithm for schizophrenia **(Moore, Buchanan et al. 2007)**; the International Psychopharmacology Algorithm Project (IPAP) **(IPAP 2009)**; and, the Expert Consensus Guidelines **(Expert 1999)**. Additionally, recent studies such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) **(Lieberman, Stroup et al. 2005)**, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) **(Jones, Barnes et al. 2006),** and their comparisons have shed more light on the National Institute for Health and Clinical Excellence (NICE) schizophrenia guideline from the United Kingdom (U.K.) **(NICE 2011)**. Each schizophrenia guideline differs slightly in scope, focus, and goals. For instance, the TMAP antipsychotic algorithm focuses on medication management, whereas the PORT, APA, and NICE guidelines evaluate both

biological and psychosocial interventions. Table 2.1 provides the content areas addressed by the five major schizophrenia guidelines/algorithms. The following points outlines suggested pharmacotherapeutic algorithm for schizophrenia **(Buchanan, Kreyenbuhl et al. ; Moore, Buchanan et al. 2007; Alvarez-Jimenez, Parker et al. 2009; Moore 2011)**:

- Stage 1 of the treatment algorithm applies only to those patients experiencing their first episode of schizophrenia or to patient off of medication and re-entering treatment who don't have a history of non-response or non-tolerance with antipsychotics.

- Stage 2 addresses pharmacotherapy in a patient who had inadequate clinical improvement with antipsychotic agent used in stage 1. Stage 2 recommends an alternate antipsychotic monotherapy with the exceptions of clozapine.

- Stage 3: Because of safety concerns and the need of white blood cell (WBC) monitoring, it is recommended that patients be tried on two different monotherapy antipsychotic trials before proceeding to stage 3 which include a trial of clozapine. Clozapine has superior efficacy in decreasing suicidal behavior, and it should also be considered as a higher treatment option in suicidal patient **(Buchanan, Kreyenbuhl et al**.)**.** Clozapine can also be considered earlier in treatment of patients with a history of violence or comorbid substance abuse (**Moore, Buchanan et al. 2007**).

- Stage 4 of the treatment algorithm includes clozapine and augmentation with FGA, SGA, or electroconvulsive therapy (ECT).

- Stage 5. Includes a trial with a single agent (FGA) or (SGS) that was not tried in stages 1 or 2.

- Stage 6: combination pharmacotherapy intervention are not evidence based and should only be implemented with time limited, careful evaluation of a patient's symptoms response and discontinuation of the combination if improvement does not occur

- If partial or poor adherence contributes to inadequate clinical improvement, the long-acting injectable antipsychotic should be considered.

Augmentation is defined as the addition of a non-antipsychotic drug to an antipsychotic drug. Augmentation agents are rarely effective for schizophrenic symptoms when used alone **(Argo 2008)**. Mood stabilizers like lithium carbonate, valproic acid and carbamazepine have been used for augmentation therapy **(Leucht, Kissling et al. 2004)**. However, the 2009 PORT recommendations do not endorse the use of mood stabilizer augmentation in treatment of medication resistant patients **(Lieberman, Stroup et al. 2005)**. Selective serotonin reuptake inhibitors (SSRIs), particularly fluoxetine and fluvoxamine, have reasonable evidence for improving negative symptoms when used as augmentation of FGAs **(Silver 2003).**

Several standardized psychiatric rating scales are available to assist in objectively rating patient's responses to antipsychotic drug. Such scales include; the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Symptom Scale (PANSS), the four-item Positive Symptom Rating Scale and the Brief Negative Symptom Assessment scales **(Miller, Chiles et al. 1999)**. Similarly, a therapeutic outcome plan should include specific monitoring for the risk of weight gain, diabetes, and lipid abnormalities associated with many of the SGAs **(coference 2004)**.

2.2 Other Drugs Used in the Treatment of Schizophrenia

Several classes of drugs are used as adjunctive therapy to treat either comorbid conditions in schizophrenia or to alleviate adverse effects of the antipsychotic agents. These agents include:

2.2.1 Benzodiazepines

Benzodiazepines are primarily used as adjunctive therapy to antipsychotics in patients experiencing severe anxiety, agitation, or irritability **(Herz and Marder 2002)**. Use of these agents is complicated by their side effects including sedation, ataxia and dependence **(Herz and Marder 2002)**.

2.2.2 Mood Stabilizing Agents

The use of lithium and anticonvulsants are used to improve labile affect and agitation **(Herz and Marder 2002)**. Despite their widespread use, there is limited empirical evidence to support their use in schizophrenia

(Citrome, Jaffe et al. 2002; McElroy and Keck PE 2002). The use of these agents is complicated by their adverse effects that may include weight gain, liver toxicity and enzyme induction **(Citrome, Jaffe et al. 2002; Comparisons. 2003)**.

2.2.3 Antidepressants

Depression is a significant comorbidity in schizophrenia **(Herz and Marder 2002)**. Antidepressants are indicated as adjunctive treatment for patients with comorbid depression, obsessive compulsive disorder or panic attacks **(Herz and Marder 2002)**. The use of these agents may be complicated by overlapping toxicities between the antidepressants and the (SGA).**(Herz and Marder 2002; Comparisons. 2003)**.

2.2.4 Antiparkinson Agents

Agents such as benztropine, procyclidine and trihexyphenidyl are widely used in patients with schizophrenia to prevent or alleviate the extrapyramidal side-effects caused by the antipsychotic agents **(Herz and Marder 2002).**

2.3 Definition of Antipsychotic Drug Combination

The body of literature available on antipsychotic drug combination is steadily increasing. Antipsychotic drug combination is the use of more than one antipsychotic drug at the same time for the same individual **(Tapp, Wood et al. 2003; Ganguly, Kotzan et al. 2004; Sernyak and**

Rosenheck 2004). The types of combinations differ and may include two SGA, an SGA plus a FGA, two FGA or various combinations involving two or more SGA or FGA drugs **(Stahl 1999; Stahl 1999; Botts, Hines et al. 2003; Tapp, Wood et al. 2003; Ganguly, Kotzan et al. 2004; Sernyak and Rosenheck 2004; Kreyenbuhl, Valenstein et al. 2007)**.

2.4 Rationale for Antipsychotic Drug Combination

There are concerns that the risks of antipsychotic combination / polypharmacy are greater than the foreseen benefits. This had led to the recommendation in most evidence-based guidelines that combined antipsychotics should be a strategy of last resort for treatment-resistant psychotic illness **(APA 1997; Lehman, Kreyenbuhl et al. 2004; Miller, Hall et al. 2004; Gaebel, Weinmann et al. 2005; Moore, Buchanan et al. 2007; IPAP 2009; NICE 2011)**. In contrast to such recommendations, studies of antipsychotic drugs report an increase in antipsychotic drug combination **(Tempier and Pawliuk 2003; Gilmer, Dolder et al. 2007)**. Prescription of combined antipsychotics in psychiatry, principally for people with schizophrenia, has been noted since 1960s **(Sheppard, Collins et al. 1969; Ito, Kubota et al. 1999; Keks, Altson et al. 1999; Markowitz, Brown et al. 1999)**. The prevalence of antipsychotic combination has been steady increasing over time and reached 50% in some studies **(Faries, Ascher-Svanum et al. 2005)**.

Most antipsychotic drug combinations are prescribed by physicians with the expectations of being able to lower the dosages of each antipsychotic drug on board and reduce adverse side effects **(Miller and Craig 2002; Stahl 2002; Tapp, Wood et al. 2003; Tapp, Wood et al. 2005; Glick, Pham et al. 2006)**. Based on several reports, physicians' rationale for combining antipsychotic drugs may be summarized as follows **(Sernyak and Rosenheck 2004; Glick and Davis 2006; Correll 2008; Correll 2010)**:

1. To improve therapeutic outcome following the partial or lack of response to antipsychotic monotherapy.
2. Attempt to lower total dose to reduce adverse effects.
3. Use in treatment of refractory patients after adequate trial of monotherapy.
4. Prescriber habit.
5. Patient and family preference.

2.5 Antipsychotic Drug Combination and Outcomes

Despite recommendations to avoid antipsychotic combination (Polypharmacy), **(Clark, Bartels et al. 2002; Stahl 2002; Lehman, Lieberman et al. 2004; Stahl 2004)** and the lack of a convincing pharmacological rationale, co-prescribing antipsychotics has remained a common and widespread practice **(Freudenreich and Goff 2002; Miller**

and Craig 2002; Jaffe and Levine 2003; Faries, Ascher-Svanum et al. 2005). Faries et al, 2005 concluded that for the majority of patients for whom combined antipsychotics were prescribed, it was a continued, deliberate treatment choice rather than a temporary or inadvertent practice **(Faries, Ascher-Svanum et al. 2005)**. Audits and surveys consistently reveal relatively high levels of prescription of combined antipsychotics internationally, in Australia, **(Keks, Altson et al. 1999)**, Canada, **(Procyshyn, Kennedy et al. 2001)**, Finland (Hemminki 1977), France **(Bret, Bonnet et al. 2002; Bret, Bret et al. 2009)**, Germany **(Hamann, Ruppert et al. 2003)**, Italy **(Biancosino, Barbui et al. 2005)**, Japan **(Ito, Kubota et al. 1999; Josiassen, Joseph et al. 2005; Yoshimura, Okamoto et al. 2006)**, China and East Asia **(Yip, Ungvari et al. 1997)**, the Netherlands **(Broekema, de Groot et al. 2007),** the USA **(Remington, Shammi et al. 2001; McCue, Waheed et al. 2003; Essock, Covell et al. 2009)** and the UK **(Paton, Lelliott et al. 2003)**. Data from the USA suggest that the introduction of SGA **(Hermann, Yang et al. 2002)** has been accompanied by a significant increase in the prevalence of SGA **(Freudenreich and Goff 2002; Miller and Craig 2002; McCue, Waheed et al. 2003; Gilmer, Dolder et al. 2007)**. The various surveys carried out internationally reveal variation in the prevalence of the prescription of combined antipsychotics across clinical samples, and across countries, depending, presumably, on the availability and costs of antipsychotic medication as well as local prescribing practice and culture, clinical experience and knowledge of psychopharmacology **(McCombs, Nichol et**

al. 2000; Kingsbury, Yi et al. 2001; Fleischhacker 2003; Sim, Su et al. 2004).

While a number of clinicians have cited antipsychotic drug ineffectiveness and patient noncompliance as the instigating factor for endorsing the use of multiple drugs, there is some evidence that antipsychotic combination could itself increase patient noncompliance **(Stahl 2002)**. Freudenreich and Goff (2002) evaluated studies on antipsychotic drug polypharmacy and analyzed the risks and efficacy of various combinations **(Freudenreich and Goff 2002)**. Adverse drug outcomes have been reported in studies involving the use of clozapine as an add-on to other antipsychotics. Increased prolactin, sialorrhea and tardive dyskinesia were reported in one study **(Shiloh, Zemishlany et al. 1997)**. Other studies of clozapine and risperidone combination resulted in hypersalivation, akathesia, worsened orthostatic hypotension and more compulsive behavior **(Henderson and Goff 1996)**. In another study, Centorrino and colleagues (2004) showed that antipsychotic drug combination can indeed elevate the risk of adverse drug effects leading to an undesirable hospital length of stay with little improvement in clinical outcomes **(Centorrino, Goren et al. 2004)**. The risk of adverse effects in this study was 56% higher in patients receiving combination compared to monotherapy **(Centorrino, Goren et al. 2004)**. Even a more recent analysis by the same authors did not show a clinical advantage to multiple antipsychotic therapeutic agents that are used concurrently **(Centorrino,**

Cincotta et al. 2008). The cost benefit impact of antipsychotic drug combination needs attention. Stahl and colleagues reported (2002) an association between antipsychotic drug combination and higher drug costs in a Medicaid population **(Stahl 2002)**.

2.6 Factors Influencing Physician Prescribing Behavior and Antipsychotic Drugs

Several factors are associated with the antipsychotic prescribing behavior of physicians in a health care system **(Tamblyn 1996; Nolan and Marcus 2000; Alexopoulos, Streim et al. 2004; Goldstein, Need et al. 2007)**. Patient factors that influence physician prescribing decisions include age, height, weight, gender, race, income, education, health status (e.g. presence of other disease characteristics), the use of multiple drugs, patient compliance and patient preferences **(Goldstein, Need et al. 2007)**. In a study by Leslie and Rosenheck (2001), it was indicated that women were more likely to receive lower doses of antipsychotic medications compared to men **(Leslie and Rosenheck 2001)**. Another study showed that women were more likely to be prescribed antipsychotic medications compared to men **(Hermann, Yang et al. 2002)**. Clinical associations with the prescription of an antipsychotic combination regimen have been identified, such as greater use of anticholinergic medication, male sex, poorer symptom control and longer periods spent in hospital **(Procyshyn, Kennedy et al. 2001; Weissman 2002; Jaffe and Levine 2003; Centorrino, Goren et al. 2004; Kreyenbuhl, Valenstein et al. 2007)**.

2.7 Research Questions and Hypotheses

This exploratory study in the outpatient sector was designed to examine three research questions as detailed below:

1. Is the current prescribing pattern of antipsychotic medications in agreement with International guidelines regarding monotherapy?
2. Is the current prescribing pattern of antipsychotic medications in agreement with International guidelines regarding maintenance dose?
3. What are the demographic and clinical factors significantly associated with antipsychotic drug combination?

2.8 The Hypotheses for the research questions

1. There is no difference in the prevalence of antipsychotic combination between this study and reported international studies.
2. The maintenance antipsychotic dose is within the recommended dose.
3. There are no significant factors associated with antipsychotic drug combination.

Table 2.1: Antipsychotic Guideline/Algorithm Recommendations**(Takeuchi, Suzuki et al. 2012)**

Type	**Antipsychotic Guideline/Algorithm Recommendations**					
	Expert 1999	**APA 2004**	**PORT 2004**	**IPAP 2005**	**TMAP 2006**	**NICE 2009**
First Episode	SGA	SGA	SGA,FGA	SGA	SGA	SGA, FGA
Second Choice	SGA	SGA, FGA, Clozapine	SGA, FGA	SGA	SGA, FGA	SGA, FGA
Third Choice	Clozapine	Clozapine	Clozapine	Clozapine	Clozapine	Clozapine
foruth Choice	Clozapine Augmentation	Clozapine Augmentation	-	Clozapine Augmentation, SGA	Clozapine Augmentation	Clozapine Augmentation
Fifth Choice	–	–	–	–	SGA, FGA –	-
Sixth Choice	-	-	-	-	Combinations	-

Chapter 3
Methodology

3.1 Study Design and Site of the Study

A cross sectional study was conducted between August 2011 and February 2012 at governmental primary psychiatric health care centers in Northern West-Bank, Palestine. The centers included in the study were those in Nablus, Jenin, Tulkaram, and Qalqilia.

3.2 Sampling Method and Sample Size

A convenience, non-probability, sampling method was used. To collect the sample, the researcher visited and stayed 2 weeks in each center and collected data from patients who met the inclusion criteria. In order to estimate with sufficient precision the prescribing pattern, particularly, antipsychotic combination, it was hypothesized a worst-case scenario level of antipsychotic combination of about 70%, to be estimated with a 95% confidence interval of 15 percentage points. Therefore, a sample size of at least 134 patients was needed.

3.3 Inclusion Criteria

All patients attending governmental primary psychiatric health centers in Northern West-Bank during the study period were invited to participate. Patients who fulfilled the following inclusion criteria were included in the analysis:

1) Their age was above 16 years old,

2) They were diagnosed with schizophrenia as defined by DSM-IV,

3) They had not been suffering from an acute attack of illness during the past year,

4) Their drug regimen had not been changed in the past 6 months as evident in their medical files.

3.4 Exclusion Criteria

Patients who had the following characteristics were excluded from the study:

1) Newly diagnosed patients

2) Schizophrenic patients who are not on any antipsychotic medication

3.5 Data Collection

Data collection forms was developed to cover all data items needed. The form covered the following areas: socio-demographic details, employment, length of psychiatric history, antipsychotic medications currently being used, and history of psychiatric hospitalization in the past.

3.6 Tested Variables

1. Chlorpromazine Dose Equivalencies (CPZeq)

The CPZeq is a measure of the relative antipsychotic potencies of neuroleptics. They are generally expressed as a ratio, relative to the arbitrary value of 1, which corresponds to the antipsychotic effects of chlorpromazine. For example, an antipsychotic drug with a CPZeq value of 100 would be 100 times more potent than chlorpromazine shown in table 3.1

The daily dose of antipsychotic medication prescribed to each patient was converted to milligram equivalents of chlorpromazine according to conversion factors derived from the literature **(Woods 2003; Xiang, Weng et al. 2008; Joseph. Dipiro, Robert L. Talbert et al. 2011)**. Since the early 1980s, established conversion factors to chlorpromazine have been available for traditional antipsychotic drugs. For second-generation antipsychotics, comparative clinical trials (the basis to establish equivalent dose) are fewer and more controversial. Therefore, we examined various sources, including randomized clinical trials, meta-analyses, and guidelines. A review by woods, (2003) reported that the equivalencies of SGA to 100mg/day of chlorpromazine: risperidone at 2mg/day, quetiapine at 75mg/day, and olanzapine at 5mg/day **(Woods 2003)**. The recommended dose ranges for these second generation drugs are: 2-8mg/day of risperidone, 300-750mg/day of quetiapine, 10-20mg/day of olanzapine, and

150-600mg/day of clozapine **(Woods 2003)**. Daily doses of depot antipsychotics were converted to approximate CPZeq using published guidelines **(Shen 2002; Woods 2003)**.

2. Total CPZeq dose

Total CPZeq was constructed by calculating a total daily dose of each antipsychotic listed in the medical file. Then each converted antipsychotic-specific CPZeq amount is added to arrive at a total dose. A maintenance dose of total CPZeq in the range of 300 – 600 mg is considered optimum .

3. Antipsychotic Combination and monotherapy

The operational definition of antipsychotic drug monotherapy is the use of one antipsychotic drug while antipsychotic drug combination is the use of two or more antipsychotic drugs. Studies of antipsychotic drug prescribing pattern in the medical literature have used various criteria for defining antipsychotic drug combination. In clinical practice, a 30 day period for overlapping two antipsychotic drugs has been used by some clinicians to fully titrate patients from one antipsychotic drug to another. This 30 day period may be seen as appropriate because it takes at least 14 days for most antipsychotic drugs to show a therapeutic effect and it also allows for switching to occur between two antipsychotic drugs during periods of titration. Given this overlap in time between the discontinuation of one antipsychotic drug and the initiation of another antipsychotic drug, the use of two antipsychotic drugs temporarily during the short period of

medication titration from one drug to another is considered as justifiable by some clinicians especially in patients experiencing acute exacerbations who need to be slowly titrated **(Shepski, Wincor et al. 1996; Humberstone, Wheeler et al. 2004; Kreyenbuhl, Valenstein et al. 2007; Gesterman BB, Lundin FE et al. (1990)**. With this understanding, the definition of antipsychotic combination may vary depending on the situation. In our study, since no changes were made in the therapeutic regimen of all patients , thus no patients was on the transitional period of changing or switching from one antipsychotic to another. Therefore, patients who were on combination therapy were actually on 2 or more medications and were not in a transitional phase of discontinuation of one drug and an initiation of another drug.

4. Positive and Negative Syndrome Scale (PANSS)

The Positive and Negative Syndrome Scale (PANSS) is the most widely used measure of symptom severity in schizophrenia **(Kay, Fiszbein et al. 1987; Van den Oord, Rujescu et al. 2006; M. Lader 2000)**. This 30-item scale is typically administered by trained clinicians who evaluate patients' current severity level on each symptom (item) by endorsing 1 of 7 options (weights) numbered 1 through 7. The PANSS has demonstrated high internal reliability **(Kay, Opler et al. 1988; Peralta and Cuesta 1994)** , good construct validity **(Kay, Opler et al. 1988)**, and excellent sensitivity to change in both short term **(Lindenmayer, Kay et al. 1986)** and long term trials **(Kay, Fiszbein et al. 1986)**. However, despite

extensive psychometric research, it is unclear how individual PANSS items differ in their usefulness in assessing the severity of schizophrenia.

Severity of schizophrenia symptoms was evaluated by PANSS or the Positive and Negative Syndrome Scale which was published in 1987 by Stanley Kay, Lewis Opler, and Abraham Fiszbein **(Kay, Fiszbein et al. 1987; Kay, Opler et al. 1988)**. It is widely used in the study of antipsychotic therapy. The PANSS consists of three sections: positive symptoms (7 items); negative symptoms (7 items); and general psychopathology (14 items). Each item has a score from 1 – 7 with the highest scores representing the highest severity. For each section, the total score was calculated by summing the scores for all items in that section. The interview with the patients to assess PANSS was carried out by the author. The author was trained on PANSS by specialist before the start of the study. Each interview took 30 – 35 minutes.

5. FGA versus SGA

For this study, the following drugs were considered FGA: Butyrophenones (Haloperidol, Droperidol); Phenothiazines (Chlorpromazine, Fluphenazine, Perphenazine, Prochlorperazine, Thioridazine, Trifluoperazine, Mesoridazine, Periciazine, Promazine, Levomepromazine, Promethazine, Pimozideand Cyamemazine); and Thioxanthenes (Chlorprothixene, Clopenthixol, Flupenthixol, Thiothixene, Zuclopenthixol). While the following drugs were considered SGA:

Clozapine, Quetiapine, Risperidone, Ziprasidone Olanzapine, Paliperidone,and Clotiapine.

6. Conformance indicators

In order to construct the indicators of conformance, we reviewed several updated guidelines regarding recommendations for maintenance pharmacological treatment of schizophrenia **(Buchanan, Kreyenbuhl et al. 2009; NICE 2011)**. We identified two major recommendations that could be evaluated using a cross-sectional medical chart review, and for which the required information was available in the medical records.

1. The first guideline recommends that the maintenance dosage of antipsychotic medication be in the range of 300 – 600 mg chlorpromazine (CPZ) equivalents per day. Our cross sectional data could not be used to determine whether a patient's current medication was prescribed for acute or maintenance treatment. However, since all patients in the study sample had been ill for a long time and their medications had not been changed since the past six months, we assumed that most patients were on maintenance doses and created a conformance indicator that assessed whether the antipsychotic dosages prescribed for patients were between 300–600 mg CPZ equivalents/day.

2. A second guideline recommends that monotherapy is the preferred and evidence based choice while combination therapy lacks evidence and support. Our cross sectional methodology could not be used to provide

information on whether patients were undergoing a trial of second alternative antipsychotic drug (switching) or not. However, we assumed that all patients were not undergoing switching because their medications have been constant since more than six months. Therefore, we drafted a conformance indicator that examined whether patients were receiving one medication or combination.

7. Cost of antipsychotic regimen

The total annual cost for antipsychotic treatment for each patient was calculated in USD (1 USD = 3.7 NIS at the time of the study). The cost of each antipsychotic drug per dose per unit was obtained from the MOH.

8. Independent Variable

Independent variables include age, gender, number of years of education, place of residence (city, village or camp), marital status (married, single and divorced), smoking, duration of the psychiatric illness, number of psychiatric hospitalizations, body weight (in kilograms), height in (meter), waist circumference (in cm), occupation and family history of diabetes and other chronic illnesses.

3.7 Data Analysis

Descriptive statistics for all study variables were computed. These descriptive statistics included frequencies and percentages for all categorical variables in addition to means, standard deviations and ranges

for all normally distributed continuous variables while median and inter quartile range for continuous variables that were not normally distributed. Variables were tested for normality using the Kolmogorov– Smirnov test. Non-parametric binomial t-test was used to test the difference in the prevalence of antipsychotic combination obtained in this study with those published elsewhere. Statistical significance for intergroup differences was assessed by the Student's t-test for continuous variables. The conventional 5 percent significance level was used throughout the study. Univariate analysis and multiple logistic regression was used to find significant factors associated with antipsychotic combination. All statistical analyses were conducted using Statistical Package for Social Sciences SPSS (**PASW version 19.0**; IBM, Somers, NY) statistical packages for Windows. Table 3.2 shows the research questions, hypothesis to be tested, variables and the analytic technique to be used to test the hypothesis.

3.8 Ethical Consideration

Approval to perform the study was obtained from the Palestinian Ministry of Health and the college of Graduate Studies at An-Najah National University.

Table 3.1 Recommended antipsychotic dosage range for the treatment of schizophrenia.

Antipsychotic medication)	CPZ equivalent dose to 100 mg CPZ (Woods 2003; Buchanan, Kreyenbuhl et al. 2009)	acute therapy dose (mg/day)	Maintenance therapy (mg/day)
Chlorpromazine	100	300-1000	300-600
Haloperidol	2	6-20	6-12
Trifluoperazine	5	15-50	15-30
Thioridazine	100	300-800	300-600
Fluphenazines decanote	13/4weeks	-	2-20
Haloperidol deaconate	40/4weeks	-	2-20
Clozapine	100	150-600	150-600
Olanzapine	4	10-20	10-20
Risperidone	2	2-8	10-20
Quetiapine	75	300-750	300-750

Table 3.2 Type of statistical analysis for each hypothesis and Research Question.

Research Question	Hypothesis	Tested Variables Dependent variable	Analytic technique
Is the current prescribing pattern of antipsychotic medications in agreement with International guidelines regarding Monotherapy/ combination?	There is no difference in the prevalence of antipsychotic combination between this study and reported international studies.	*Independent variable:* prevalence of combination therapy (polypharmacy) in the current study *Test proportion:* Reported prevalence of antipsychotic combination in neighboring countries and international studies.	Non-Parametric Binomial t test.
Is the current prescribing pattern of antipsychotic medications in agreement with International guidelines regarding maintenances dose?	The antipsychotic maintenance dose is within the recommended dose.	*Independent variable:* prevalence of correct maintenance dose *Test proportion:* Correct proportion of the maintenance dose	Non-Parametric Binomial t test.
What are the demographic and clinical predictors of antipsychotic drug combination?	There are not predictors of antipsychotic drug combination.	Independent variables: Mono versus combination therapy *Dependent Variable:* Demographics and other variables	Univariate and regression analysis

Chapter 4

Results

4.1 General demographic characteristics of the study sample

During the study period, 250 clients were included in the study; 68 (27.2%) were female and 182 (72.8%) were male. The mean age of the patients was 41.9 ± 11.8 [95% CI: 40.5 – 43.4] years. Figure 1 shows age categories of the sample while Figure 2 shows distribution of age categories stratified with gender. No significant difference in age was found between male and female patients (40.3 ± 12.4 for females versus 42.5 ± 11.5 years for males; p = 0.2). More than half of the patients came from villages (145, 58%) while the remaining (105, 42%) came from cities or camps. The majority of the patients [213 (85.2%)] had less than school education and more than half (153; 61.2%) were smokers. The majority of the patients (197; 78.8%) were unemployed. More than half (138; 55.2%) of the patients were either unmarried or divorced.

The median duration of illness was 15 years (Q1 – Q3: 9 - 20). The median number of psychiatric hospitalization of the patients during their lifetime was 1 years (Q1 – Q3: 0 – 3). Based on normal values for waist circumference (WC); 56 (82.4%) female patients had WC above the normal value while only 58 (31.9%) male patients had a WC above the normal value. Details regarding basic demographic and clinical characteristics of the patients are shown in Table 4.1.

4.2 Medications used by the study sample

The total number of antipsychotic drugs used by the patients was 406 with a mean of 1.6 ± 0.7 (95% CI: 1.5 – 1.7) per client. The antipsychotics were distributed as follows: 348 from the FGA and 58 from the SGA. The total number of adjuvant medications used by the patients was 249 with an average of 1 ± 0.7 (95% CI: 0.9 – 1.1) medication per patient.

The most common antipsychotic medication used was chloropromazine tablet (128; 31.5%), followed by fluphenazine IM depot injection (125; 30.8%), haloperidol tablet (74; 18.2%), clozapine (35, 8.6%), olanzapine (15, 3.7%), haloperidol decanoate (11, 2.7%), risperidone (8, 2%), trifluperazine (7, 1.7%), thioridazine (1, 0.2%) and zuclopenthixol (2, 0.5%). The most common adjuvant medications used by the patients were: the anticholinergic/ antiparkinsonian drug, trihexyphenidyl (177; 71.1%) followed by antidepressants (29; 11.7%) and mood stabilizers (26; 10.4%) and benzodiazepine (anxiolytics) (17; 6.8%). Frequency of medications used is shown in Table 4.2.

4.3 Conformance to Prescribing Indicators

4.3.1 Antipsychotic monotherapy / combination

One hundred and twenty four patients (49.6%) were using antipsychotic monotherapy while 126 (50.4%) patients were using antipsychotic combination. The various antipsychotic combinations are shown in Table

4.3. The most common combination was "FGA + FGA" (78; 61.9%) followed by "FGA + FGA + FGA" (24; 19%) and "FGA + SGA" (17; 13.5%). The prevalence of antipsychotic drug combination in the current study was significantly higher than those reported in many countries shown in Table 4.4.

Analysis of cost indicated that the average annual cost of antipsychotic medications was 229 ± 202 USD per client (minimum: 48.7; maximum: 1168 USD). The average annual cost in USD per client was greater but not significantly different between patients on monotherapy versus those on antipsychotic combination (217 ± 200.7 USD for monotherapy versus 240.6 ± 203.5 USD for combination therapy; p = 0.4).

One hundred and twenty two patients out of 250 included patients in the study gave consent to undergo the PANSS test. For the 122 patients , the means of positive, negative and psychopathology symptoms score were 21.2 ± 3.6 (95% CI: 20.5 – 21.8), 20.5 ± 4.2 (95% CI: 19.8 – 21.3), and 44.7 ± 7.2 (95% CI: 43.4 – 46) respectively. There was no significant difference in positive (P = 0.3), negative (P = 0.06) and psychopathology symptoms (P = 0.5) scores between patients on Monotherapy and combination therapy shown in Table 4.5.

4.3.2 Antipsychotic maintenance dose

The average CPZeq dose measured in mg for the 250 patients was 436.9 ± 257.6 (95% CI: 403 – 471). No significant difference was found in CPZeq dose between male and female patients (386.8 ± 247.7 mg for females versus 455.5 ± 283.7 mg; P = 0.63).

The average CPZeq for patients receiving FGA only was 467.2 ± 284.2 (95% CI: 427 – 507.5 mg), for those receiving SGA was 216.7 ± 125.7 (95% CI: 172 – 261) and for those receiving FGA and SGA was 496.7 ± 208.7 (95% CI 406.5 – 587). Figure 3 shows the box plot for CPZeq stratified with the type of FGA antipsychotic regimen. Patients on antipsychotic combination had a mean CPZeq of 614.3 ± 267.1 (95% CI: 567.2 – 661.4 mg) while those on monotherapy had a mean CPZeq of 256.6 ±127.5 (95% CI 233.9 – 279.3 mg) ($p < 0.01$). Even among patients who were using FGA only, the mean CPZeq was significantly higher among patients with combination compared with those on monotherapy ($p<0.001$).

Categorization of CPZeq dose showed that 88 (35.2%) patients were using sub-therapeutic doses (<300 mg CPZeq), 105 (42.2%) were using optimum dose (300 – 600 mg CPZeq) and 57 (22.8%) were using supra

therapeutic doses (> 600 mg CPZeq). Only 7 (2.8%) patients were using supra-maximal dose (CPZeq>1000 mg).

4.4 Factors significantly associated with antipsychotic combination

Univariate analysis for antipsychotic combinations is shown in Table 4.6. It showed that antipsychotic combination was a significantly associated with the following variables: smoking (P=0.04), duration of illness (P=0.01), number of psychiatric hospitalization (P = 0.001), use of depot antipsychotic agents (P<0.01), use of anticholinergics (P< 0.01). Multiple logistic regression was used by including all significant variables into the model analysis. Results showed that the following variables are significant predictors of antipsychotic combination: use of depot medications, use of anticholinergic agents and use of total CPZeq > 600 mg show Table 4.7.

Factors that were significantly and positively associated with antipsychotic combination were using anticholinergic agents (P<0.001), using depot psychotropic formulations (P<0.001), overutilization of conventional antipsychotics (P<0.001) as well as prescribing higher doses of antipsychotics (P <0.001).

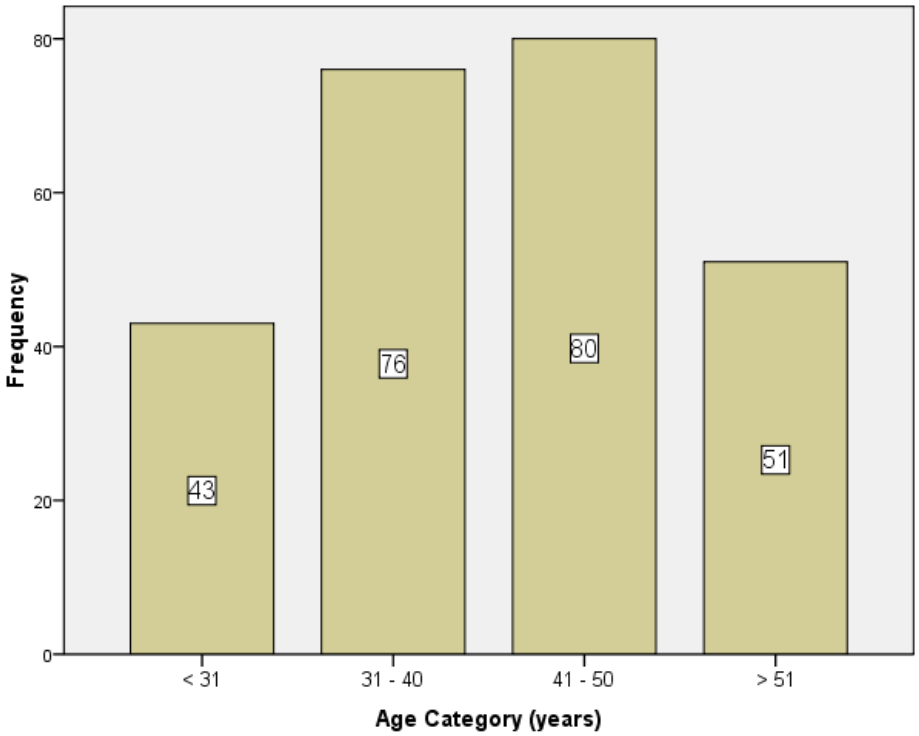

Figure 1 Age categories of the sample

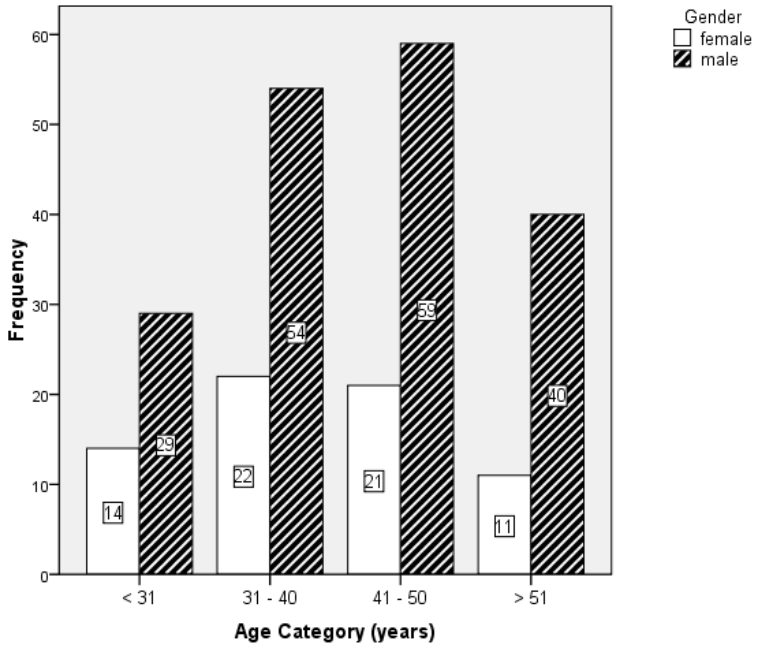

Figure 2 Distribution of age categories stratified with gender

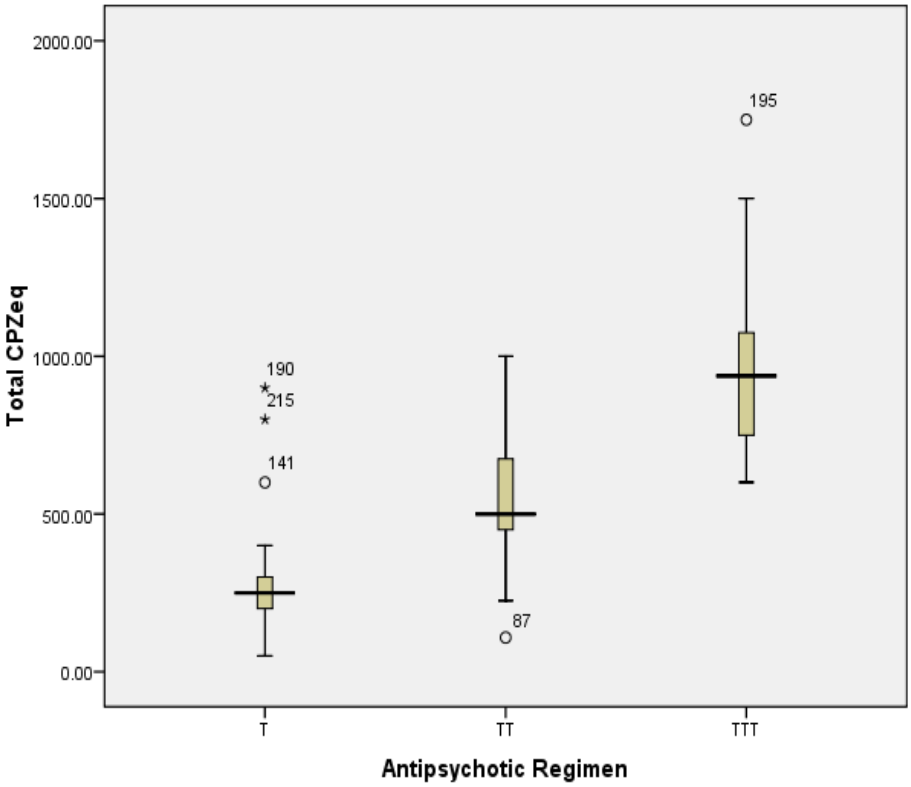

Figure 3 CPZeq for different antipsychotic regimen

Abbreviations: (T Typical , TT Typical+ Typical, TTT Typical+ Typical+ Typical)

Table 4.1 General characteristics of the study sample

Variable	*N* (%) or Median (Q1–Q3) or Mean ±SD
Gender	
- Male	182 (73.8%)
- Female	68 (27.2%)
Age (years)	41.9 ± 11.8
Age category	
- Less than 30	43 (17.2%)
- 30 – 40	76 (30.4%)
- 40 – 50	80 (32%)
- > 50	51 (20%)
Residence	
- City	105(42%)
- Village/ Camp	145 (58%)
Education	
- School education or less	213 (85.2%)
- College education	37 (14.8%)
Marital Status	
- Married	138 (55.2%)
- Single/ Divorced	112 (44.8%)
Smoker	
- Yes	153 (61.2%)
- No	97 (38.8%)
Occupation	
- Not working	219 (87.6%)
- Working	31 (12.4%)
Duration of psychiatric illness (years)	15 (Q1 – Q3: 9 – 20)
- ≤ 10 years	89 (35.6%)
- > years	161 (64.4%)
Number of psychiatric hospitalization	1 (Q1 – Q3: 0 – 2)

Abbreviations: Q1–Q3= lower quartile–upper quartile; SD= standard deviation.

Table 4.2 Antipsychotic and adjuvant medications used in the treatment of schizophrenia

Antipsychotic Medications		**Adjuvant medications**	
Medication	**N (%)**	**Medication**	**N (%)**
Chloropromazine Tablet	128 (31.5%)	Anticholinergic/ Anti-Parkinsonian	177 (71.1%)
Fluphenazine Depot	125 (30.8%)	Anti-depressants	29 (11.7%)
Haloperidol Tablet	74 (18.3%)	Mood stabilizers/ anticonvulsants	26 (10.4%)
Clozapine Tablet	35 (8.6%)	Anxiolytics/ Hypnotics	17 (6.8%)
Olanzapine Tablet	15 (3.7%)	Total	247 (100%)
Haloperidol Depot	11 (2.7%)		
Risperidone Tablet	8 (2.0%)		
TrifluoperazineTablet	7 (1.7%)		
Zuclopenthixol Depot	2 (0.5%)		
Thioridazine Tablet	1 (0.2%)		
Total	406 (100%)		

Table 4.3 Types of antipsychotic regimens used in the treatment of schizophrenia

Category	Frequency (%)
One SGA	32 (12.8)
SGA + SGA	1 (0.4)
SGA + SGA + FGA	1 (0.4)
SGA + FGA	17 (6.8)
SGA + FGA + FGA	4 (1.6%)
One FGA	92 (36.8)
FGA + FGA	78 (31.2)
FGA + FGA + FGA	24 (9.6)
Total	250 (100)

Abbreviations: FGA= First Generation Antipsychotics; SGA= Second Generation Antipsychotic.

Table 4.4 Comparison of prevalence of antipsychotic combination with those reported in other countries.

Country	Prevalence of antipsychotic combination	Current study (Palestine)	P Non- parametric binomial test
South Africa (**Koen, Magni et al. 2008)**	28.6%	50.4%	< 0.01
Nigeria **(Adeponle, Obembe et al. 2007)**	92%		< 0.01
Canada **(Procyshyn, Honer et al. 2010)**	25.7%		< 0.01
China **(y.-t.xiang, y.-z.weng et al. 2007)**	17.6%		< 0.01
USA **(Procyshyn, Kennedy et al. 2001)**	27.5%		<0.01
India **(Ramadas, Kuttichira et al. 2010)**	31%		<0.01

Abbreviation: USA: United States of America

Table 4.5 Comparison of positive, negative and psychopathology scores between patients on Monotherapy and combination therapy.

	Monotherapy	Combination therapy	P value
Positive	20.8 ±3.1	21.5±4	0.3
Negative	19.7±3.8	21.2±4.5	0.06
Psychopathology	44.1±6.3	45.1±7.8	0.5

Table 4.6 Univariate analysis for prescribing monotherapy versus combination therapy.

Variable	Reference Category	β	P value	Odds ratio with 95% CI
Gender	Male	0.43	0.14	1.5 (0.88 – 2.7)
Age	Continuous variable	0.008	0.5	1.0 (1.0-1.03)
Education	School education	0.338	0.4	1.4 (0.7-2.8)
Marital status	Single	-0.2	0.4	0.8 (0.5-1.3)
Smoking	Not smoking	0.45	0.04	1.7 (1.02-2.9)
Occupation	Not working	0.055	0.9	1.1 (0.5-2.2)
Waist circumferences	Normal WC	-0.16	0.5	0.9 (0.52-1.4)
Duration of psychiatric illness	< 10 years	0.7	0.01	2 (1.2-3.4)
Number of hospitalization	< 2	1.02	0.001	2.8 (1.5-5.1)
Family history of DM	No family history	-0.16	0.53	0.9 (0.42-1.4)
Depot	No depot	2.0	< 0.001	7.4 (4.2-12.9)
Anticholinergic	No anticholinergics	1.9	<0.001	6.7 (3.5-12.8)
SGA	No SGA	-0.4	0.2	0.7 (0.4-1.2)
CPZeq	Continuous variable	-5.5	<0.001	1.01 (1.0 – 1.01)

Abbreviations: CI = confidence interval; β = coefficient of predictor variables; DM= diabetes mellitus; SGA= Second Generation Antipsychotic; CPZeq= Chlorpromazine Dose Equivalencies.

Table 4.7 Multilogistic regression for variables significantly associated with prescribing antipsychotic combination.

Variable	β	P value	Odds ratio with 95% CI
Smoker	0.181	0.661	1.199 (0.534-2.692)
Duration of psychiatric illness > 10 years	-0.435	0.327	0.647 (0.271-1.545)
Number of psychiatric hospitalization ≥ 2	0.614	0.229	1.849 (0.679-5.034)
Use of depot antipsychotic agents	1.270	0.002	3.560 (1.572-8.061)
Use of anticholinergic agents	1.336	0.005	3.804 (1.511-9.578)
Total CPZeq	0.010	<0.001	1.010 (1.007-1.013)

Abbreviations: CI = confidence interval; β = coefficient of predictor variables; CPZeq= Chlorpromazine Dose Equivalencies.

Chapter 5

Discussion

This study aimed at investigating the prescribing pattern of antipsychotics in governmental primary psychiatric healthcare centers in northern West-Bank of Palestine. The results of the study showed that antipsychotic combination and use of supra-therapeutic doses are common. Furthermore, the study showed that clinical benefits of antipsychotic combination are not significantly different from those of monotherapy. Predictors of prescribing antipsychotic combination include use of depot antipsychotic medications, use of anticholinergic drugs and receiving a CPZeq dose > 600 mg.

Benchmark levels of conformance to international recommendations of antipsychotic prescribing were reported by several international studies **(Lehman, Buchanan et al. 2003; Owen, Hudson et al. 2008)**. The quality of antipsychotic prescribing is usually complicated by the nature of the disease which makes the patients at risk of inadequate care or even neglect **(Lehman 1998; McAlpine and Mechanic 2000; McNulty, Duncan et al. 2003)**. In this study, we developed 2 indicators to measure conformance and appropriateness of antipsychotic prescribing with treatment guidelines for patients with schizophrenia: (1) the antipsychotic monotherapy and (2) antipsychotic maintenance dosing. The rationale behind the development of

indicators of conformance of prescribing is that such indicators will maximize positive therapeutic outcomes. Accordingly, measuring the gap between clinical practice and recommended guidelines is useful in assessing the quality of care delivered to schizophrenic patients without the need to evaluate patient outcomes **(Norcini 2003)**. The conformance indicators that we have developed and used in this study represented a minimal set of requirements needed for the care of patients with psychosis.

Many authors have reviewed the literature regarding the practice of combination and have generally concluded that antipsychotic combination has little support in the medical literature **(Gibson A, Patel NC et al. 2008)**. The NICE guideline does recognize that antipsychotic combination should only be considered after a failed period of monotherapy (this would usually encompass a failed trial of clozapine) **(NICE 2011)**. Interestingly, one study examined previous clozapine prescription in those on polypharmacy and surprisingly found that only 4% had been given a trial of clozapine before being commenced on combination **(Miller and Craig 2002)**. This finding suggests that antipsychotic combination is being considered earlier in a patient's management plan and is not being reserved for truly treatment-resistant cases.

Different methodologies have been used to assess the prescribing appropriateness. The results in this study showed that antipsychotic combination and use of supra-therapeutic doses are common. Rates of

combination antipsychotic vary across studies. In the US, rates of antipsychotic combinations used to vary between 13% in outpatient clinics and 50% in inpatients **(Freudenreich, Henderson et al. 2007)**. Another study in USA indicated that about a third (35.7%) of the patients were treated predominately with monotherapy (>300 days), 26.9% were treated predominately with combination (>300 days) and 30.2% had a mix of both substantial monotherapy and combination treatment periods (61– 300 days of each) **(Faries, Ascher-Svanum et al. 2005)**. The frequency of antipsychotic combination in two Chinese populations was approximately 17% while in Japan and other East-Asian countries_was 90% and 45%, respectively **(Sim, Su et al. 2004; Xiang, Weng et al. 2007)**. In United Kingdom 17.4 % of the antipsychotic prescriptions were in the context of combination **(Ranceva, Ashraf et al. 2010)**. In Jordan the rate of antipsychotic combination among psychiatric in-patients was 97.8%**(Alshara, Al-Shareef et al. 2010)**. These discrepancies in prevalence of antipsychotic combination across studies may be accounted for by differences in the definition of antipsychotic combination. Although most studies defined combination as any time with more than one antipsychotic **(Xiang, Weng et al. 2007; Satake, Hazama et al. 2011)**, others have set specific time requirements, such as at least 14 days of concurrent antipsychotic use **(Ganguly, Kotzan et al. 2004)**. Moreover, differences in study methods can generate different results too **(Faries, Ascher-Svanum et al. 2005; Xiang, Weng et al. 2007; Kahiloğullari, Örsel et al. 2008)**.

Regarding antipsychotic dosing, only 43% of patients in this study received the recommended antipsychotic maintenance dose of 300–600 mg CPZ equivalents, while 26% received doses below that recommended by treatment guidelines and 32% received above the recommended doses. Similar results were reported in the PORT evaluation **(Lehman and Steinwachs 1998)** where 29.1% of patients had antipsychotic doses within the recommended range; 31.9% above and 39.1% below. In the VA clinic study **(Chen, Nadkarni et al. 2000)** Chen et al. (2000) found 53% of patients received antipsychotic doses within a range of 300–1000 mg CPZ equivalents, 42% below 300 CPZeq and 5% above 1000 mg CPZeq. Similarly, 8% of our patients were receiving antipsychotic doses above 1000 mg CPZeq; 9 of these 14 patients were on clozapine.

A major complication when comparing antipsychotic combination with monotherapy is the large number of antipsychotics which make the possibilities for combination prescriptions vast and the number of trials required to examine the efficacy of all possible combinations would be large. Therefore, there are only a small number of randomized controlled trials comparing clinical benefits of antipsychotic monotherapy with combination therapy. Some studies have shown clinical benefits of combination therapy. One such trial compared clozapine alone versus combination of clozapine and risperidone in the management of severe treatment-resistant schizophrenia. Forty patients were studied over a 12-week period and an improvement in negative and positive symptoms of

schizophrenia without increased rates of agranulocytosis, weight gain or seizures was seen. The authors concluded that the 'combination appeared to be safe and well tolerated' while also 'improving the overall symptoms – both the positive and negative' **(Josiassen, Joseph et al. 2005)**. Another study examined the combination of sulpiride and clozapine and again showed a benefit of combination therapy in a small subgroup of patients **(Shiloh, Zemishlany et al. 1997)**. In this study no increase in extrapyramidal side-effects was reported in the subgroup receiving combination therapy, but problems with hyperprolactinaemia were reported. However, the rates and severity of hyperprolactinaemia were similar to those seen in studies looking at sulpiride alone, and were therefore not thought to be related to the addition of clozapine. Conversely, the evidence of efficacy of antipsychotic combination is not all favorable. One study compared olanzapine monotherapy to olanzapine combined with sulpiride and found no significant difference in positive or negative symptoms **(Kotler, Strous et al. 2004)**. Other studies examining the combination of risperidone and clozapine showed no significant improvement in positive or negative symptoms but did show increased rates of sedation, akathisia, hyperprolactinaemia and elevated fasting blood glucose **(Anil Yagcioglu, Kivircik Akdede et al. 2005; Honer, Thornton et al. 2006; Gibson A, Patel NC et al. 2008)**. A further study looking at combination of FGA and SGA found that there was little evidence of an improvement in outcome and there was a significant increase in adverse effect burden **(Taylor 2002)**. Another study found that use of combination

antipsychotic agents was associated with an increased incidence of metabolic syndrome, although the increased incidence could not be solely related to antipsychotic usage and was also linked to clinical and demographic factors **(Correll, Frederickson et al. 2007)**. These studies have all added to the uncertainty regarding the efficacy of antipsychotic polypharmacy, and the *BNF* states that the 'prescribing of more than one antipsychotic at the same time is not recommended and may constitute a hazard' **(British Medical Association 2008)**.

Many experts have suggested adding a stronger dopamine receptor antagonist for those who continue to experience problematic positive symptoms **(Sernyak and Rosenheck 2004)** . Gibson et al examined possible antipsychotic combinations which could be beneficial based upon pharmacological factors and named four potentially beneficial combinations, namely clozapine plus olanzapine, aripiprazole plus quetiapine, quetiapine plus olanzapine, and aripiprazole plus loxapine **(Gibson A, Patel NC et al. 2008)**.These combinations are thought to have a more potent effect on the D_2 receptor than would be seen with each drug used in isolation, thus in theory improving the symptoms of schizophrenia.

As in Covell et al. (2002), our logistic regression did not find patient age and gender to have an impact on antipsychotic drug combination. This is contrary to the results of **(Ganguly, Kotzan et al. 2004; Kreyenbuhl, Valenstein et al. 2007)**. that showed an increase in antipsychotic

combination among male patients. Equivocally, **(Chakos, Glick et al. 2006)** saw an increase in antipsychotic combination among female patients. Based on this study, there was no significant association between any socio-demographic variables and prescription pattern (monotherapy vs. polypharmacy). Moreover, we found that antipsychotic combination regimen was not associated with better patients' clinical outcome compared to antipsychotic monotherapy regimens; even though patients on antipsychotic combination received significantly higher CPZeq daily doses of antipsychotics, larger number of adjuvant anticholinergic psychotropic medications, overutilization of conventional antipsychotics agents and overutilization of typical antipsychotics in its depot formulation.

A number of randomized clinical trials comparing patients on antipsychotic monopharmacy using clozapine with patients on antipsychotic combination using clozapine and respiridone concerning clinical outcomes were done and their results varied. For example, Josiassen (2005) found that antipsychotic combination using the later combination was more effective at symptoms reduction than antipsychotic monotherapy using clozapine **(Josiassen, Joseph et al. 2005)**. Freudenreich (2007), Honer (2006) and kotler (2004) found that there was no difference between antipsychotic combination (clozapine + risperidone) and antipsychotic monotherapy (clozpaine) in symptoms improvement on Positive and Negative Symptom Scale (PANSS) **(Kotler, Strous et al. 2004; Honer, Thornton et al. 2006; Freudenreich, Henderson et al.**

2007). Furthermore, Honer et al., (2006) observed that antipsychotic combination led to greater worsening on verbal working memory compared to antipsychotic monotherapy **(Honer, Thornton et al. 2006)**. In addition , a double blind randomized control trial found no significant change in symptoms observed with antipsychotic monotherapy augmentation on BPRS **(Shim, Shin et al. 2007)**. On the other hand, an observational study of amisulpride added to clozapine for psychosis unresponsive to clozapine monotherapy observed that clozapine combination led to greater improvement in symptoms on BPRS **(Agelink, Kavuk et al. 2004)**.

Concerning daily antipsychotic dosages and prescription pattern, Kreyenbuhl et al, (2007) observed that dosages prescribed for patients receiving polypharmacy were the same or modestly higher than those prescribed for patients receiving monotherapy **(Kreyenbuhl, Valenstein et al. 2007)**. Another study observed that CPZeq dose of patients on antipsychotic combination was significantly higher than those on antipsychotic monotherapy which was in accordance with our findings **(Hayhurst, Drake et al. 2010)**. Also Barnes TR 2011 found that polypharmacy is a major contributor to high dose prescribing **(Barnes and Paton 2011)**. Our finding regarding the association between anticholinergic agents use and antipsychotic combination appear consistent with previous studies and it may be partly accounted for by the expected higher occurrence of EPS in the antipsychotic combination group and partly by

the attempt to prevent the anticipated EPS in patients receiving antipsychotic combination **(Xiang, Weng et al. 2007; Hong and Bishop 2010; Xiang, Wang et al. 2011)**. However, there are risks beyond the continuous use of anti-cholinergic agents such as memory impairment, delirium and reverse the effect of atypical antipsychotics on cognitive deficit **(Xiang, Weng et al. 2007)**. Our finding concerning the association of antipsychotic combination with overutilization of depot conventional antipsychotic was also proofed by other studies. Researchers found that antipsychotic combination was associated with more use of depot antipsychotics, anticholinergic drugs and doses of antipsychotics compared with patients on antipsychotic monotherapy **(Xiang, Weng et al. 2007; Xiang, Weng et al. 2008)**.

5.1 Strength and limitations of the study

This study is considered the first of its type and one of the few in mental health services in Palestine. Several healthcare centers were included in the study and a relatively good sample size was obtained. However, this study has few limitations. The cross sectional design of the study limits interpretation of the results. Most variables used in this study relied on information obtained from medical files which are subject to errors. Another limitation of the study is the short period during which the data were collected. This might have limited the detection of the full picture of prescribing pattern. The comparison made between the results

obtained in this study with those published in other studies is limited by the fact that different researchers have different methodology and different operational definition of the antipsychotic combination. Although, this study showed that antipsychotic combination is common, but further studies are required to investigate the real intentions of the physician and whether prescribing of the combination is preceded by failure trails of Monotherapy. Furthermore, more research is required to characterize the benefits and risks of antipsychotic combinations using different clinical tools of psychiatric assessment.

5.2 Conclusion and recommendation

Finally, in conclusion, a gap exists between national treatment recommendations for schizophrenia and current practice in community mental health centers, and prescribing pattern in this study was not in accordance with guidelines. Guidelines are designed to improve quality of care, thus educational interventions are important for physicians working in psychiatry regarding current guidelines for schizophrenia treatment.

Concern over the use of antipsychotic combination strategies is both a clinical and a political dilemma as policy makers struggle with the lack of evidence base for justifying the effectiveness and cost effectiveness of these combinations.

Clinicians have to take into account important consideration when choosing an antipsychotic for an individual patient and when screening and monitoring for physical problems. It will be a task for further guideline revision to develop explicit algorithms for differential drug indications depending on the individual symptom profile and risk status concerning potential side effects such as new-onset DM, weight gain, hyperlipidemia, or sexual and cardiac dysfunction.

Furthermore, psychiatric rehabilitation strategies should be designed to enable people to compensate for, or eliminate, the environmental and interpersonal barriers as well as the functional deficits created by a disability related to this illness. The goal of rehabilitation is to recover meaning and value in one's life through work, education, and socializing, as well as increased autonomy.

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Appendices

السلطة الوطنية الفلسطينية
وزارة الصحة- نابلس
الإدارة العامة للتعليم الصحي

Palestinian National Authority
Ministry of Health - Nablus
General Directorate of Higher & Continuing Education

الرقم: ٢٠١١/٩٧٠/٠٢٤
التاريخ: ٢٠١١/٠٥/٠٢

Ref.: .....
Date: .....

الأخ مدير عام الرعاية الصحية الأولية والصحة العامة المحترم،،،

تحية واحترام،،،

الموضوع: تسهيل مهمة طلاب – جامعة النجاح الوطنية

تماشياً مع سياسة وزارة الصحة المتعلقة بتعزيز التعاون مع الجامعات والمؤسسات الأكاديمية بإتاحة فرص التدريب أمام الطلبة والخريجين والباحثين في المؤسسات الوطنية وإسهاماً في تنمية قدراتهم.

يرجى تسهيل مهمة طلاب ماجستير الصحة النفسية/ جامعة النجاح الوطنية التالية اسماؤهم بعمل مقابلات مع مرضى الصحة النفسية في عيادات (طولكرم، نابلس، قلقيلية، جنين) وسحب دم لمرضى الفصام العقلي:

1- سامي شاكر العيويني	**Among prevalence of dyslipidemia schizophrenic client in northern West Bank**
2- هشام زاهر زهران	**Blood profile of selected schizophrenic client in northern Palestine**
3- صلاح علي دلال	**Prevalence & imperial glucose resolution (IGR) among schizophrenic client**
4- جهاد محمد يتي عودة	**Prescribing pattern of antipsychotic schizophrenic client in northern Palestine**

- شريطة
- موافقة المرضى أو ذويهم.
- الحفاظ على سرية معلومات المرضى
- موافاتنا بنسخة من نتائج البحث.

مع الاحترام،،،

الدكتور سعيد الهموز
مدير عام التعليم الصحي

وارد
2011

نسخة/ الأخ نائب الرئيس للشؤون الأكاديمية المحترم- جامعة النجاح الوطنية.

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An-Najah
National University
Faculty of Graduate Studies
Dean's Office

جامعة
النجـــاح الوطنية
كلية الدراسات العليا
مكتب العميد

التاريخ : 2011/5/18

حضرة الدكتورة عايدة القيسي المحترمة
منسق برنامج ماجستير تمريض الصحة النفسية المجتمعية

تحية طيبة وبعد،

الموضوع : الموافقة على عنوان الاطروحة وتحديد المشرف

قرر مجلس كلية الدراسات العليا في جلسته رقم (235)، المنعقدة بتاريخ 2011/5/12، الموافقة على مشروع الأطروحة المقدم من الطالب / جهاد محمد بني عودة، رقم تسجيل 10953995، تخصص ماجستير تمريض الصحة النفسية المجتمعية، عنوان الأطروحة:

(نمط وصف أدوية الشيزوفرينيا عند مرضى الشيزوفيرنيا في شمال الضفة الغربية)
(Prescription Pattern of Antipsychotics in Patients with Schizophrenia in North West Bank)

بإشراف : 1) د. وليد صويلح 2) د. انسام صوالحه

يرجى اعلام المشرف والطالب بضرورة تسجيل الاطروحة خلال اسبوعين من تاريخ اصدار الكتاب، وفي حال عدم تسجيل الطالب/ة للاطروحة في الفترة المحددة له/ا ستقوم كلية الدراسات العليا بإلغاء اعتماد العنوان والمشرف.

وتفضلوا بقبول وافر الاحترام ،،،

عميد كلية الدراسات العليا

25 -05- 2011

د. محمد أبو جعفر

نسخة : د. رئيس قسم الدراسات العليا للعلوم الطبيعية المحترم
: ق.أ.ع. القبول والتسجيل المحترم
: مشرف الطالب
: الطالب
: الملف

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An-Najah
National University
Faculty of Medicine

بسم الله الرحمن الرحيم

جامعة
النجاح الوطنية
كلية الطب

IRB Approval letter

Study title:
Prescription pattern of antipsychotics in Patients with schizophrenia in North West-Bank

Submitted by:
Jihad M. Bani Odeh

Date Reviewed:
Jan 8, 2012

Date approved:
Feb 13, 2012

Your study titled" Prescription pattern of antipsychotics in Patients with schizophrenia in North West-Bank ". Was reviewed by An-Najah National University IRB committee & approved on Feb 13, 2012

IRB

Samar Musmar,MD, FAAFP
IRB Committee Chairman,
An-Najah National University

نابلس - ص.ب ٧٠٧,٧ هاتف: ٠٩/٢٣٤٢٩٠٢/٤/٧/٨/١٤ (٠٩)(٩٧٢)، فاكسميل ٢٣٤٩٧٣٩(٠٩)(٩٧٢)
Nablus - P.O.Box 7,707 - Tel. (972)(09)2342902/4/7/8/14 - Facximile (972)(09)2349739
Web Site:www.naiah.edu

Data collection sheet

NO.....

Diaphragmatically Data

1. Name .....
2. Age: .....
3. Location ☐ City ☐ Village ☐ Camp .....
4. Education ☐ Elementary ☐ Secondary ☐ Diploma ☐ B.A
5. Material Status: ☐ Married ☐ Single ☐ Divorce
6. Smoker ☐ yes ☐ no
7. Occupation: ☐ employee ☐ labor ☐ non
8. Type of job: .....
9. File number in clinic.....

Physical Data:

- Weight .....
- Height .....
- Waist circumstances: .....
- BP.....

History of Mental Illness:

1. Diagnosis .....
2. Duration of the disorder.....
3. How many times admitted to hospital.....

Medical history for clients and family:

1. .....
2. .....
3. .....
5. Any body in family have DM (Yes, No).
6. Any body in family have problem in lipid (Yes, No).
7. Any body in family have problem in renal function (Yes, No).
8. Do you take any antibiotic now (Yes, No).

Drug profile:

Drug Name	Strength	Route	Frequency	Duration

جامعة النجاح الوطنية

كلية الدراسات العليا

نمط وصف أدوية الشيزوفرينيا عند مرضى الشيزوفرينيا في شمال الضفة الغربية

إعداد

جهاد محمد بني عودة

أشراف

أ.د. وليد صويلح

د. انسام صوالحة

قدمت هذه الأطروحة استكمالاً لمتطلبات درجة الماجستير لتخصص تمريض الصحة النفسية المجتمعية بكلية الدراسات العليا في جامعة النجاح الوطنية في نابلس – فلسطين .

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نمط وصف أدوية الشيزوفرينيا عند مرضى الشيزوفرينيا في شمال الضفة الغربية

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الملخص

الخلفية: يختلف نموذج وصف الدواء لمرضى الشيزوفرينيا باختلاف الدول والمناطق ويعزى هذا الاختلاف إلى عوامل عدة تتضمن السياسات الصحية، سعر الدواء وتوفره، تأهيل الكادر الصحي والأنظمة الصحية المفضلة.

الأهداف: تهدف هذه الدراسة الى تقييم نمط الوصفات الطبية لمرضى الشيزوفرينيا ومدى مطابقتها لمباديء التوجه العالمي للمرضى الذين يتلقون خدمات طبية حكوميه وكذلك تم الاستقصاء والتنبؤ عن الوصف الدوائي لهم.

منهج البحث: تم أخذ عينة قطعية من أربع مراكز صحية عاملة في شمال الضفة الغربية، وذلك باستخدام ملفات المرضى وجمع المعلومات السريرية والديموغرافية والمرضية. تم اعتماد التوصيات العالمية لمرضى الشيزوفرينيا للبحث عن مؤشرات تماثلية معها. وتم التحليل الوصفي والإحصائي باستخدام الرزم الإحصائية للعلوم الاجتماعية (SPSS – 19).

النتائج: أشارت نتائج الدراسة لـِ 250 مريض متوسط أعمارهم بين 41.5 ± 10.3 أن الأدوية المستخدمة من قبل المرضى الذين شملتهم الدراسة كان عددها 406، وجد أن 348 (85.7%) دواء كان من الجيل الأول (FGS). كما أن مدى انتشار التعاطي لأكثر من دواء كان (50,4%) من مجموع 126 مريض. لم تجد الدراسة أي فارق معنوي للأعراض الموجبة عند مستوى الدالة (P=0.3) وكذلك السالبة عند مستوى الدالة (P=0.06) والأعراض المرضية النفسية الأخرى عند مستوى الدالة (P=0.5) من مجموع علامات أعراض مرضى

الشيزوفرينيا الذين يتلقون علاجاً واحداً مقارنة بالذين يتلقون أكثر من علاج. بالإضافة إلى أنه لم يلاحظ أي فارق معنوي في السعر السنوي للذين يستخدمون دواءً واحداً مقارنة بمن يستخدم أكثر من دواء.

وجدت الدراسة أن 105 مرضى (42%) يستخدمون الجرعة المثلى لدواء الكلوروبرومازين (CPZeq)، (300–600 ملغم)، أما المتبقون من المرضى فيستخدمون الجرعات الكبيرة والأكبر للدواء. كما أظهر التحليل الإحصائي دلالة معنوية واضحة لاستخدام الحقن العضلي الشهري للأدوية المضادة للكولين والجرعة العالية للكلوربرومازين (CPZeq) للمرضى الذين يتلقون اكثر من دواء.

المناقشة والاستنتاجات: لقد أشارت نتائج الدراسة إلى عدم توافق الوصف الدوائي لمرضى الشيزوفرينيا مع التوصيات العالمية. كما أن شيوع استخدام أكثر من دواء لم تكن له أي منافع طبية أو مردوداً اقتصادياً.