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Assessment of Liver and Kidney Functions in Patients Receiving Antipsychotic and Antiepileptic Drugs in Gaza

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بناءً على موافقة عمادة الدراسات العليا بالجامعة الإسلامية بغزة على تشكيل لجنة الحكم على أطروحة الباحثة/ رئيسة خالد رباح المصري لنيل درجة الماجستير في كلية العلوم قسم العلوم الحياتية-تحاليل طبية وموضوعها:

Assessment of Liver and Kidney Functions in Patients Receiving Antipsychotic and Antiepileptic Drugs in Gaza

وبعد المناقشة التي تمت اليوم الاثنين 26 شعبان 1433هـ، الموافق 2012/07/16م الساعة التاسعة والنصف صباحًا بمبنى طيبة، اجتمعت لجنة الحكم على الأطروحة والمكونة من:

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واللجنة إذ تمنحها هذه الدرجة فإنها توصيها بتقوى الله ولزوم طاعته وأن تسخر علمها في خدمة دينها ووطنها.

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Assessment of liver and kidney functions in patients receiving antipsychotic and antiepileptic drugs in Gaza.

Abstract

Background: many drugs affect liver and kidney functions, among these, drugs used to treat psychotic patients such as chlorpromazine (CPZ) which is used to treat schizophrenia and Trihexyphenidyl- hydrochloride (T.H.P) which is used to treat side effect of antipsychotic medication, another drug which is used to treat epilepsy is valproic acid (VPA) which may affect the liver and kidney functions.

Objective: This study aims at assessing liver and kidney functions in patients receiving antipsychotic and antiepileptic drugs for more than one year .

Materials and methods: The present study is a case control study comprised of 220 subjects including 110 psychiatric and epileptic patients from Mental health clinics in Gaza and 110 healthy people as a control group. Experimental work was done by using five ml blood were collected from each subject into vacutainer plain tubes. Serum Gamma glutamyltransferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), Serum urea, creatinine, uric acid, alkaline phosphatase (ALP), serum total and direct bilirubin (TB, DB) were assayed biochemically using biosystem autoanalyze. Spss was used to analyze obtained data.

Results: The liver and kidney function tests among epileptic patients receiving Valproic Acid (VPA) showed high statistically significant differences between cases and control groups with respect to AST test. While liver and kidney function tests in psychiatric patients suffered from schizophrenia receiving chlorpromazine (CPZ) with Trihexyphenidyl hydrochloride (T.H.P) showed, significant differences between cases and control group in relation to AST, ALP, GGT, DB , creatinine and uric acid tests

Keywords: liver & kidney function tests , antipsychotic & antiepileptic drugs, Gaza, Palestine

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تقييم وظائف الكبد والكلى لدى المرضى النفسيين ومرضى الصرع في غزة

مستخلص الدراسة

المقدمة: هناك العديد من الأدوية التي تؤثر على وظائف الكبد والكلى، منها الأدوية التي تستخدم لعلاج المرضى النفسيين مثل كلوربرومازين الذي يستخدم لعلاج انفصام الشخصية، وترايهكسفينديل هيدروكلوريد و الذي يستخدم لعلاج الآثار الجانبية للأدوية النفسية، و دواء حامض الفالبرويك الذي يستخدم لعلاج الصرع.

الهدف: تقييم وظائف الكبد والكلى لدى المرضى النفسيين ومرضى الصرع الذين يتعاطون الادوية لأكثر من سنة.

الطرق والأدوات: هذه الدراسة مكونة من 220 شخصاً من بينهم 110 مريضًا مصابون بالصرع والمرض النفسي تم تجميعهم من عيادات الصحة النفسية في غزة، و110 شخصاً سليماً كعينة ضابطة. وقد تمت الفحوصات المخبرية لهذه الدراسة بسحب 5 مل دم من كل مريض وإجراء عليها فحوصات الكبد والكلى بواسطة تقنية التحليل الالى، وتم استخدام برنامج Spss فى تحليل البيانات التى حصلنا عليها.

النتائج : أظهرت فحوصات الكبد والكلى لدى مرضى الصرع الذين يتناولون حامض الفالبرويك ارتفاع في فحص الأسبرتيت أمينوترانسفيريز، عند مقارنته بنتائج العينة الضابطة وهذا الارتفاع ذو دلالة إحصائية، بينما لا يوجد أي دلالات إحصائية في الفحوصات الأخرى مثل الجاما جلوتميل ترانسفيرز، والألنين أمينوترانسفيريز، واليوريا، والكرياتنين، و حامض اليوريك ، والالكالين فوسفتيز، والبليروبين الكلى والمباشر.

وأظهرت فحوصات الكبد والكلى لدى المرضى النفسيين الذين يعانون من مرض انفصام الشخصية الذين يتناولون علاج الكلوربرومازين مع ترايهكسفينديل هيدروكلوريد انه يوجد ارتفاعات في فحوصات الجاما جلوتميل ترانسفيرز، والأسبرتيت أمينوتراتسفيريز، والكرياتنين، و حامض اليوريك ، والألكالين فوسفتيز، والبليروبين المباشر، عند مقارنتها بنتائج العينة الضابطة، بينما لا توجد أي ارتفاعات في فحوصات الألنين أمينو ترانسفيرز، واليوريا، والبيليروبين الكلي.

الكلمات المفتاحية: تقييم وظائف الكبد و الكلى ، الادوية المضادة للذهان و الادوية المضادة للصرع ، غزة – فلسطين

Dedication

To Allah for the blessing of Islam and mind

To primer minister of my home my lovely mother

To my dear father

To my brothers

To my sisters

To my teacher since the childhood to the old

To all my friends

To anyone who is lighted the mind of someone else

Special dedication to all patients in Gaza Strip

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List of Abbreviations

1. ALP Alkaline phosphatase.
2. ALT Alanine aminotransferase.
3. AST Aspartate aminotransferase.
4. CBZ Carbamazepine
5. CPZ Chlorpromazine hydrochloride.
6. CYP Cytochrome P450.
7. DB Direct bilirubin.
8. GABA Gamma aminobutyric acid .
9. GGT Gamma glutamyl transferase .
10. GIT Gastrointestinal tract.
11. IV Intravenous administration .
12. PHT Phenytoin
13. SGOT AST.
14. SGPT ALT.
15. TB Total bilirubin .
16. T.H.P Trihexyphenidyl hydrochloride.
17. VPA Valproic acid.

Introduction

1.1 Overview

Psychosis: from the Greek "psyche", for mind or soul, and "-osis ", for abnormal condition literally means abnormal condition of the mind, and is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality" **(1)** . People suffering from psychosis are said to be psychotic. People with psychosis may have one or more of the following: hallucinations, delusions, or thought disorder. The exact cause of psychotic disorders is unknown. Psychosis may appear as a symptom of a number of mental disorders including mood and personality disorders, schizophrenia, and delusional disorder. Schizophrenia is a particular type of psychosis that is, a mental disorder caused by some inherent dysfunction of the brain. it is characterized by delusions, hallucination (often in the form of voices), and thinking or speech disturbances **(2)**. This mental disorder is a common affliction, occurring among about one percent of the population **(3)**. Many antipsychotic drugs are available for the treatment of schizophrenia. These drugs such as: Chlorpromazine, Haloperidol, Risperidone, exert blocking effects on a wide range of receptors including dopamine and adrenoceptor, muscarinic, H1 histaminic, and serotonin (5-HT2). Dopamine receptor effects quickly became the major focus of interest. Dopamine receptors control neural signaling that modulates many important behaviors, such as spatial working memory **(4).**The epilepsies are one of the most common serious brain disorders, which can occur at all ages, and have many possible presentations and causes.

Although incidence in childhood has fallen over the past three decades in developed countries **(5)**. It rounds 50 cases per 100 000 of the population**.** The aim of drug therapy is to prevent, cure or control various disease states. To achieve this, adequate drug doses must be delivered to the target tissues.

After the absorption of the drug, it is metabolized in the liver, The liver is the largest organ of the human body, weighs approximately 1500 g, and is located in the upper right corner of the abdomen. The liver metabolizes virtually every drug or toxin introduced in the body**(6).** Most drugs are lipophilic (fat soluble), enabling easy absorption across cell membranes. In the body, they are rendered hydrophilic (water soluble) by biochemical processes in the hepatocytes to enable inactivation and easy excretion. Metabolism of drugs occurs in 2 phases. In the phase 1 reaction, the drug is made polar by oxidation or hydroxylation.

Cytochrome P450s play a central role in the metabolism and disposition of an extremely wide range of drugs and chemical carcinogens **(7).** Most of these intermediate products are transient and highly reactive. These reactions may result in the formation of metabolites that are far more toxic than the parent substrate and may result in liver injury.

Phase 2 reactions may occur within or outside the liver. They involve conjugation with a moiety (i.e., acetate, amino acid, sulfate, glutathione, glucuronic acid) that further increases solubility. Subsequently, drugs with high molecular weight may be excreted in bile, while the kidneys excrete the smaller molecules **(8).** Removal of a drug from the body may occur via a number of routes, the most important being through the kidney into the urine. other routes include the bile, intestine, lung, or milk in nursing mothers. kidney is Small, dark red organs with a kidney bean shape which lies against the dorsal body wall in a retroperitoneal position in the superior lumbar region where they receive some protection from the lower part of the rib cage. the function of the kidney is the clearance of nitrogenous wastes while regulating water, electrolytes and acid base- balance of the blood .

1.2 General objective

This study aims to assess liver and kidney functions in patients receiving antipsychotic and antiepileptic drugs for more than one year in Gaza .

1.3 Specific objectives

To examine changes in the levels of**:**

1. Serum alanine aminotransferase (ALT).
2. Aspartate aminotransferase (AST).
3. Alkaline phosphatase (ALP).
4. Total bilirubin (TB), and Direct bilirubin (DB).
5. Gamma glutamyl transferase (GGT).
6. Urea, creatinine, and uric acid in patients receiving antipsychotic and antiepileptic drugs .

1.4 Significance

Although antipsychotic drugs are used in Gaza for long time, their toxic effects have not been investigated. It is well known that many of these drugs affect liver and or kidney functions. For this reason and due to increased number of patients receiving antipsychotic drugs in our area, this study has been designed to study the effects of these drugs on liver and kidney function of those patients and to alert physicians about the harmful consequences of these drugs so they could initiate early action to prevent or delay such consequences. According to the knowledge of researcher, this study is the first to be conducted in Gaza strip .

LITERATURE REVIEW

The aim of drug therapy is to prevent, cure or control various disease states. To achieve this goal, adequate drug doses must be delivered to the target tissues .

2. 1Transfer of drugs from GIT across cell membranes

In general, drugs may cross cell membranes by **(9)**

_ Passive diffusion

_ Carrier transport

2.2 Bioavailability

Bioavailability is used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation, one of the principal pharmacokinetic properties of drugs. By definition, when a medication is administered intravenously, its bioavailability is 100%. However, when a medication is administered via other routes (such as orally), its bioavailability decreases (due to incomplete absorption and first-pass metabolism) or may vary from patient to patient due to inter-individual variation **(10).**

2.2.1 Factors influencing bioavailability

Whether a drug is taken with or without food will also affect absorption, other drugs taken concurrently may alter absorption, first-pass metabolism and intestinal motility alters the dissolution of the drug and may affect the degree of chemical degradation of the drug by intestinal microflora. Disease states affecting liver metabolism or gastrointestinal function will also have an effect **(11).** Other factors may include**:**

- The drug formulation (immediate release, or delayed release).
- Enzyme induction/inhibition by other drugs/foods:
    - Enzyme induction (increase rate of metabolism). e.g. Phenytoin (antiepileptic) induces CYP1A2, CYP2C9, CYP2C19 and CYP3A4
    - Enzyme inhibition (decrease rate of metabolism). e.g. grapefruit juice inhibits CYP3A .

2.3 Drug distribution

After administration and absorption, drugs are initially present in plasma and may be partly bound to plasma proteins. They may subsequently gain access to interstitial fluid and intracellular water, depending on their physicochemical properties (in particular, their lipid solubility and ionic dissociation), blood flow, capillary permeability and the degree of binding of the drug to plasma and tissue proteins, consequently they may be rapidly distributed in other tissues and organs. When distribution is complete, their concentration in plasma water and extracellular fluid is approximately equal **(12).** Some drugs are extensively protein-bound and are predominantly present in plasma. Similarly, ionized compounds cannot readily penetrate most cell membranes and in contrast lipid-soluble drugs with a relatively low molecular weight are widely distributed in tissues. For instance, ethyl alcohol, urea and some sulphonamides are evenly distributed throughout body water.

2.4 Drug metabolism

Most drugs are eliminated by drug metabolism, which mainly occurs in the liver. Nevertheless, certain drugs are partly or completely broken down by other tissues. Such as metabolized by the gut (e.g. morphine, chlorpromazine), the kidney (e.g. midazolam, dopamine) or the lung (e.g. angiotensin, prilocaine). Nevertheless, the liver is mainly responsible for the breakdown of drugs. Hepatic metabolism decreases the concentration of the active drug in plasma, and thus promotes its removal from the site of action. This mainly involves the enzymatic conversion of lipid-soluble non polar drugs into water-soluble polar compounds **(13)** which can be filtered by the renal glomerulus or secreted into urine or bile.

Metabolism usually reduces the biological activity of drugs, and most metabolites have less inherent activity than their parent compounds. In addition, their ability to penetrate to receptor sites is limited because of their poor lipid solubility. Although almost all tissues in the body have some ability to metabolize chemicals, smooth endoplasmic reticulum in liver is the principal "metabolic clearing house" for both endogenous chemicals (e.g., cholesterol, steroid hormones, fatty acid and proteins), and exogenous substances (e.g. drugs**) (14).**

Drug metabolism is usually divided into two phases: phase 1 and phase 2. Phase 1 reaction is thought to prepare a drug for phase 2. However many compounds can be metabolized by phase 2 directly. Phase 1 reactions involves oxidation, reduction, hydrolysis, hydration and many other rare chemical reactions **(15)**. These processes tend to increase water solubility of the drug and can generate metabolites which are more chemically active and potentially toxic. Most of phase 2 reactions take place in cytosol and involve conjugation with endogenous compounds via transferase enzymes. Chemically active phase 1 products are rendered relatively inert and suitable for elimination by this step. A group of enzymes located in the endoplasmic reticulum, known as cytochrome P-450, is the most important family of metabolizing enzymes in the liver **(16).**

2.5 The Liver

The liver is the largest organ of the human body, weighs approximately 1500 g **(17),** and is located in the upper right corner of the abdomen. The organ is closely associated with the small intestine, processing the nutrient-enriched venous blood that leaves the digestive tract. The liver performs over 500 metabolic functions, resulting in synthesis of products that are released into the blood stream (e.g. glucose derived from glycogenolysis, plasma proteins, clotting factors and urea), or that are excreted to the intestinal tract (bile). Also, several products are stored in liver parenchyma (e.g. glycogen, fat and fat soluble vitamins) **(18).** Almost all blood that enters the liver via the portal tract originates from the gastrointestinal tract as well as from the spleen, pancreas and gallbladder. A second blood supply to the liver comes from the hepatic artery, branching directly from the celiac trunc and descending aorta. The portal vein supplies venous blood under low pressure conditions to the liver, while the hepatic artery supplies high-pressured arterial blood. Since the capillary bed of the gastrointestinal tract already extracts most O2, portal venous blood has a low O2 content. Blood from the hepatic artery on the other hand, originates directly from the aorta and is, therefore, saturated with O2 **(19).** The liver alters exogenous and endogenous chemicals , foreign molecules, and hormones to make them less toxic or less biologically active. This process is called metabolic detoxification **(13).**

2.6 Kidney

The kidney performs important physiological functions including maintenance of water and electrolyte balance, synthesis, metabolism and secretion of hormones and excretion of waste products from metabolism. In addition, the kidneys play a major role in excretion of drugs, hormones and xenobiotics **(20)** Although the kidney will generally metabolize endogenous or exogenous chemicals to compounds with reduced biological activity, there are several instances in which metabolism will produce a toxic intermediate that may result in mutagenesis or cell necrosis **(21).**

2.7 Cytochrome P450

Cytochrome P450 (abbreviated **CYP**, **P450**, infrequently **CYP450**) is a very large and diverse superfamily of hemoproteins **(22).** Usually they form part of multi-component electron transfer chains, called P450-containing systems. The most common reaction catalysed by cytochrome P450 is a monooxygenase reaction, e.g. insertion of one atom of oxygen into an organic substrate (RH) while the other oxygen atom is reduced to water:

$$RH + O_2 + 2H^+ + 2e^- \rightarrow ROH + H_2O$$

The name **cytochrome P450** is derived from the fact that these are colored ('chrome') cellular ('cyto') proteins, with a "pigment at 450 nm", so named for the characteristic peak formed by absorbance of light at wavelengths near 450 nm when the heme iron is reduced (often with sodium dithionite) and complexed to carbon monoxide **(23).**

2.7.1 CYP 450s in humans

Human CYPs are primarily membrane-associated proteins, located either in the inner membrane of mitochondria or in the endoplasmic reticulum of cells. CYPs metabolize thousands of endogenous and exogenous compounds. CYPs are responsible for the biosynthesis of physiologically important compounds such as steroids, fatty acids, fat-soluble vitamins and bile acids, the conversion of alkanes and aromatic compounds as well as the degradation of herbicides and insecticides **(24)**. Most CYPs

can metabolize multiple substrates, and many can catalyze multiple reactions, which accounts for their central importance in metabolizing the extremely large number of endogenous and exogenous molecules. In the liver, these substrates include drugs and toxic compounds as well as metabolic products such as bilirubin. Cytochrome P450 enzymes are present in most other tissues of the body, and play important roles in hormone synthesis and breakdown (including estrogen and testosterone synthesis and metabolism), cholesterol synthesis, and vitamin D metabolism. The Human Genome Project has identified 57 human genes coding for the various cytochrome P450 enzymes **(25)**.

2.7.2 Mechanism of action

The active site of cytochrome P450 contains a heme iron center. The iron is tethered to the P450 protein via a thiolate ligand derived from a cysteine residue. Because of the vast variety of reactions catalyzed by CYPs, the activities and properties of the many CYPs differ in many aspects. In general, the P450 catalytic cycle proceeds as follows:

1: The substrate binds to the active site of the enzyme, in close proximity to the heme group, on the side opposite to the peptide chain. The bound substrate induces a change in the conformation of the active site often displacing a water molecule from the distal axial coordination position of the heme iron **(26).**

2: The change in the electronic state of the active site favors the transfer of an electron from NAD(P)H via cytochrome P450 reductase or another associated reductase. This takes place by way of the electron transfer chain, reducing the ferric heme iron to the ferrous state **(27).**

3: Molecular oxygen binds covalently to the distal axial coordination position of the heme iron. The cysteine ligand is a better electron donor than histidine, with the oxygen consequently being activated to a greater extent than in other heme proteins. However, this sometimes allows the bond to dissociate, the so-called "decoupling reaction", releasing a reactive superoxide radical, interrupting the catalytic cycle.

4: A second electron is transferred via the electron-transport system, either from cytochrome P450 reductase, ferredoxins, or cytochrome b5, reducing the dioxygen adduct to a negatively charged peroxo group. This is a short-lived intermediate state.

5: The peroxo group formed in step 4 is rapidly protonated twice by local transfer from water or from surrounding amino-acid side chains, releasing one water molecule, and forming a highly reactive iron(V)-oxo species. as shown in fig.1

6: Depending on the substrate and enzyme involved, P450 enzymes can catalyse any of a wide variety of reactions. A hypothetical hydroxylation is shown in fig.1 After the product has been released from the active site, the enzyme returns to its original state, with a water molecule returning to occupy the distal coordination position of the iron nucleus **(28)**.

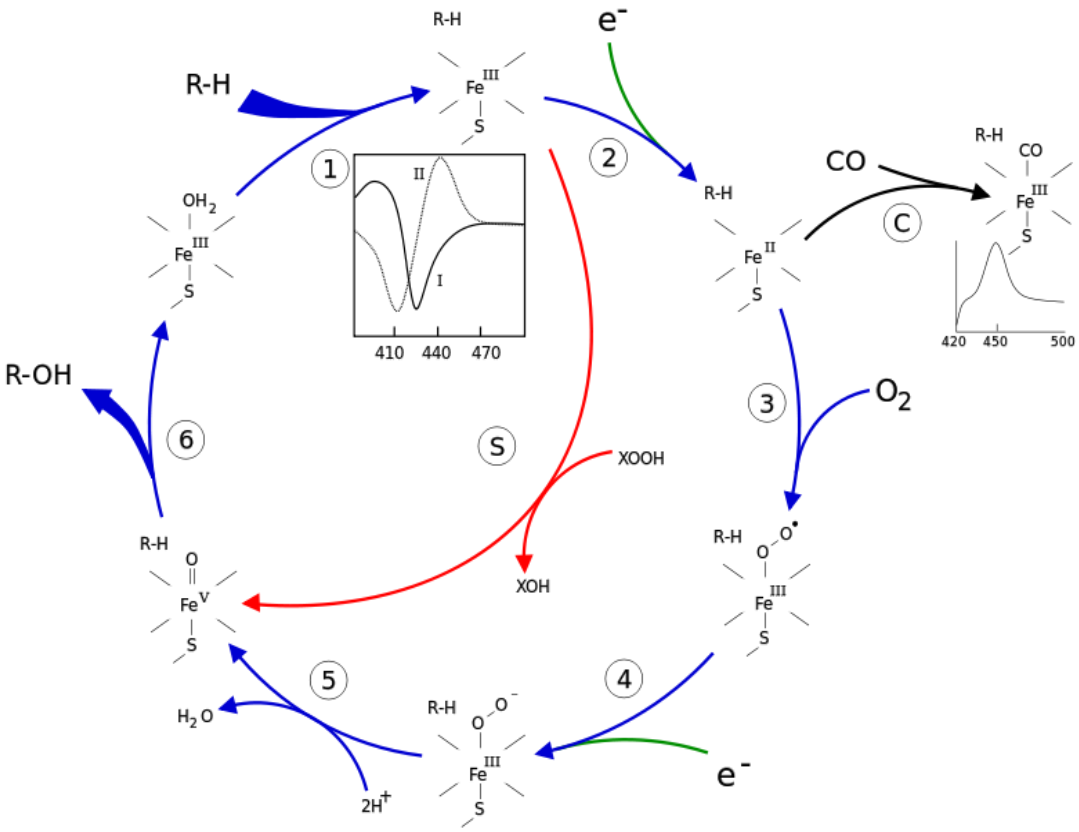

Figure1: mechanism of action of CYP *450*.[29]

2.7. 3 Phase 2 reactions

Phase 2 reactions (synthetic reactions) involve the conjugation of other chemical groups with the oxidized, reduced or hydrolysed products of phase 1 reactions. Some

relatively polar drugs may only be metabolized by phase 2 reactions. The metabolic changes that occur during phase2 reactions usually involve the addition of glucuronide, sulphate, acetate, glycine or methyl groups to the products of phase 1 reactions. The most important of these reactions is glucuronide conjugation.

2.7. 3.1Glucuronide conjugation

The conjugation of drugs to glucuronides is mainly dependent on enzyme systems in the hepatic endoplasmic reticulum. The microsomal enzyme glucuronyl transferase catalyses the transfer of glucuronide residues from UDP glucuronide to unconjugated compounds **(21)**. This process is responsible for the conjugation of endogenous compounds (e.g. bilirubin, thyroxine) as well as many drugs (e.g. morphine, steroid hormones).

2.8 Mechanism of liver damage

The pathophysiologic mechanisms of hepatotoxicity are still being explored and include both hepatocellular and extracellular mechanisms. The following are some of the mechanisms that have been described (**30):**

1. Disruption of the hepatocyte: Covalent binding of the drug to intracellular proteins can cause a decrease in ATP levels, leading to actin disruption. Disassembly of actin fibrils at the surface of the hepatocyte causes blebs and rupture of the membrane.
2. Cytolytic T-cell activation: Covalent binding of a drug to the P-450 enzyme acts as an immunogen, activating T cells and cytokines and stimulating a multifaceted immune response.
3. Toxic metabolites may alter plasma membrane, mitochondria, intracellular ion homeostasis, or degradative enzyme activity **(31).**
4. Many chemicals damage mitochondria. Its dysfunction releases excessive amount of oxidants which, in turn, injure hepatic cells **(32).**
5. Bile duct injury: Toxic metabolites excreted in bile may cause injury to the bile duct epithelium. Injury to hepatocyte and bile duct cells lead to accumulation of bile acid inside liver. This promotes further liver damage (**33)**

The classic view on the pathogenesis of drug-induced liver injury is that the so-called parent compounds are made hepatotoxic by metabolism (formation of neo-substances that react abnormally), mainly by cytochromes P-450 (CYP**)(34).** Activation of some enzymes in the cytochrome P-450 system such as CYP2E1 also lead to oxidative stress **(35).** Chemicals produce a wide variety of clinical and pathological hepatic injury. Biochemical markers (i.e. alanine transferase, aspartate transferase, glytamile transferase, alkaline phosphatase and bilirubin) are often used to assess liver damage **(36).**

2.9 Neurotransmitters

Neurotransmitters, are endogenous chemicals that transmit signals from a neuron to a target cell across a synapse, have long been thought to be involved in the development of schizophrenia.

2.9.1 Dopamine

Dopamine is a catecholamine neurotransmitter found in neurons of both the central and peripheral nervous systems **(37).** It is stored in vesicles in axon terminals and released when the neuron is depolarized **(38).** Dopamine interacts with specific membrane receptors to produce its effects. In the brain, this phenethylamine functions as a neurotransmitter, activating the five types of dopamine receptors—D_1, D_2, D_3, D_4, and D_5—and their variants. Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area. Dopamine is also a neurohormone released by the hypothalamus. Its main function as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary. Dopamine has many functions in the brain, including important roles in behavior and cognition, voluntary movement, motivation and inhibition of prolactin production (involved in lactation), sleep, mood, attention, and learning **(39).** These effects are terminated by re-uptake into the presynaptic neuron by a dopamine transporter, or by metabolic inactivation by monoamine oxidase B (MAO-B) or catechol-o-methyltransferase (COMT). Dopamine is widely distributed in the brain and is one of the neurotransmitters that enables communication in the circuits that link subcortical with cortical brain regions **(40).** Recent studies **(41)** have suggested that various positive symptoms of schizophrenia

correlate with abnormalities in presynaptic dopamine storage, release, transport, and reuptake in mesolimbic systems.

2.9.2 Serotonin

Serotonin is 5-hydoxytryptamine which is often abbreviated to 5-HT. It is made from the amino acid, tryptophan. Serotonin is converted to melatonin in the pineal gland, which lies deep at the centre of the human brain, The average adult human possesses only 5 to 10 mg of serotonin, 90 % of which is in the intestine **(42)** and the rest in blood platelets and the brain **(43)**. Tryptophan, derived from food, is transported to the brain to make the neurotransmitter serotonin. At the appropriate place inside a brain cell, two enzymes and vitamin B6 transform tryptophan to serotonin. Serotonin is then transferred to the sending end of the neuron, where it is used as a molecular messenger to carry information across the synapse to the receiving neuron. The serotonin molecules can then bind to receptor proteins within the postsynaptic cell, which causes a change in the electrical sate of the cell. This change in electrical state can either excite the cell, passing along the chemical message, or inhibit it. Excess serotonin molecules are taken back up by the presynaptic cell and reprocessed **(44).** The serotonin synthesis equation is:

STEP 1. Tryptophan-----> 5-Hydroxytryptophan via enzyme tryptophan hydroxylase. STEP 2. 5-Hydroxytryptophan (5HT)----> Serotonin via enzyme 5HT-Decarboxylase. The functions of serotonin are numerous and appear to involve control of appetite, sleep, memory and learning, temperature regulation, mood, cardiovascular function, muscle contraction, endocrine regulation and depression **(45).** Low serotonin levels are believed to be the cause of many cases of mild to severe depression which can lead to symptoms such as anxiety, fear feelings of worthlessness, insomnia and fatigue and suicide. Too little also leads to an increased appetite for carbohydrates and trouble sleeping, which are also associated with depression and other emotional disorders **(46)**

2.9.3 Gamma-Amino Butyric acid (GABA)

Gamma-Amino Butyric acid is an amino acid which acts as a neurotransmitter in the central nervous system. It inhibits nerve transmission in the brain **(47),** calming nervous activity. GABA is formed within GABAergic axon terminals and released into the synapse, where it acts at one of two types of receptors: GABAA, which controls

chloride entry into the cell, and GABAB, which increases potassium conductance, decreases calcium entry, and inhibits the presynaptic release of other transmitters **(48)**.

GABA does not penetrate the blood-brain barrier; it is synthesized in the brain. It is synthesized from glutamate using the enzyme L-glutamic acid decarboxylase **(49**) and pyridoxal phosphate (which is the active form of vitamin B6) as a cofactor via a metabolic pathway called the GABA shunt. This process converts glutamate, the principal excitatory neurotransmitter, into the principal inhibitory neurotransmitter (GABA) **(50).** After release from the presynaptic axon terminals, GABA is rapidly removed by uptake into both glia and presynaptic nerve terminals and then is catabolized by GABA transaminase to succinic semialdehyde. Succinic semialdehyde is converted to succinic acid by succinic acid semialdehyde dehydrogenase and then enters the Krebs cycle .

2.10 Psychosis Disorder

2.10.1 Schizophrenia

Schizophrenia is one of the terms used to describe a major psychiatric disorder that alters process of thinking, emotional responsiveness **(51)**, most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, and it is accompanied by significant social or occupational dysfunction **(52).**

Typically, the problems of schizophrenia are preceded by a 'prodromal' period **(53)**, this is often characterized by some deterioration in personal functioning. Difficulties may include memory and concentration problems, social withdrawal, unusual and uncharacteristic behaviour, bizarre ideas, poor personal hygiene, and reduced interest in and motivation for day-to-day activities. The prodromal period is typically followed by an acute phase marked by characteristic positive symptoms of hallucinations, delusions, and behavioural disturbances .

2.10.1.1 Prevalence

- Affecting nearly 1 % of the world's population **(54).**
- Schizophrenia affects men and women equally **(55).** Men with an earlier age of onset. Behavioral deficits, and a poorer response to chemotherapy **(56).**

- Schizophrenia typically occurs in late adolescence or early adulthood**(57)**, at the very time that people are making their way from the family into the world outside. Most of the time people do not get schizophrenia after age 45 **(58).** Schizophrenia is rarely diagnosed but possible before age 10 **(59).**
- The standardized mortality ratio (SMR; ratio of observed deaths to expected deaths) for all-cause mortality is 2.6 for patients with schizophrenia compared to the general population **(60)**, excess deaths mainly from suicide during the early phase of the disorder and accidents .

2.10.1.2 Symptoms of schizophrenia

Schizophrenia is often described in terms of positive and negative symptoms **(61)** The term Positive symptoms are psychotic behaviors not seen in healthy people but are present in schizophrenia. These unusual experiences are most common in schizophrenia, but can occur in other mental disorders . They include;

1. Delusions
2. Hallucinations**(62)**
3. Disturbances in thought and speech.

2.10.1.3 Subtypes of schizophrenia

1. Paranoid Subtype

The defining feature of the paranoid subtype is the presence of auditory hallucinations or prominent delusional thoughts about persecution or conspiracy **(63).** However, people with this subtype may be more functional in their ability to work and engage in relationships than people with other subtypes of schizophrenia.

2. Disorganized Subtype

As the name implies, this subtype's predominant feature is disorganization of the thought processes. As a rule, hallucinations and delusions are less pronounced, although there may be some evidence of these symptoms **(64)**. These people may have significant impairments in their ability to maintain the activities of daily living. Even the more routine tasks, such as dressing, bathing or brushing teeth, can be impaired, emotional processes of the individual can be impaired as well.

3. **Catatonic Subtype**

The predominant clinical features seen in the catatonic subtype involve disturbances in movement. Affected people may exhibit a dramatic reduction in activity, to the point that voluntary movement stops, as in catatonic stupor. Alternatively, activity can dramatically increase, a state known as catatonic excitement. Other disturbances of movement can be present with this subtype **(65).**

4. **Undifferentiated subtype:** Psychotic symptoms are present (no single type of symptoms prominent than other) but the criteria for paranoid, disorganized, or catatonic types have not been met.
5. **Residual subtype:** Where positive symptoms are present at a low intensity only

It is possible for schizophrenia to co-exit with other mental illnesses . Schizophrenia puts individuals at especially high risk for depression and suicide attempts .when a person experiences both schizophrenia and a mood disorder they are diagnosed with Schizoaffective Disorder .

2.10.1.4 Chlorpromazine

While current antipsychotic drug treatments control positive symptoms in most patients, negative symptoms and cognitive impairments are much less improved by these agents **(66)** Antipsychotic medication can be divided into two major classes. Conventional antipsychotic medications, first introduced in the 1950s, are usually referred to as either “typical” or “first -generation” antipsychotics .

Chlorpromazine (Thorazine), was the first antipsychotic medication, All of these medications reduce dopamine activity by blocking dopamine receptors, especially the D2 subtype, and these drugs have similar efficacy for the positive symptoms of schizophrenia. They differ from each other, however, in side-effect profiles. Drug induced movement abnormalities are the main side effect associated with the typical antipsychotics **(67).** The cause of the motor side effects is not established, but is assumed to be due to excessive dopamine D2 receptor blockade. The motor symptoms typically decline following the discontinuation of medication. In the 1990’s, new antipsychotic medications were developed. These new medications are called second generation, or “atypical” antipsychotics. They differ significantly from one another in terms of the neurotransmitter receptors that they occupy. However, they all act as dopamine

antagonists to some extent, in addition to affecting other neurotransmitter systems, and they have a reduced risk of both the early and late emerging movement disorders **(68)**

Chlorpromazine (as chlorpromazine hydrochloride, abbreviated CPZ; marketed in the United States as Thorazine and elsewhere as Largactil) is a typical antipsychotic **(69)**. Chlorpromazine was the first drug developed with specific antipsychotic action, and would serve as the prototype for the phenothiazine class of drugs . Chlorpromazine works on a variety of receptors in the central nervous system, producing anticholinergic, antidopaminergic, antihistaminic, and weak antiadrenergic effects. Both the clinical indications and side effect profile of CPZ are determined by this broad action: its anticholinergic properties cause constipation, sedation, and hypotension, and help relieve nausea **(70).**

2.10.1.4.1 Pharmacokinetics

Chlorpromazine, and many other phenothiazine derivatives, are highly lipophilic molecules that readily bind with membranes and proteins. Around 95-98% of the drug is bound in the plasma; 85% of the drug is bound to the plasma protein albumin. It is a dopamine inhibitor, increases dopamine turnover in the brain, and stimulates prolactin release, Chlorpromazine is widely distributed in the body and crosses the blood-brain barrier to achieve higher concentrations in the brain than in the plasma **(71),** The drug can also enter fetal circulation and breast milk. Bioavailability of CPZ is Only about 32% of the administered dose which is available to the systemic circulation in the active form. Over time and multiple administrations, bioavailability may drop to 20%. Peak concentrations are achieved in 1 to 4 hours **(72).** CPZ is slowly absorbed from the intramuscular injection site with the peak plasma concentration occurring 6–24 hours after administration of the drug. The oral bioavailability is estimated to be 30–50% that of intramuscular doses and about 10% that of intravenous doses due to extensive first pass metabolism in the liver. Its elimination half-life is 16–30 hours. Chlorpromazine is typically degraded by the liver by the action of cytochrome-P450 family enzymes, usually CYP2D6 **(73).** Less than 1% of the unchanged drug is excreted via the kidneys in the urine. In which 20-70% is excreted as conjugated or unconjugated metabolites, whereas 5-6% is excreted in feces. Often, due to their high lipophilic character, these and other metabolites may be detected in the urine up to 18 months **(74).**

2.10.1.4.2 Dosage

Adults**:** Initially 25mg three times daily or 75mg at bedtime, increasing by daily amounts of 25mg to the effective maintenance dose. The usual maintenance dose is in the range of 75 to 300 mg daily, although some patients may require up to 1.0 g daily (**75**). oral dose for children aged over 5 years is usually one-third to one-half of the adult dose. Daily doses should not normally exceed 75 mg for children over 5 years of age (**76**).

2.10.1.5 Trihexyphenidyl hydrochloride (T.H.P)

Trihexyphenidyl hydrochloride is a type of anticholinergic drug that works by blocking the effects of acetylcholine neurotransmitter **(77**). Trihexyphenidyl is used alone or together with other medicines to treat Parkinson's disease. This helps decrease muscle stiffness, sweating, and the production of saliva, and helps improve walking ability in people with Parkinson's disease, and to treat involuntary movements due to the side effects of certain psychiatric drugs (antipsychotics such as chlorpromazine, haloperidol). These compounds have also been reported to improve negative and depressive symptoms of schizophrenia**(78).** Trihexyphenidyl is rapidly absorbed from the gastrointestinal tract. The onset of action is within 1 hour after oral dosing. The peak activity is noted after 2 to 3 hours. It is excreted in the urine, probably as unchanged drug **(79),** its brand name is Artane.

2.10.1.5.1 Dosage

Trihexyphenidyl is available in 2-mg and 5-mg tablets, it should be started at a dose of 1 to 2 mg orally two to three times daily or as needed, to a maximum daily dose of 15 mg per day in Parkinson's disease. In extrapyramidal side effects : Usually, 5 to 15 mg daily are needed in 2 or 3 divided doses. Some patients, however, are successfully treated with as little as 1 mg daily**(80).**

2.11 Neurological disorder

2.11.1 Epilepsy

Epilepsy: (The word “epilepsy” is derived from Latin and Greek words for “seizure” . It's a common chronic neurological disorder characterized by seizures **(81),** the tendency to have recurrent attacks is known as epilepsy. The brain is a highly complex and sensitive organ. It controls and regulates all our actions, movements, sensations, thoughts and emotions. It is the site of memory, and it regulates the involuntary inner workings of the body such as the function of the heart and lungs. The brain cell work together, communicating by means of electric signal. Occasionally there is an abnormal electrical discharge from a group of cells, and the result is a seizure. The type of seizure will depend upon the part of the brain where the abnormal electrical discharge arises **(82).** Epilepsy is serious brain disorder. It is universal, with no age, sex, geographical, social class or racial boundaries**(83).** Some seizures are hardly noticed—perhaps a feeling of "pins and needles" in one thumb for a few seconds. During other seizures, the person may become unconscious, fall to the floor, and jerk violently for several minutes.

2.11.1.1 Causes of epilepsy

There is no single cause of epilepsy. Many factors can injure the nerve cells in the brain or the way the nerve cells communicate with each other. In approximately 65% of all cases there is no known cause. The idiopathic epilepsies are those in which there is a clear genetic component, and they probably account for a third of all new cases of epilepsy. In significant proportion of cases however, no cause can be determined and these are known as the cryptogenic epilepsies. possible explanations for cryptogenic epilepsy include as yet unexplained metabolic or biochemical abnormalities and microscopic lesions in the brain resulting from brain malformation or trauma during birth or other injury. The term symptomatic epilepsy indicate that a probable cause has been identified .

The following are some of the most frequently identified causes :

- **Brain injury**: The onset of seizures after a brain injury often occurs after such a delay, even of many years. Researchers believe that this delay results from

reorganization of nerve connections in the injured areas. The brain makes an attempt to fix the injury by growing new connections, but the result is a circuit that is more electrically excitable and prone to produce seizures **(84).**

- **Head Trauma** at birth
- **Stroke**: During a stroke, brain cells die or are injured by blockage of blood flow to a part of the brain. About 10% of strokes lead to subsequent epilepsy.
- **Tumors**
- **Infection**: some condition known to have a risk of resulting in epilepsy is meningitis.
- **Vascular Malformations** : abnormal blood vessels in the brain are common causes of epilepsy. Blood is brought to the brain by arteries. It flows into small capillaries, where oxygen is transferred to the brain cells, and then is carried out by veins. The brain cells near the malformation may be irritated by bleeding or lack of oxygen. The response to this irritation can be seizures **(85).**
- **Mutations** in several genes have been linked to some types of epilepsy. Several genes that code for protein subunits of voltage-gated and ligand-gated ion channels have been associated with forms of generalized epilepsy and infantile seizure syndromes**(86).** One speculated mechanism for some forms of inherited epilepsy are mutations of the genes that code for sodium channel proteins; these defective sodium channels stay open for too long, thus making the neuron hyper-excitable. Glutamate, an excitatory neurotransmitter, may, therefore, be released from these neurons in large amounts, which by binding with nearby glutamatergic neurons triggers excessive calcium (Ca^{2+}) release in these post-synaptic cells. Such excessive calcium release can be neurotoxic to the affected cell. Another possible mechanism involves mutations leading to ineffective GABA (the brain's most common inhibitory neurotransmitter) action.
- **In some cases things that happen in the environment** can trigger epileptic seizures (photosensitive seizure is defined as a seizure produced by flashing lights or certain visual patterns, for example television and video games. About 3% of people with epilepsy will have photosensitivity .
- The commonest cause in young infants are hypoxia , intercranial trauma during birth, metabolic disturbances, congenital malformations of the brain or infection.

2.11.1.2 Diagnosis

1. A person should only be diagnosed as having “epilepsy” if there are recurrent manifestations i.e. there should be at least two or more unprovoked similar episodes at least 24 hours apart. Hence, the first episode of a seizure is called a “single seizure” and not epilepsy.
2. Epilepsy can also be divided into active and inactive epilepsy, with active epilepsy being defined as two or more epileptic seizures in the last five years that are unprovoked by any immediate identified cause.
3. epilepsy can be diagnosed on the basis of reports of patients and eyewitnesses.

Electroencephalography (EEG), which records electrical activity from the surface of the head can, in some cases, support the diagnosis**(87).**

2. 11.1.3 Treatment of Epilepsy

Antiepileptic drugs commonly used for treating epilepsy are carbamazepine, phenytoin, primidone, phenobarbital, and more recently, sodium valproate. All display a similar efficacy; major differences have to do with their adverse-effect profiles **(88).**

Mechanism of action of antiepileptic drugs

Three main mechanisms appear to be important in the action of antiepileptic drugs**(89)**.

- Enhancement of GABA action.
- Inhibition of sodium channel function.
- Inhibition of calcium channel function . Other mechanisms include inhibition of glutamate release and block of glutamate receptors.

2.11.1.3.1 Valproic acid

Valproic acid (VPA, 2-propylpentanoic acid), a short branched chain fatty acid, it has been used worldwide for decades, in the form of sodium valproate, as an antiepileptic drug with therapeutic value for absence, partial, complex, myoclonic, tonic-clonic seizures **(90),** and photosensitive epilepsies**(91).** Valproate is believed to affect the function of the neurotransmitter GABA in the human brain, Its mechanism of

action includes enhanced neurotransmission of GABA (by inhibiting GABA transaminase, then GABA would increase in concentration). Valproic acid also blocks the voltage-gated sodium channels and T-type calcium channels. These mechanisms make valproic acid a broad spectrum anticonvulsant drug. Valproic acid is usually absorbed rapidly from the GIT. Peak serum concentrations are recorded at 1-4 hours. Valproic acid is greater than 80-95% protein bound. However, this percentage decreases during acute overdose, when protein-binding sites are saturated **(92).** Valproic acid is metabolized primarily in the liver by means of conjugation to form a glucuronide ester and by means of oxidation by mitochondria. Less than 5% is excreted unchanged in the urine. Many of the metabolites are biologically active and contribute to anticonvulsant action. They may also be responsible for ongoing toxicity (e.g. persistent coma) even as serum levels of valproic acid return to normal. The elimination half-life varies from 5-20 hours. The half-life may be increased in neonates, in patients with liver disease, and in those ingesting an acute overdose. The half-life is 4-14 hours in children, 8-17 hours in adults, and up to 30 hours in those with an acute overdose. Valproic acid increases serum levels of carbamazepine, phenobarbital, and primidone mainly by inhibiting various cytochrome P450 (CYP450) isoenzymes involved in their metabolism**(93**).

serious complications of valproic acid, including hepatotoxicity(with an overall incidence of 1 in 20,000, but a frequency as high as 1 in 600 or 1 in 800 in high-risk groups such as infants below 2 years of age receiving anticonvulsant polytherapy) **(92)** and hyperammonemic encephalopathy, may occur. These complications may also arise following acute VPA overdose **(94)**. VPA has significant side effects: weight gain, tremor, hair loss, GI upset, blood count decreases, hepatic or pancreatic injury, bone weakness over time (osteoporosis), birth defects in up to 10%. Brand names of valproic acid are depakine, Depakote, Depakene, Depakote ER, Depacon, Valparin and Stavzor .

2.11.1.3.1.1 Dosage

The usual dosage of valproic acid is 1-15 mg/kilogram of body weight per day and may be increased to 30 mg/kilogram of body weight per day. It is usually taken two to three times a day.

2.12 Prevalence of psychotic disorders among Palestinian population

After the global financial crisis that caused the increase in poverty and unemployment, and caused an increase in the incidence of mental illness in general. 450 million people in the world suffer from a mental or behavioral disorder **(95)**, More than 150 million suffer from depression at any point in time **(96)**, 25 million suffer from schizophrenia **(97),** and more than 90 million suffer from an alcohol or drug use disorder, and nearly one million patients die annually by suicide **(98).** While in the Gaza Strip frequented more than 35 000 patients between the different mental illnesses. In general there are gradually increase of incidence rate of mental disorder. In 2009 there were 1,697 patients visits PHC centers with increase percentage 38.4% if compared with 2008, there's 13.1 % schizophrenic patients from new cases of mental disorders reported in 2009 **(99).**

2.13 Prevalence of epilepsy disease among Palestinian population

It is known that epilepsy is a chronic neurological disorder that affects people of all ages, its around 38 million people worldwide have epilepsy **(95)** , While in Gaza there's 16.6 % epileptic children from new cases of mental disorders reported in 2009 **(99).**

2.14 Previous studies

Lomas et al **(1955).,** had recorded a number of cases where they developed jaundice after treatment by CPZ **(100).**

Willmore et al **(1978).,** tested hepatic function in 25 cases treated with valproic acid. Alteration of hepatic function tests occurred in four of 25 patients treated with valproic acid. An average dose reduction in three patients of 10 mg per kilogram per day resulted in reversion of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) to normal. The drug was discontinued in one patient. Careful monitoring of hepatic function is required of patients being treated with valproic acid **(101).**

Green **(1984).,** reported 49 fatal cases of hepatotoxicity caused by sodium valproate, analysed in detail the childhood fatalities reported in the United Kingdom **(102)**. All of the seven children in this series had some pre-existing problem in addition to epilepsy; three or four had degenerative disease, four or five had developmental delay, and two had hepatomegaly. Most had refractory myoclonic epilepsy. All were on combinations of anticonvulsant drugs at the time of presentation and all the severe reactions occurred within 10 weeks of starting treatment.

Callaghan et al **(1994).,** showed that GGT and ALP may not be sensitive indicators of hepatocellular damage in patients taking anticonvulsant drugs as raised levels may only reflect enzyme induction **(103)**. So they examined Serum F protein, which is found in high concentration in the liver and levels are not influenced by enzyme induction. They measured serum F protein levels in patients taking carbamazepine (CBZ) and phenytoin (PHT) as monotherapy and in patients receiving multiple drugs, they compared the results with patients taking sodium valproate (VPA). Serum F protein levels were elevated in 6%, 22% and 13% of patients receiving CBZ, PHT and VPA, respectively. Raised GGT levels were reported for both the CBZ (26%) and PHT (78%) groups. Raised ALP levels were observed in 16%, 25% and 4% of the CBZ, PHT and VPA groups respectively.

Cˇ epelaka et al **(1998).,** evaluated the effects of VPA or CBZ monotherapy and VPA + CBZ comedication on the number of hepatic enzyme activities in sera of epileptic children; ALT, AST and GGT activities in sera of children treated with VPA(n = 42), or CBZ (n =36) taken as a monotherapy, with VPA+ CBZ combined therapy (n =36). The effect of VPA alone is greater on the activity of AST than on other enzymes, while CBZ therapy changes primarily the activities of GGT. The mean catalytic activity of AST was significantly elevated in groups on VPA, CBZ and VPA + CBZ treatment as compared to the control values. Changes in the ALT activity followed different patterns. The maximal increase was observed in the CBZ group with a smaller increase in the group on VPA+ CBZ polytherapy, whereas only 15% of patients receiving VPA showed an increase of the enzyme and GGT elevated in 23% of patient receiving VPA **(104).**

De-ming and Mei-rong **(2000).,** evaluated the influence of antipsychotic drug on liver function of schizophrenic patients. Eighty-six schizophrenic patients were randomly divided into two groups. One group received the treatment of typical antipsychotic drug (chlorpromazine), another received the treatment of atypical antipsychotic drug (risperidone). The indeces of liver function in all patients were compared respectively before the treatment, after 4 and 8 weeks of treatment. The Results of Liver function in the patients of schizophrenia group became remarkably abnormal after four weeks of treatment. The influence of atypical antipsychotic drug on liver function was lower than typical antipsychotic drug. There was significant difference between them **(105) .**

Altunbaşak et al **(2001).,** investigated the effects of valproic acid (VPA) on renal tubular function, they examined 15 ambulatory children with epilepsy who received VPA for at least 6 months. None of the patients had mental retardation. Fourteen age and sex-matched children were used as a control group. No statistically significant differences were found between patients and control subjects with respect to blood urea nitrogen (BUN), creatinine (Cr), uric acid, creatinine clearance (Ccr), tubular reabsorption of phosphorus (TRP), urinary Ca:creatinine ratio, urinary pH and mean urinary beta2-microglobulin concentrations ($P>0.05$) **(106)**.

Garcia-Unzueta et al **(2003).,** analyzed the effects of antipsychotics on liver function tests in a population of outpatients suffering from schizophrenia, 54 schizophrenic patients . were Versus 54 sex- and age- healthy controls. Concentrations of AST, ALT, GGT, alkaline phosphatase, albumin, and bilirubin were determined using a Technicon Dax (Technicon Instruments Corp., Tarrytown, NY). Data was analyzed with the statistical package SPSS for Windows 7.0. Transaminases concentrations were slightly elevated in study patients compared to healthy controls, but without statistical significance. Patients with depot neuroleptic treatment (fluphenazine, a phenotiazine) had higher GGT (P=0.005), and lower concentrations of both serum albumin and bilirubin (P=0.054 and 0.056, respectively) than patients on oral treatment. Typical/ atypical antipsychotic treatment and the dosage of neuroleptic treatment (converted to mg of chlorpromazine/day) did not correlate with liver function tests **(107**).

Lackmann **(2004).,** recorded a case of a 4-year-old boy with long-term sodium valproate therapy who suddenly developed clinically relevant thrombocytopenia and signs of hepatotoxicity. Reduction of the VPA dosage led to clinical and laboratory parameter improvement, while discontinuation of therapy was not necessary **(108**).

TsingHua **(2004).,** studied the difference in the effect on indices of liver function in schizophrenic patients treated with risperidone, clozapine or chlorpromazine. The indices of liver function in schizophrenic patients had been measured and analyzed before and after 4 and 8 weeks using risperidone, clozapine or chlorpromazine in 30 cases respectively. There was no significant difference in the liver function caused by risperidone ($P > 0.05$). ALT levels were significantly higher caused by clozapine firstly, and then AST there was a significant difference ($P < 0.01$). ALT levels were higher in the liver function caused by chlorpromazine, but after 5 weeks it was lower to the normal ranges. While bilirubin in cases treated with chlorpromazine showed a significant difference ($P < 0.01$) **(109**).

Attilakos et al **(2006).,** Investigated by a long-term, prospective method, whether treatment with VPA monotherapy may alter serum uric acid concentrations and liver function tests in 28 ambulatory epileptic children. ALT, AST, GGT, lactate dehydrogenase (LDH), and creatinine (Cr) were also measured before and at 6, 12 and

24 month. No statistically significant changes in serum uric acid, creatinine, and GGT were detected while serum ALT, AST concentrations were significantly increased **(110) .**

Sonmez FM et al **(2006).,** assessed the effect of phenobarbital, carbamazepine and valproate on serum lipid profiles and lipoprotein (a) in 64 children with epilepsy aged between 1 and 15 years. The children were separated as group 1 (18 children), treated with phenobarbital, 5 mg/kg/day; group 2(22 children), treated with carbamazepine, 10 to 15 mg/kg/day; and group 3 (24 children), treated with sodium valproate, 20 mg/kg/day. Plasma lipoprotein (a), total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein A and apolipoprotein B levels, and liver enzymes alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and GGT were determined before the initiation of the treatment and at 3, 6, and 12 months of the treatment period. The mean age of children in group 1 was significantly low compared with those in groups 2 and 3 ($P < 0.05$). The mean pretreatment lipid levels among the groups were not significantly increased. The mean lipoprotein (a) levels were significantly increased in all groups at 3, 6, and 12 months of the treatment period ($P < 0.05$). The increase in ALT, AST, ALP, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol at 3, 6, and 12 months was statistically significant in group 1 ($P < 0.05$). The higher levels in lipoprotein (a) (mean > 30 mg/dL) were observed only in carbamazepine-treated patients at 6 and 12 months. The percentage of children with lipoprotein (a) levels over 30 mg/dL was 44%, 63%, and 33% in the phenobarbital-, carbamazepine-, and valproate-treated children, respectively **(111**).

Demirciog˘lu et al **(2008).,** aimed to determine the effects of carbamazepine, and valproic acid on the serum lipids and liver function test. Thirty-eight epileptic children (18 males, 20 females, mean age 8.6 ± 3.9 years) were evaluated for serum lipids and liver function test results at the onset, the second and sixth months of antiepileptic therapy. The results of the children receiving carbamazepine (n = 31) and valproic acid (n = 7) were compared. In addition, the values obtained at different periods of treatment were compared within each group. The differences in the serum lipid levels and liver (ALP, SGOT,SGPT, Total, Direct bilirubin and GGT) function test results of the

children in the carbamazepine group and the valproic acid group were not statistically significant throughout the study. However, the total cholesterol, low-density lipoprotein, total cholesterol/high- density lipoprotein, and GGT levels were significantly increased in the carbamazepine group during treatment ($P < 0.05$) but not in the valproic acid group **(112).**

Ghozzi et al **(2011).,** evaluated the relationship between plasma concentrations of VPA and the occurrence of side effects especially hepatotoxicity in patients receiving high doses of VPA. From 128 patients treated by high doses of VPA, only 73 were included in this study. The work showed that adverse effects and clinical signs of liver toxicity may be present in VPA concentrations generally considered in the therapeutic range especially when used in high doses and or combined with antiepileptic drugs like phenobarbital or carbamazepine and benzodiazepines **(113).**

Chapter 3

Materials and Methods

3.1. Study design

The present study is a case control study .

3.2. Setting of the study

This study was carried out at Mental health clinics in Gaza.

3.3. Target population

The target population was psychiatric and epileptic patients from Mental Health Clinics in Gaza. All patients were receiving antipsychotic drugs (CPZ with T.H.P) or antiepileptic drug (VPA) for more than one year .

3.4. Study Sample

Study sample comprised 220 subjects including 110 psychiatric and epileptic patients (55 psychiatric male and 55 epileptic children) from Mental Health Clinics in Gaza and 110 healthy people as a control group .

3.5. Ethical consideration

The necessary approval to conduct the study from Helsinki committee in the Gaza strip was obtained (Annex 1) and coordination with the Ministry of Health was fulfilled (Annex 2). The participants were given a full explanation about the purpose of the study and assurance about the confidentiality of the information obtained through the questionnaire and blood analysis .

3.6. Data collection

An interview used for filling in the questionnaire which was designed for matching the study need. Face to face interviews were conducted by researcher to collect data. The questionnaire included personal and medical information (the name, age, disease, drug, duration of treatment).

3.7. Blood sampling and processing

Blood samples were collected by the researcher from all subjects, five ml blood were obtained from each subject into vacutainer plain tubes and were left short time to allow blood to clot, then serum samples were obtained by centrifugation at 3000 rpm for 10 min. Serum samples were kept in the deep freeze (-20 °C) until assayed.

3.8. Biochemical analysis

Serum Gamma glutamyltransferase (GGT), aspartate aminotransferase (AST), alanineaminotransferase (ALT), Serum urea, creatinine, uric acid, alkaline phosphatase (ALP), serum total and direct bilirubin (TB, DB) were analyzed using autoanlyzer biosystem A 15 (French)

3.8.1. Determination of serum Urea

Serum urea was determined using LABKIT.

Method : Urease –GLDH. Kinetic.

Principle

Enzymatic determination was done according to the following reaction

$$\text{Urea} + H_2O + 2H^+ \xrightarrow{\text{Urease}} (NH4)^+_2 + CO_2$$

$$NH^+_4 + \alpha\text{-Ketoglutarate} + NADH \xrightarrow{\text{GLDH}} H_2O + NAD^+ + \text{L-Glutamate}$$

GLHD = Glutamate dehydrogenase

Reagents composition

Components		Concentration
Reagent : R1		
Buffer	TRIS pH 7.8	80 mmol/L
	α Ketoglutarate	6 mmol/L
	Urease	75000 U/L
R2		
Enzymes	GLDH	60000 U/L
	NADH	0.32 mmol/L
UREA CAL	Urea aqueous primary standard 50 mg/dl	

Preparation and stability of working reagent

Working reagent (WR)

R1 buffer (4 vol.) + R 2 substrate (1vol.) were mixed together .

The (WR) was stable for 1 month at 2-8°C.

UREA CAL: Ready to use .

Once open it was stable up to 1month when stored tightly closed at 2-8 °C.

Procedure

Wavelength	340 nm
Temperature	37 C/ 15-25°C
Cuvette	1cm light path

Reading against distilled water was performed .

	Blank	Standard	Sample
WR (ml)	1.0	1.0	1.0
Standard (µl)	-	10	-
Sample (µl)	-	-	10

1. Mixing and reading the absorbance after 30 seconds (A1) and 90 seconds (A2) was performed.
2. Calculation: ΔA=A1-A 2 was done .

Calculation

$$\text{Urea in the sample (mg/dl)} = \frac{(\Delta A)\text{Sample}}{(\Delta A)\text{ Calibrator}} \times 50 \text{ (Calibrator conc.)}$$

3.8.2. Determination of serum Creatinine

Serum creatinine was determined according to Jaffe using LABKIT .

Method : Jaffe Colorimetric - Kinetic.

Principle

The rate of formation of a colored complex between Creatinine and alkaline picrate was measured .

Reagents composition

Components		Concentration
Reagent 1 (Picric Reagent)	Picric Acid	17.5 mmol/L
Reagent 2 (Alkaline Reagent)	Sodium hydroxide	0.29 mol/L
Creatinine Cal	Creatinine aqueous primary calibrator	2 mg/dl

Preparation and stability of working reagent

Mixing 1volume of R1 with 1volume of R 2 was performed .

The (WR) is stable for 10 days at 2-8°C.

Procedure

Wavelength	492 nm (490-510)
Temperature	37C/ 15-25°C
Cuvette	1cm light path

Reading against distilled water was performed .

	Blank	calibrator	Sample
WR(ml)	1.0	1.0	1.0
calibrator (µl)	-	100	-
Sample(µl)	-	-	100

Mixing and reading the absorbance after 30 seconds (A1) and 90 seconds (A2) was performed.

Calculation

$$\text{Creatinine in the sample (mg/dl)} = \frac{(\Delta A)\text{Sample}}{(\Delta A)\text{ Calibrator}} \times 2 \text{ (Calibrator conc.)}$$

3.8.3. Determination of serum Uric acid

Serum uric acid was determined according to Globe Diagnostics S.R.I

Method : Enzymatic colorimetric

Principle

The rate of formation of purple quinoneimine whose intensity of colour is proportional to the concentration of uric acid is measured .

Reagents composition

Components	**Concentration**
Borate Buffer pH 7.0	180 mmol/L
Uricase	> 50 U/L
Cholesterol esterase (CHE)	> 300 U/L
4-aminopherazone	0.25 mmol/L
ESPT(N-ethyl-N-(hydroxi-3-sulphopropil)-p-toluidine	1 mmol/L
Peroxidase(POD)	> 100 U/L
NaN3	≤ 0.095 g/L
Standard : Uric acid	6 mg /dl

Preparation and stability of working reagent

The reagent is ready for use .

Procedure

Wavelength	550 nm (540-560nm)
Temperature	20, 25or 37C°C
Optical path	1cm
Reaction	End point

	Blank	Standard	Sample
Reagent A	1 ml	1 ml	1 ml
Standard	-	25 µl	-
Sample	-	-	25 µl

Mixing and reading the absorbance after 10 min at 37°C or for 15 min at 20-25 °C was performed.

Calculation

$$\text{Uric acid in the sample (mg/dl)} = \frac{(\Delta A)\ \text{Sample}}{\Delta(A)\ \text{Standard/ Cal}} \times \text{standard/Cal. Conc.}$$

3.8.4. Determination of serum Alanine aminotransferase (ALT)

Serum ALT was determined according to Globe Diagnostics S.R.I

Method

Optimized UV test according to Scandinavian Committee on Enzymes (SCE).

Principle

Enzymatic determination was done according to the following reaction

ALT

L-Alanine + 2-Oxoglutarate ⟷ L-Glutamate + Pyruvate

LDH

Pyruvate + NADH +H ⟷ L-Lactate + NAD

Reagents composition

Components	Concentration
Reagent A	
TRIS buffer	28 mmol/L
EDTA –Na2	5.86 mmol/L
L-Alanine	568 mmol/L
LDH	≥ 1700 U/L
Sodium azid	2 g / L
Reagent B	
2-Oxoglutarate	68 mmol/L
NADH	1.12 mmol/L
Sodium azid	0.095 g/ L

Preparation and stability of working reagent

Mix 10 volumes of reagent A+ 1volume of reagent B (monoreagent) was done .

WR was stable for : 4 weeks at 2-8 °C

5 days at 15-25 °C

Procedure

Wavelength	340 nm, Hg 365 nm, Hg 334 nm
Temperature	37°C
Optical path	1cm
Reaction	Kinetic

All reagents reached to working temperature before use

Monoreagent Procedure	
Monoreagent	1000 µl
Sample	100 µl
Mixing and reading absorbance after 1 min then again after 1, 2 and 3 min was done .	

Calculation

From absorbance reading calculation Δ A/min and multiply by the corresponding factor from the table below was performed

ALT activity (U/L) = Δ A/min X factor (f)

Monoreagent procedure

340 nm f =1746

365 nm f = 1780

365 nm f = 3235

3.8.5. Determination of serum Aspartate aminotransferase (AST)

Serum AST was determined according to Globe Diagnostics S.R.I

Method: Optimized UV test according to Scandinavian Committee on Enzymes (SCE).

Principle

Enzymatic determination was done according to the following reaction

$$\text{L-Aspartate} + \text{2-Oxoglutarate} \xrightarrow{\text{AST}} \text{L-Glutamate} + \text{Oxalacetate}$$

$$\text{Oxalacetate} + \text{NADH} + \xrightarrow{\text{MDH}} \text{L-Malate} + \text{NAD+}$$

Reagents composition

Components	Concentration
Reagent A	
TRIS buffer	28 mmol/L
EDTA –Na2	5.68 mmol/L
L-Aspartate	284 mmol/L
MDH(Malate dehydrogenase)	≥ 800 U/L
Sodium azid	2 g / L
R B	
2-Oxoglutarate	68 mmol/L
NADH	1.12 mmol/L
Sodium azid	0.095 g/ L

Preparation and stability of working reagent

Mix 10 volumes of reagent A+1volume of reagent B (monoreagent) was done .

WR was stable for : 4 weeks at 2-8 °C

5 days at 15-25 °C

Procedure

Wavelength	340nm, Hg 365, Hg334nm
Temperature	37°C
Optical path	1cm
Reaction	Kinetic

All reagents reached to working temperature before use

Monoreagent Procedure	
Monoreagent	1000 µl
Sample	100 µl
Mixing and reading absorbance after 1 min then again after 1, 2 and 3 min was done .	

Calculation

From absorbance reading calculation Δ A/min and multiply by the corresponding factor from the table below was performed

AST activity (U/L) = Δ A/min X factor (f)

Monoreagent procedure

340 nm f =1746

334 nm f = 1780

365 nm f = 3235

3.8.6. Determination of serum Alkaline phosphatase (ALP)

Serum ALP was determined according to Cromatest

Method : Kinetic

Principle

Enzymatic determination was done according to the following reaction

$$\text{4-Nitrophenylphosphate} + H_2O \xrightarrow[pH > 9]{\text{ALP, Mg}} \text{4-Nitrophenol} + Pi$$

Reagents composition

Components	Concentration
Reagent 1 ALP buffer . DEA buffer Magnesium chloride biocides	 1.25 mol/L pH 10.2 0.6 mmol/L
Reagent 2 ALP substrate .4-NPP biocides	 50 mmol/L

Preparation and stability of working reagent

Working reagent (WR)

R1 (4vol.) +R2 (1vol.) were mixed.

The (WR) was stable for 5 days at 20-25°C or 15-30 days at 2-8°C

Procedure

Wavelength	405 nm
Temperature	25 /30/ 37°C
Cuvettes	1cm pathlength

Reading against distilled water was performed .

Working reagent	1.0 mL
Samples or control	20 µL

1-reagents were mixed and incubated for 1 min and initial absorbance was performed, the absorbance readings were repeated exactly after 1, 2 and 3 min was done .

2-The difference between a absorbance's and calculation the mean of results to obtain the average change in absorbance per min (ΔA/min) was obtained .

Calculation

U/L = Δ A/min X 2764

3.8.7. Determination of serum Gamma glutamyltransferase (GGT)

Serum GGT was determined according to International Federation of Clinical Chemistry (IFCC) by Diasys Diagnostic Systems GmbH

Method : Kinetic photometric test

Principle

Reagents composition

Components	Concentration
Reagent 1	
TRIS pH 8.25	135 mmol/L
Glycylglycine	135 mmol/L
Reagent 2	
L-Gamma-glutamyl-3-carboxy-4-nitroanilide	22 mmol/L

Preparation and stability of working reagent

Sample start

R1 (4 vol.) + R 2 (1vol.) were mixed .

WR: was stable 4 weeks at 2-8 °C or 5 days at 15-25 °C

Procedure

Wavelength	405 nm (400-420 nm)
Temperature	37°C
Optical path	1cm

Reading against reagent blank was performed .

Sample Start	Blank	Sample
Sample /Calibrator	-	100 µL
Dist .Water	100 µL	-
Monoreagent	1000 µ L	1000 µ L
Mixing, incubation for approx.1min was performed, then reading again after 1, 2, and 3 min was done .		

Calculation

U/L = Δ A/min X 1309

3.8.8. Determination of serum Bilirubin (Total and Direct)

Serum bilirubin was determined according to diazotized sulfanilic by Biosystem S.A

Method: Colorimetric

Principle

Coloured complex formed as a result of reaction between direct bilirubin in the sample and diazotized sulfanilic acid, both direct and indirect bilirubin coupled with diazo in the presence of cetrimide .

Reagents composition

Bilirubin (Total)

Components	Concentration
Sulfanilic acid Hydrochloric acid Cetrimide	29 mmol/L 0.2 mol/L 50 mmol/L
sodium nitrite	11.6 mmol/L

Bilirubin (Direct)

Components	Concentration
Sulfanilic acid Hydrochloric acid	35 mmol/L 0.24 mol/L
sodium nitrite	3.5 mmol/L

Bilirubin Standard: reconstituted with 5 ml distilled water .
It was stable for 4 hours at 15-30 °C or for 2 month at -18°C when frozen in aliquots.

Preparation and stability of working reagent

Working reagent: transferred the contents of one reagent BT vial into a reagent AT bottle for total bilirubin, or one reagent BD vial into a reagent AD bottle for direct bilirubin was done. Other volumes prepared in proportion: 1ml reagent BT + 4 ml reagent AT or 1 ml reagent BD +4 ml reagent AD. It was stable for 20 days at 2-8 °C .

Procedure

Wavelength	540 nm (520 -560 nm)
Temperature	37°C
Cuvette	1cm light path

Procedure for Total Bilirubin

	Reagent blank	Sample blank	Sample	Standard
Distilled water	100 µL	-	-	-
Sample	-	100 µL	100 µL	-
Standard(S)	-	-	-	100 µL
Reagent (AT)	-	1 mL	-	-
Working reagent	1 mL	-	1 mL	1 mL

1) Mixing the stand tubes for 2 minutes at room temperature was done.
2) Reading the absorbance (A) of the sample blanks at 540 nm against distilled water was performed.
3) Reading the absorbance (A) of the samples and standard at 540 nm against the reagent blank was done .

Procedure for Direct Bilirubin

	Reagent blank	Sample blank	Sample
Distilled water	100 µL	-	-
Sample	-	100 µL	100 µL
Reagent (AD)	-	1 mL	-
Working reagent	1 mL	-	1 mL

1. Mixing the stand tubes for exactly 5 minutes at 37°C was done
2. Reading the absorbance (A) of the sample blanks at 540 nm against distilled water was performed.
3. Reading the absorbance (A) of the samples and of the standard at 540 nm against the reagent blank was done .

Calculation

$$\text{Sample (mg/dl)} = \frac{\text{A sample - A sample blank}}{\text{A standard}} \times \text{C standard}$$

In calculation of Direct Bilirubin, the absorbance of the standard in Total Bilirubin was used.

3.9. Statistical analysis

Data were computer analyzed using SPSS (Statistical Package for Social Science), then the variables of the study were conducted to multiple statistical tests according to types of variables such as (t – test , chi –square test (X^2)). Result analyzed were expressed as mean ± SD. result was considered statistically significant if the p-value was less than 0.05 .

Chapter 4

Results

4.1. General characteristics of study population

The present study is a case control study which included 220 subjects from both genders; 110 healthy controls and 110 patients receiving drugs for more than one year, 55 of patients suffered from epilepsy and receiving valproic acid as antiepileptic drug while the remaining of cases were psychiatric patients and receiving chlorpromazine with T.H.P as antipsychotic drug. patients comprised 55 males and 55 children's.

4.2. Distribution of patients according to disease

As shown in Table 4.1, the percentage of patients suffering from schizophrenia was 44.5%, while those suffering from epilepsy was 47.3% and those having mental retardation was 8.2% , of the study cases.

Table 4.1 : Distribution of cases with respect to diseases

Disease	Number (n=110)	Percent (%)
Schizophrenia	49	44.5
Epilepsy	52	47.3
Mental Retardation	9	8.2

4.3.Distribution of patients according to residency

Table 4.2 reveals that there was 33.6% of cases from North Governorate, while 30.9% were from Gaza, 27.3% from Middle Zone and 8.2% from South Governorate .

Table 4.2: Distribution of patients according to residency

Governorate	Number (n=110)	Percent (%)
North	37	33.6
Gaza	34	30.9
Middle	30	27.3
South	9	8.2

4.4 Age of subjects

Table 4.3 shows there was no significant difference between cases and control groups in relation to their age. The mean age of children control is 7.9 ± 3.52 while the mean age in male control is 36.8±13.97. The mean age of epileptic children is 8.7±3.70 while the mean age in male psychiatric patients is 40.1 ± 10.90. This applies to patients who were receiving VPA (t= -1.138, p = 0.258), as well as those who were receiving CPZ & T.H.P (t = -1.355, P = 0.178) .

4.3 Age distribution of the study population

Age	**Control (n=55) Mean ± SD**	**Case (n=55) Mean ± SD**	**T**	**P-value**
VPA	7.9±3.52	8.7±3.70	-1.138	0.258
CPZ & T.H.P	36.8±13.97	40.1±10.90	-1.355	0.178

VPA: Valproic acid, CPZ: chlorpromazine hydrochloride, T.H.P: Trihexyphenidyl hydrochloride.

4.5 Distribution of subjects based on receiving regular or irregular treatment

Table 4.4 shows that 37 patients received VPA regularly and 18 patients irregularly , 50 patients received CPZ with T.H.P regularly and 5 patients received drugs irregularly.

Table 4.4 Distribution of cases based on regularity of drug treatment

Type of treatment	Regular (n=87)	Irregular (n=23)	X^2	P-value
VPA	37	18	9.290	0.002
CPZ& T.H.P	50	5		

VPA: Valproic acid, CPZ: chlorpromazine hydrochloride, T.H.P: Trihexyphenidyl hydrochloride

4. 6. Assessment of liver function in epileptic patients receiving Valproic. acid

Table 4.5 shows the results of liver function tests among epileptic patients receiving VPA as antiepileptic drug, there was no significant difference (t = -1.320, p =.190) between cases (26.60±12.03 u/l) and control (24.07±7.54 u/l) in ALT test. There was high statistically significant difference (t = - 4.306, p = 0.000) between cases (34.38±14.06 u/l) and control (25.13±7.52 u/l) in AST test. While there was no significant difference observed in ALP test (t = 1.470, p = 0.145) when compared between cases (472.1± 168.3 u/l) and control (519.1±167.5 u/l), the same result was found in GGT test (t = -1.678, p=0.096) when compared between cases(17.4±6.2 u/l) and control(15.9±3.3 u/l), also there was no significant difference(t = 0.585, p = 0.560) between Total bilirubin in cases (0.79±0.28 mg/dl) and control (0.82±0.16 mg/dl). In Direct bilirubin there was no significant difference (t = -1.127, p = 0.262) between cases (0.24 ± 0.15 mg/dl) and controls (0.21±0.09 mg/dl).

Table 4. 5 : Liver function tests of study population receiving Valproic Acid.

Parameter	Control (n=55) Mean ± SD	Case (n=55) Mean ± SD	T	P value
ALT(u/l)	24.07±7.54	26.60±12.03	-1.320	0.190
AST(u/l)	25.13±7.52	34.38±14.06	-4.306	0.000
ALP (u/l)	519.1±167.5	472.1±168.3	1.470	0.145
GGT(u/l)	15.9±3.3	17.4±6.2	-1.678	0.096
Total Bilirubin(mg/dl)	0.82±0.16	0.79±0.28	0.585	0.560
Direct Bilirubin(mg/dl)	0.21±0.09	0.24±0.15	-1.127	0.262

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: Gamma glutamyl transferase .

4.7. Assessment of kidney function in epileptic patients receiving Valproic. acid

Table 4.6 illustrates that there was no significant difference (t = - 0.179, p = 0.858) between epileptic patients (25.69±9.2 mg/dl) who were receiving VPA and control (25.42±6.6 mg/dl) in Urea test. likewise there was no significant difference (t= - 0.871, p = - 0.386) between cases (0.66±0.15 mg/dl) and control (0.64±0.14 mg/dl) in Creatinine test. As well, there was no significant difference (t= - 0.579, p = 0.564) between cases (4.24±1.21 mg/dl) and control (4.11±1.03 mg/dl) in Uric acid test .

Table 4. 6 : Kidney Function Tests of study population receiving Valproic acid.

Parameter	Control (n=55) Mean ± SD	Case (n=55) Mean ± SD	T	P-value
Urea (mg/dl)	25.42±6.6	25.69±9.2	-0.179	0.858
Creatinine (mg/dl)	0.64±0.14	0.66±0.15	-0.871	0.386
Uric acid (mg/dl)	4.11±1.03	4.24±1.21	-0.579	0.564

4.8. Assessment of liver function in psychiatric patients who were receiving chlorpromazine with Trihexyphenidyl hydrochloride.

Table 4.7 administrate the liver test among psychiatric patients suffered from schizophrenia who were receiving CPZ with T.H.P drugs, there was no significant difference (t = -1.799, p = 0.075) between cases (28.06 ± 12.8 u/l) and control (24.31±8.6 u/l) in ALT test. There was statistically significant difference (t = - 2.965, p = 0.004) between cases (29.73±6.9 u/l) and control (25.31±8.7 u/l) in AST test. There was significant difference in ALP test (t = -2.320, p = 0.022) when compared between cases (209.4±87.2 u/l) and control (178.5±46.3 u/l). There was significant difference in GGT test (t= - 2.838, p=0.005) when compared between cases (30.9±30.2 u/l) and control(19.2±5.1 u/l). There was no significant difference (t = - 1.477, p=0.143) in Total bilirubin between cases (0.94±0.38 mg/dl) and control (0.85±0.17 mg/dl). In Direct bilirubin there was significant difference (t = -3.485, p = 0.001) between cases (0.35±0.32 mg/dl) and controls (0.19±0.05 mg/dl).

Table 4. 7 : Liver function tests of study population receiving chlorpromazine with Trihexyphenidyl hydrochloride

Parameter	Control (n=55) Mean ± SD	Case (n=55) Mean ± SD	T	P-value
ALT(u/l)	24.31±8.6	28.06±12.8	-1.799	0.075
AST(u/l)	25.31±8.7	29.73±6.9	-2.965	0.004
ALP (u/l)	178.5±46.3	209.4±87.2	-2.320	0.022
GGT(u/l)	19.2±5.1	30.9±30.2	-2.838	0.005
Total Bilirubin(mg/dl)	0.85±0.17	0.94±0.38	-1.477	0.143
Direct Bilirubin(mg/dl)	0.19±0.05	0.35±0.32	-3.485	0.001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: Gamma glutamyl transferase .

4.9. Assessment of kidney function in psychiatric patients receiving chlorpromazine with Trihexyphenidyl hydrochloride

Table 4.8 administrates the kidney test among psychiatric patients suffered from schizophrenia who were receiving CPZ with T.H.P drugs. There was no significant difference (t = - 0.891, p = 0.375) between cases (28.71±10.22 mg/dl) and control (27.24±6.8 mg/dl) in Urea test. There was statistically significant difference (t = -6.681, p = 0.000) between cases (1.03±.18 mg/dl) and control(0.81±0.17 mg/dl) in Creatinine test. There was significant difference in Uric acid test (t = -2.208, p = 0.029) when compared between cases (6.25±5.70 mg/dl) and control (4.53±.95 mg/dl) .

Table 4.8 : Kidney function tests of study population receiving chlorpromazine with Trihexyphenidyl hydrochloride.

Parameter	Control (n=55) Mean ± SD	Case (n = 55) Mean ± SD	T	P-value
Urea (mg/dl)	27.24±6.8	28.71±10.22	-0.891	0.375
Creatinine (mg/dl)	0.81±0.17	1.03±0.18	-6.681	0.000
Uric acid (mg/dl)	4.53±0.95	6.25±5.70	-2.208	0.029

4.10. Assessment of liver function in epileptic patients according to regular or irregular treatment

Table 4.9 Illustrates that there was no significant difference (t = 1.418, p = 0.162) between irregular (23.3±7.2 u/l) and regular patients (28.2 ± 13.6 u/l) in ALT test, while there was significant difference (t= 2.673, p=0.010) in AST in irregular (27.5±10.0 u/l) and regular (37.7±14.6 u/l) patients. There was no significant difference (t=1.138 p = 0.260) of irregular (435.2±165.7 u/l) versus regular (490.0±168.8 u/l) in ALP. likewise there was no significant difference in GGT (t = 0.549, p = 0.585), total bilirubin (t = 0.511, p = 0.612), and direct bilirubin (t = 0.786, p= 0.435) between irregular case (16.8±6.3 u/l , 0.76±0.35 mg/dl, 0.23±0.11 mg/dl) and regular case (17.8±6.2 u/l , 0.80±0.25 mg/dl, 0.26±0.22 mg/dl) .

Table 4.9: Liver function tests of patients with respect to regular or irregular treatment of Valproic Acid.

Parameter	Regular (n=37) Mean ± SD	Irregular (n=18) Mean ± SD	T	P-value
ALT(u/l)	28.2±13.6	23.3±7.2	1.418	0.162
AST(u/l)	37.7±14.6	27.5±10.0	2.673	0.010
ALP (u/l)	490.0±168.8	435.2±165.7	1.138	0.260
GGT(u/l)	17.8±6.2	16.8±6.3	0.549	0.585
Total Bilirubin(mg/dl)	0.80±0.25	0.76±0.35	0.511	0.612
Direct Bilirubin(mg/dl)	0.26±0.22	0.23±0.11	0.786	0.435

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: Gamma glutamyl transferase .

4.11. Assessment of kidney function in epileptic patients according to regular or irregular treatment

Table 4.10 Illustrates that there was no significant difference (t = - 0.514, p = 0.610) between irregular (26.6 ± 10.5 mg/dl) and regular patients (25.24 ± 8.6 mg/dl) in Urea test, also there was no significant difference (t = 0.053, p = 0.958) in Creatinine between irregular (0.66±0.14 mg/dl) and regular (0.66 ± 0.15 mg/dl) patients. Likewise there was no significant difference in Uric acid (t = - 0.517, p = 0.607) between irregular case (4.36 ± 1.19 mg/dl) and regular case(4.17±1.23 mg/dl) .

Table 4.10: Kidney function tests of patients classified according regular or irregular treatment of Valproic Acid.

Parameter	Regular (n=37) Mean ± SD	Irregular (n=18) Mean ± SD	T	P-value
Urea (mg/dl)	25.24±8.6	26.6±10.5	-0.514	0.610
Creatinine (mg/dl)	0.66±0.15	0.66±0.14	0.053	0.958
Uric acid (mg/dl)	4.17±1.23	4.36±1.19	-0.517	0.607

4.12. Assessment of liver function in psychiatric patients according to regular or irregular treatment

Table 4.11 reveals that there was no significant difference (t =1.263, p = 0.212) between irregular (21.2±11.4 u/l) and regular patients (28.7 ±12.8 u/l) in ALT test, also there was no significant difference (t = 0.913, p = 0.365) in AST in irregular (29.5 ± 6.8 u/l) and regular (32.4 ± 7.5 u/l) patients. likewise there was no significant difference in ALP (t = 0.849, p = 0.400), GGT (t = 0.129, p= 0.898), Total bilirubin (t = 0.088, p = 0.930) and Direct bilirubin (t = 0.843, p = 0.843) among irregular case (206.2 ± 85 u/l, 30.8 ± 31.6 u/l, 0.92 ± 0.51 mg/dl, 0.33 ± 0.30 mg/dl) and regular ones (241.0 ± 112.4 u/l, 32.6 ± 8.5 u/l, 0.94 ± 0.38 mg/dl, 0.46 ± 0.47 mg/dl)

Table 4.11 : Liver function tests of patients classified with regular or irregular treatment of chlorpromazine with Trihexyphenidyl hydrochloride

Parameter	Regular (n=50) Mean ± SD	Irregular (n=5) Mean ± SD	T	P-value
ALT(u/l)	28.7±12.8	21.2±11.4	1.263	0.212
AST(u/l)	32.4±7.5	29.5±6.8	0.913	0.365
ALP (u/l)	241.0±112.4	206.2±85.0	0.849	0.400
GGT(u/l)	32.6±8.5	30.8±31.6	0.129	0.898
Total Bilirubin(mg/dl)	0.94±0.38	0.92±0.51	0.088	0.930
Direct Bilirubin(mg/dl)	0.46±0.47	0.33±0.30	0.843	0.843

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: Gamma glutamyl transferase .

4.13. Assessment of Kidney function in psychiatric patients according to regular or irregular treatment

Table 4.12 reveals that there was no significant difference (t = - 0.112, p = 0.912) between irregular (29.2 ± 7.3 mg/dl) and regular patients (28.7 ± 10.5 mg/dl) in Urea test, also there was no significant difference (t = - 0.387, p = 0.700) in Creatinine in irregular (1.06 ± 0.11 mg/dl) and regular (1.03 ± 0.18 mg/dl) patients. likewise there was no significant difference in Uric acid (t = -1.081, p = 0.341), among irregular cases (14.1 ± 17.9 mg/dl) and regular case (5.47 ± 1.71 mg/dl).

Table 4. 12 : Kidney Function tests of patients on regular or irregular treatment of chlorpromazine with Trihexyphenidyl hydrochloride

Parameter	Regular (n=50) Mean ± SD	Irregular (n=5) Mean ± SD	T	P-value
Urea (mg/dl)	28.7±10.5	29.2±7.3	-0.112	0.912
Creatinine (mg/dl)	1.03±0.18	1.06±0.11	-0.387	0.700
Uric acid (mg/dl)	5.47±1.71	14.1±17.9	-1.081	0.341

Chapter 5

Discussion

5.1 . Assessment of liver function in epileptic patients receiving Valproic acid

In the present study we examined the liver function test in epileptic children receiving VPA for more than one year. The results showed that ALT, GGT, ALP, Total and Direct bilirubin were not statistically significant when these results were compared with those of control group. On the other hand, AST activity was statistically significant among the study population. These findings are in agreement with other researchers **(104)** those assessed liver function in 42 epileptic children who were treated with VPA, found only 15% of patients receiving VPA showed 6.3 cases of 42 epileptic children had elevated level of ALT enzyme while GGT elevated in 23% of patient receiving VPA which means about 9.6 cases had elevated level of GGT, In our study it was 14.5% cases of epileptic children who had elevated level of ALT enzyme, whereas in GGT elevated in 16.3% cases of epileptic children. Other researchers obtained the same results with the exception of AST where they found no difference between patients and control groups **(111).** This controversy between the present findings and theirs may be due to different sample size and the fact that their target group might have administered the drug for longer periods. The present findings showed a significant difference in relation to AST, which is due to the fact that AST is distributed in many other organs beside liver. Muscle cells contain appreciable amounts of this enzyme. It is well known that antiepileptic drugs affect muscles causing their

relaxation, which may be the cause of elevated activity of AST in these patients. Among our patients, 14.5% of them had elevated levels in ALT and 16.3% with GGT. This finding could be explained on the basis that these administered high doses over a long period of time. Other studies (**101, 108)** correlated high doses with abnormal liver functions. We expect that these children patients did not receive special care and attention from their families in relation to drug administration.

Other studies **(110)** reported the same results with a slight difference in relation to ALT and AST where they significantly increased after two years of treatment with VPA. These difference may be due to the fact that their target group might have administered the drug for longer periods. Elevated level in these enzymes may be due to genetic, environmental factors or preexisting of another disease affected the liver. Our findings showed no significant difference in relation to ALP, TB, DB, and GGT which coincides with other studies **(112**).

Other study **(101)** tested hepatic function in 25 cases treated with VPA. Four patients had abnormal liver function test results. When the dose of VPA was reduced to 10 mg/kg/day, liver function became normal. This finding emphasized role of dose adjustment. In the present study most of patients probably receive the correct dose of VPA. Also other study **(113)** evaluated the relationship between plasma concentrations of VPA and the occurrence of side effects especially hepatotoxicity in patients receiving high doses of VPA. The study showed that adverse effects and clinical signs of liver toxicity may be present in VPA concentrations generally considered in the therapeutic range especially when used in combination with antiepileptic drugs like phenobarbital or carbamazepine and benzodiazepines.

A documented study in **UK (102)** reported 49 cases of hepatotoxicity caused by VPA which ends in death. However, most of those children had other pre-existing problems in addition to epilepsy. Other studies looked for more sensitive indicators than GGT and ALP for liver damage such as serum protein F **(103).** They found that serum protein F levels were elevated in 13% of patients receiving VPA, GGT levels were not raised, ALP elevated levels were observed in 4% of VPA groups. These performing more sensitive indicators to detect the signs of liver damage progression as early as possible is recommended moreover. every community has its own traditions and habits which affect their attitudes towards administering drugs regularly or intermittently or even stop drug administration without physician advice. In addition we cannot ignore the deteriorating economic conditions of our society which acts as a barrier of purchasing the drugs regularly.

5.2 Assessment of kidney function in epileptic patients receiving VPA.

The present study showed no significant differences between patients and control group in relation to kidney function. All tests (urea, creatinine, and uric acid) proved to be normal in both groups. This findings is in agreement of Altunbasak et al **(106)** who found no statistically significant differences between patients and control subjects with respect to blood urea nitrogen, creatinine, uric acid , and creatinine clearance. Other study **(110)** evaluated the effect of VPA on renal enzyme activities in sera of epileptic children. They found that creatinine and uric acid were not statistically significant, similar to present finding . It seems that the kidney is not affected by the metabolites of VPA and these molecules do not cause nephrotoxicity. The dose of VPA is considered to be in the therapeutic range. It means VPA is safe for long term treatment and not toxic to liver or kidney when used in suitable dose.

5.3. Assessment of liver function in psychiatric patients who were receiving chlorpromazine and trihexyphenidyl hydrochloride.

Our study showed that patients who were receiving CPZ with T.H.P had abnormal liver function tests namely AST, ALP, GGT, and DB. These findings are in agreement with those obtained by Garcia-Unzueta et al **(107).** They assessed liver function in 54 schizophrenic patients and recorded elevated levels of ALP, GGT, and bilirubin. However De-ming and Mei-rong **(105)** evaluated the influence of antipsychotic drug on liver function of eighty-six schizophrenic patients who were randomly divided into two groups. One group received the treatment of typical antipsychotic drug (CPZ), another received the treatment of atypical antipsychotic drug (risperidone). The indeces of liver function in all patients were compared respectively before the treatment, and after 4 and 8 weeks of treatment. Despite of short duration of treatment, the results of liver function in the patients of schizophrenia group became remarkably abnormal after four weeks of treatment. TsingHua **(109)** studied the difference in liver function in schizophrenic patients treated with CPZ. ALT levels were elevated after 8 weeks of treatment but after 5weeks it returned to its normal level.

It is noted that the AST enzyme was significantly high among the cases. These results may be due to the decomposition of red blood cells, especially that direct bilirubin was elevated to significant level. This indicated the presence of post-liver problems such as hepatocellular damage, intrahepatic and extrahepatic biliary tract obstruction which might lead to appearance of jaundice among the patients **(100)** .

The variability in the findings of the above mentioned researchers might be due to many factors like socio-economic and, cultural ones. The commitment of patients to the prescribed dose and the high level of health care may contribute to understanding of this variability. However, the present finding was in agreement with the majority of other

studies . For this it is recommended to conduct regular assessment of liver function for patients receiving CPZ. with emphasis on detection of early markers like protein F.

5. 4 Assessment of kidney function in psychiatric patients receiving chlorpromazine and trihexyphenidyl hydrochloride.

Our findings showed that kidney function is affected by the administration of CPZ & T.H.P. This is indicated by significant differences between cases & control groups in relation to creatinine & uric acid, on the contrary urea levels were not significant. Kidney impairment may be due to the fact that some CPZ is excreted unchanged in urine and due to high lipophilic characters of its metabolites, it may be detected in the urine up to 18 months which may cause long term toxicity of the kidney **(74) .**

Chapter 6

Conclusion and Recommendation

6.1 Conclusion

1. Among the cases the percentage of patients who were suffering from schizophrenia was 44.5%, while those suffering from epilepsy represented by 47.3% , 8.2% had mental retardation.
2. In this study 67.3% patients received VPA regularly and 32.7% patients irregularly, 90.9% patients were receiving CPZ with T.H.P regularly and 9.1% patients received drugs irregularly .
3. In epileptic children receiving VPA as antiepileptic drugs, there was high statistically significant difference between cases and control in AST test.
4. There was no significant difference between epileptic patients who were receiving VPA and control groups in relation to blood urea test. likewise there was no significant difference between cases and control in creatinine and uric acid tests .
5. Among psychiatric patients suffered from schizophrenia there was high statistically significant difference between cases and control groups in AST, ALP, GGT, and DB tests ($P< 0.05$).
6. The kidney test among psychiatric patients suffered from schizophrenia who were receiving CPZ with T.H.P drugs, there was high statistically significant difference between cases and control groups in creatinine test and uric acid ($p < 0.05$). which means that the kidneys were affected in psychiatric patients.

6.2 Recommendations

1. The patients should be regularly tested for kidney and liver function every month .
2. Monitoring drug levels in the blood should be carried out regularly.
3. Follow-up patients in their homes is recommended.
4. Introduction of more sensitive tests for liver damage like protein F.
5. More research as are needed to be conducted such as the effect of anti-epileptic & antipsychotic drugs on endocrine glands .
6. Lactate dehydrogenase (LDH) and lipids especially lipoprotein (a) levels and weight should be monitored in patients receiving VPA .
7. Laboratory tests which detect early damage of the kidney e.g. renal enzymes and microalbumin are recommended.
8. New a typical antipsychotic drugs should be used to treat Mental Disorders.

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Annex 1

Palestinian National Authority
Ministry of Health
Helsinki Committee

السلطة الوطنية الفلسطينية
وزارة الصحة
لجنة هلسنكي

التاريخ6/12/2010

Name: **Raisa El Masry**

الاسم: رئيسة المصري

I would like to inform you that the committee has discussed your application about:

نفيدكم علماً بأن اللجنة قد ناقشت مقترح دراستكم حول:-

Assessment of liver and kidney function in patients receiving antipsychotic and antiepileptic drugs in Gaza.

In its meeting on December 2010
and decided the Following:-
To approve the above mention research study.

و ذلك في جلستها المنعقدة لشهر ديسمبر 2010
و قد قررت ما يلي:-
الموافقة على البحث المذكور عاليه.

Signature
توقيع

Member	Member	Chairperson
عضو	عضو	

Conditions:-

- Valid for 2 years from the date of approval to start.
- It is necessary to notify the committee in any change in the admitted study protocol.
- The committee appreciate receiving one copy of your final research when it is completed.

Annex 2

Palestinian National Authority
Ministry of Health
Mental Health General Administration

السلطة الوطنية الفلسطينية
وزارة الصحة
الإدارة العامة للصحة النفسية

التاريخ:16/3/2011

الأخ/ د. عايش سمور حفظه الله،،،

مدير عام الصحة النفسية

السلام عليكم ورحمة الله وبركاته،،،

أنا الطالبة رئيسة خالد المصري طلبة ماجستير تحاليل طبية وأعمل بحث بعنوان تأثير الادوية النفسية على الكبد والكلي.

لذا أرجو من سيادتكم مساعدتي بسحب عينات دم من المرضي الذين يأخذون دواء Depakionأو Largactil من منطقة الجنوب.

وتفضلوا بقبول فائق الاحترام والتقدير،،،

مقدمه
الطالبة/رئيسة المصري

السلطة الوطنية الفلسطينية
وزارة الصحة
الإدارة العامة لتنمية القوى البشرية

The Palestinian National Authority
Ministry of Health
Directorate General of Human Resources Development

الرقم :.../466/10 التاريخ: 2010/04/15

الأخ الدكتور/ فؤاد العيسوي المحترم،،،
مدير عام الرعاية الأولية

تحية طيبة وبعد،،،

الموضوع/ تسهيل مهمة باحث

بخصوص الموضوع أعلاه، نرجو تسهيل مهمة الطالبة/ رئيسة خالد رباح المصري والتي تعمل في الرعاية الأولية – مركز شهداء بيت حانون والملتحقة ببرنامج ماجستير العلوم الحياتية – تخصص تحاليل طبية الجامعة الإسلامية حيث ستقوم بإجراء بحث التخرج بعنوان:

"تقييم وظائف الكبد لدي المرضي النفسيين الذين يتناولون Depakine and Dargactil "

حيث ستقوم الطالبة بالاطلاع علي ملفات المرضي الذين يعانون من أمراض نفسية ويتناولون علاج Depakine and Dargactil، والمترددين علي عيادات الصحة النفسية بالرعاية الأولية بالإضافة إلي أخذ جزء من عينة الدم التي تسحب لهؤلاء المرضي في مراكز الرعاية الأولية حسب النظام المتبع لديهم وبما لا يتعارض مع مصلحة العمل وضمن ضوابط وأخلاقيات البحث العلمي، دون تحمل الوزارة أي أعباء مع أخذ الموافقة الخطية من الأشخاص الذين تشملهم العينة قبل إجراء البحث.

وتفضلوا بقبول خالص الاحترام والتقدير،،،،،،،

مرفق طيه/
- تعهد والتزام

د. ناصر رأفت أبو شعبان
مدير عام تنمية القوى البشرية

وزارة الصحة
الإدارة العامة للرعاية الأولية
الرقم: ٦١٣٨٠
التاريخ: ٢٠١٠/٤/٢١

صورة لـ/
- الملف

السلطة الوطنية الفلسطينية
وزارة الصحـــــة
الإدارة العامة للرعاية الأولية

Palestinian National Authority
Ministry Of Health
General Administration of P.H.C

الرقم :

التاريخ: 2010/12/19

السادة / مدراء صحة المناطق المحترمين

السلام عليكم ورحمة الله وبركاته ،،،،

الموضوع: تسهيل مهمة باحث

نفيدكم بأن الطالبة / رئيسة خالد المصري والتي تعمل بالرعاية الأولية ملتحقة ببرنامج ماجستير العلوم الحياتية – تخصص تحاليل طبية – الجامعة الإسلامية ستقوم بإجراء بحث التخرج بعنوان

تقييم وظائف الكبد لدى المرضى النفسيين الذين يتناولون Depakine and Dargactil

حيث ستقوم الطالبة بالإطلاع على ملفات المرضى الذين يعانون من أمراض نفسية ويتناولون Depakine and Dargactil والمترددين على عيادات الصحة النفسية بالإضافة الى اخذ جزء من عينة الدم التي تسحب لهؤلاء المرضى في مراكز الرعاية .

للتكرم بتسهيل مهمتها بما لا يتعارض مع مصلحة العمل وضمن ضوابط وأخلاقيات البحث العلمي .

واقبلوا التحية ،،،،

مدير عام الرعاية الأولية
بوزارة الصحة
الدكتور / فؤاد عبد الحليم العيسوي

وزارة الصحة
الإدارة العامة للرعاية الأولية
الرقم: ٣٧١٣
التاريخ: ٢٠ / ١٢ / ٢٠١٠

- تتم على جميع المراكز الصحية

السلطة الوطنية الفلسطينية
وزارة الصحة
الإدارة العامة للمستشفيات

Palestinian National Authority
Ministry Of Health
Hospitals General Administration

الرقم:أ.م

التاريخ:12-10-2010

السيد/ مدير عام مجمع الشفاء الطبي المحترم،،
السيد/ مدير عام مجمع ناصر الطبي المحترم،،
السيد/ مدير مستشفى النصر للأطفال المحترم،،
السيد/ مدير مستشفى التخصصي للأطفال المحترم،،
السيد /مدير مستشفى كمال عدوان المحترم،،،
تحية طيبة وبعد ،،

الموضوع/ تسهيل مهمة باحث.

إشارة إلى الموضوع أعلاه وإلحاقاً لكتاب تسهيل مهمة الباحثة/ رئيسة خالد المصري نفيدكم علماً أن موافقتنا على تسهيل مهمة الباحثة يتضمن فقط تعبئة الاستبيان واخذ جزء من العينات المسحوبة أصلاً للمرضى بهدف التشخيص والعلاج ولا يشمل استخدام أجهزة وأدوات ومواد وزارة الصحة وعليها تحمل إجراء الفحوصات المخبرية على حسابها الخاص خارج وزارة الصحة دون تحمل الوزارة أي أعباء و بما لا يتعارض مع مصلحة العمل وضمن ضوابط وأخلاقيات البحث العلمي.

وتفضلوا بقبول فائق الاحترام،،،،

د. محمد الكاشف
مدير عام المستشفيات

الاخ الدكتور كمال الدعوس
لتسهيل المهمة على ان لا يتعارض
مع مصلحة العمل والوزارة

الإدارة العامة للمستشفيات
صادر
رقم: ٤٤٧
التاريخ: ١٣/١٠/٢٠١٠

- صورة للسيد مدير عام تنمية القوى البشرية

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FROM :

The Palestinian National Authority
Directorate General of Human Resources Development

السلطة الوطنية الفلسطينية
الإدارة العامة لتنمية القوى البشرية

الرقم: ١٠/٤٦٥

التاريخ: 2010/04/15

الأخ الدكتور/ عايش سمور المحترم،،،

مدير عام الإدارة العامة للصحة النفسية المجتمعية

تحية طيبة وبعد،،،

الموضوع/ تسهيل مهمة باحث

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صورة لـ/
- الملف