EVIDENCE BASED PHARMACOGENETICS STUDY OF THE USE OF ANTIPSYCHOTICS IN TREATMENT OF SCHIZOPHRENIA

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SUMMARY

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Schizophrenia is a chronic, severe and disabling psychiatric disorder. Although no cure as such, has been developed effective treatment now exists. The first breakthrough in treatment, was the introduction of Chlorpromazine. The typical drugs of which Chlorpromazine was the first, were superseded by Atypical drugs their prototype drug was Clozapine. Clozapine is seen as 'unique' as it can be used to treat 'treatment-resistant' patients, who do not benefit from other drugs. However not all the patients who are given Clozapine, experience a response. This variability in response can range from benefit to serious adverse effects. So the aim in this project was to determine what predicts response. There are many factors, which may influence how well an individual responds to a certain drug such as age, dose, gender and genetics. This project will discuss how genetics can influence variability in response. To do this polymorphisms within receptor subtypes were examined for their link to clozapine response.

Clinical studies which have investigated the association between polymorphisms within receptor subtypes and the prediction of response to clozapine were identified through systematic searches of various databases. If the inclusion criteria was fulfilled then the studies were retrieved. Relevant data was then extracted from each study, and tabulated, to await qualitative analysis.

The majority of the studies involved Dopamine and Serotonin receptor subtypes. Studies involving Adrenaline, Glutamate and Histamine were also retrieved. Findings were very contradictory, this may be due to factors such as ethnic heterogeneity, difficulty in measuring response and an insufficient sample size.

Although no firm conclusions could be reached, due to the conflicting findings reported, there may be several potential associations between polymorphisms and clozapine response. These possible links should be investigated further through replication studies. It is hoped that if associations are identified this would go some way to replacing the 'trial and error' approach of finding the correct medication for a patient that is currently practiced. Instead patients would get the right drug according to their genotype.

Keywords: clozapine, response, polymorphism(s), receptor, genetic(s)

Dedication

To my dad, mum and sister

Acknowledgements

I would like to thank Professor Wilson for taking on my project, when he already had many other commitments, it is much appreciated, as is all the time and effort that was put in. The comments and suggestions of Dr Marriott and Professor Griffiths on drafts of this thesis are gratefully acknowledged. I am also thankful to Professor Griffiths for all her help and support.

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List of Abbreviations

(-)1438A/G – A novel G to A base change at position -1438

5-HT – Serotonin (5-HT) receptor genes

5-HT2A – Serotonin 5-HT2A receptor subtype

5-HT2C - Serotonin 5-HT2C receptor subtype

5-HT3 - Serotonin 5-HT3 receptor subtype

5-HT5A - Serotonin 5-HT5A receptor subtype

5-HT6 - Serotonin 5-HT6 receptor subtype

α_{1A} – Adrenergic receptor subtype 1A

α_{2A} – Adrenergic receptor subtype 2A

AIMS - Abnormal Involuntary Movement Scale

BP (bp) – Base Pair

BPRS - Brief Psychiatric Rating Scale

C267T – A Thymidine to Cytosine substitution at position 267

c-AMP - Cyclic Adenosine Monophosphate

CGI - Clinical Global Impression

CYP P450 – Cytochrome P450

CYP1A2 – Cytochrome 1A2

CYP2C19 – Cytochrome 2C19

CYP2D6 – Cytochrome 2D6

CYP3A4 – Cytochrome 3A4

Cys23Ser – A Serine to Cysteine subsitution at position 23

D_2, D2 – Dopamine 2 subtype receptor

D_3, D3 – Dopamine 3 subtype receptor

D_4 , D4 – Dopamine 4 subtype receptor

DMEs - Drug Metabolising Enzymes

DSM-III – Diagnostic and Statistical Manual , 3rd Version

DSM-IV-R - Diagnostic and Statistical Manual , 4th version , revised

EBM – Evidence Based Medicine

EI - The Efficacy Index

EM - extensive metabolisers

EPS – Extra Pyramidal Side-effects

fMRI - functional Magnetic Resonance Imaging

GAF - Global Assessment of Functioning

GAS – Global Assessment Scale

Gly11Arg – A Glycine to Arginine substitution at position 11

H1 – Histamine subtype 1 receptor gene

His452Tyr – A histidine to tyrosine amino acid substitution at position 452

HRR - Haplotype Relative Risk

ICD –10 – International Classification Disease, 10th version .

Ins/Del – A Insertion/Deletion polymorphism

LSD - Lysergic Acid Diethylamide

MRI - Magnetic Resonance Imaging

NMDA – N-methyl D-Asparate

PANSS - Positive and Negative Syndrome Scale

PANSS–N – Positive and Negative Symptom Scale – Negative symptom scale

PANSS–P - Positive and Negative Symptom Scale – Positive symptom scale

PDA - Partial Dopamine Antagonists

PET - Positron Emission Tomography

PM - Poor metabolisers

QTc – Corrected Q-T Interval

SANS - Scale for the Assessment of Negative Symptoms

SE - Side Effect score

Ser9Gly – A Serine to Glycine substitution at position 9

Ser311Cys – A Serine to Cystine substitution at position 311

SNP - Single Nucleotide Polymorphism

T102C – A Thymine to Cytosine substitution at position 102

TD – Tardive Dyskinesia

TS - Therapeutic Score

UM - Ultra-rapid metabolisers

U.S / U.S.A – United States / United States of America

VNTR - Variable number of tandem repeats

WHO – World Health Organisation

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CHAPTER 1

1.1 - Introduction

Schizophrenia is a severe, chronic and disabling psychiatric disorder, which causes sufferers to lose touch with reality (Vaswani 2001). It is characterized by a significant disruption to thinking and perception (Widschwendter 2005) that affects the most basic of human attributes such as language and an individuals sense of self (Vanderzeypen 2003). Schizophrenia is one of a number of related mental disorders known as psychoses. These are defined as disorders of the severest kind (Mueser 2004), in which there is extreme disruption to personality. All of them have varying patterns of onset and outcome. Psychotic illnesses can be characterized by a number of symptoms including hallucinations, delusions and disturbances in thought (Andreasen 2000). These symptoms are not easily recognized in the early stages as signs of schizophrenia; over time symptoms often worsen to include manifestations, for example seeing things which are not there (hallucinating). As the disorder progresses to the first psychotic episode many more symptoms are associated; these can be categorized into positive or negative symptoms (NICE 2002, Andreasen 1985, Chang 1990).

As yet no definitive cause for this disease has been identified, but effective treatment is now available in the form of antipsychotic agents (Neuroleptics) (Davis 1975, Lydiard 1988). As the name suggests, they act against the symptoms produced by this psychotic disorder. Although these do not cure this illness, they help to alleviate some of the symptoms. Antipsychotics drugs have been divided into two groups: 'Typicals' and 'Atypicals'. Typicals are the older, more conventional agents such as chlorpromazine, whereas Atypicals are the newer agents, such as Clozapine. Since the

introduction of Atypicals (around 1990 with the introduction of Clozapine), many controversies have arisen, concerning for example, dose / response (NICE 2002), associated extra-pyramidal side effects (EPS) and risk / benefit. This project will focus on Clozapine and will look to answer the question of interindividual variability in response to this drug. Interindividual variability in response remains a significant issue, as it is still unclear what makes some patients respond to the drug while others may have no effect.

1.2 – History of Schizophrenia

Even after hundreds of years, schizophrenia remains a disorder which can cause fascination and controversy. However the word 'schizophrenia', is less than a century old (Hell 1995) with the disorder being first identified as a mental illness by Dr Emile Kraepelin (Kraepelin 1971) in 1887. It is thought, however, that this illness has been with man throughout history without being recognized and diagnosed (Crighton 1996, Heinrichs 2003).

Schizophrenia can be traced back to Egypt, as far as the second millennium before Christ through written documents. A recent study looking into Roman and ancient Greek literature, has demonstrated that it is likely that the general population did have an understanding of psychotic illnesses (Evans 2003).

Early theories believed that mental illnesses were caused by evil possessing the body (Palha 1997, Mirsky 2005) and the cure would be to exorcise the demons by means ranging from fairly safe methods, such as exposing the individual to certain types of music, to dangerous ones, such as drilling holes into the patients skull to release the demons (Mirsky 2005).

Dr Emile Kraepelin, (Kraepelin 1971) a German Psychiatrist, was one of the first individuals to distinguish between the different mental disorders. He used the term 'dementia praecox' (Barrett 1998), to identify individuals with the symptoms that we now recognise as those of schizophrenia. This early non-specific concept of madness, defined by Kraepelin as 'dementia praecox', was around for many thousands of years before being recognised as a specific mental illness by Kraepelin in 1887 (Crighton 1996). Kraepelin was the first to distinguish between what he called 'dementia praecox' and manic depression. Kraepelin believed that 'dementia praecox ' was essentially a disease of the brain and more importantly, a form of dementia. Dementia Praecox, meaning early dementia, was named so to distinguish it from other forms of dementia such as Alzheimers disease which occurs in later life. A definition of dementia praecox is any of several psychotic disorders characterised by distortions of reality and disturbances of thought and language and withdrawal from social contact. This term is no longer in scientific use because more accurate expressions are now available. The majority of Kraepelins work focused on younger individuals suffering from dementia.

The term 'schizophrenia' was coined in 1911 by Swiss psychiatrist Eugen Bleuler (Bleuler 1950, Hell 1995). He was the first to divide the symptoms of schizophrenia into positive and negative. The change in the name of the disease to schizophrenia, arose because the name given by Kraepelin was considered to be misleading. Firstly, schizophrenia is not a form of dementia (Schoenholtz 2005) as it does not lead to mental deterioration. Secondly it can develop in later in life, as well as in early life (Schoenholtz 2005).

The origin of the word 'schizophrenia' comes from the Greek for 'split ' schizo, and 'mind' phrene, which describes the disorganised thinking of sufferers with this illness (Benedetti 1995). A common misconception, which arises from Bleuler definition (Ban 2004), is that schizophrenia is the idea of a split mind or multiple personalities (Stotz-Ingenlath 2000). Even now, the definition of this illness is continuing to change as scientists endeavour to accurately outline the different forms of mental illnesses. This is made much harder since the cause of these diseases remains unknown and therefore definitions can only be based on observations of the symptoms experienced by sufferers.

A similarity between both Kraepelin's and Bleuler's definition is that both tried to subdivide the disorder according to its symptoms and prognoses (Andreasen 1997). This approach has continued (Andreasen 1997) and currently five types of schizophrenia are outlined in the DSM-III (Diagnostic and Statistical Manual, 3rd version). These are catatonic, disorganized, paranoid, residual and undifferentiated. The first three types were originally described by Kraepelin (Ban 2004).

Newer versions of the DSM, such as DSM-IV-R (4th version revised) (American Psychiatric Association 1994), still use these classifications but they have been shown not to be helpful in predicting outcome to this disorder. Therefore accurate diagnoses are not possible (DSM-IV). The majority of researchers are now using other systems to classify the different types of this disorder. They use a range of characteristics, such as the prevalence of negative symptoms vs positive symptoms, the progression of the disorder, the type and severity of symptoms over a period of time and the co-occurrence of other disorders. It is hoped that by linking the various types of schizophrenia according to their clinical symptoms, this may aid the determination of

different causes and aetiologies of these mental disorders. Over the last two decades there has been accumulating evidence to suggest that Schizophrenia is a genetic and biologically based disorder (Mohammadi 2001). Further support for the above theory, comes from dynamic brain imaging systems which clearly shows the wave of tissue destruction which occurs in the brain of individuals with schizophrenia.

There is hope that advances in the understanding of the genetic basis of the disease will one day, help answer essential questions regarding causes and aetiologies.

1.3 – Epidemiology

This disease affects 1 in every 100 people worldwide (1 % worldwide) (American Psychiatric Association 1994) and is one of the ten leading causes of global disability in the world. It is equally prevalent in men and women (Carpenter 1994) but the age of onset varies between the genders. In men, the first signs of this illness are generally seen in their mid 20s whereas in women similar signs appear in their late 20s. It has been postulated that this later onset in women could be linked to the effects of oestrogen (Kulkarni 2001) on reduced sensitivity of D2 receptors in the central nervous system (Hafner 1999). The commonest forms of schizophrenia usually afflict individuals in the age range of 15-45. It is more than likely that people suffering from this illness have a genetic predisposition for the illness since the risk of having this illness is nine times greater when a sibling is also affected and twelve times greater risk when a parent is affected (Gottesman 2001). The 1% - 1.5% prevalence (see fig 1) rate for Schizophrenia has remained constant across time, and within various cultures and countries. The social disability and economic cost associated are enormous (Andreasen 1990) because of the severity of the disease and common significant impairment experienced by patients. Despite, its 1-1.5% prevalence,

schizophrenia is more common than a number of other diseases. For example Schizophrenia is twice as common as Alzheimers (see fig 1). Overall schizophrenia is the most serious and disabling of the mental illnesses.

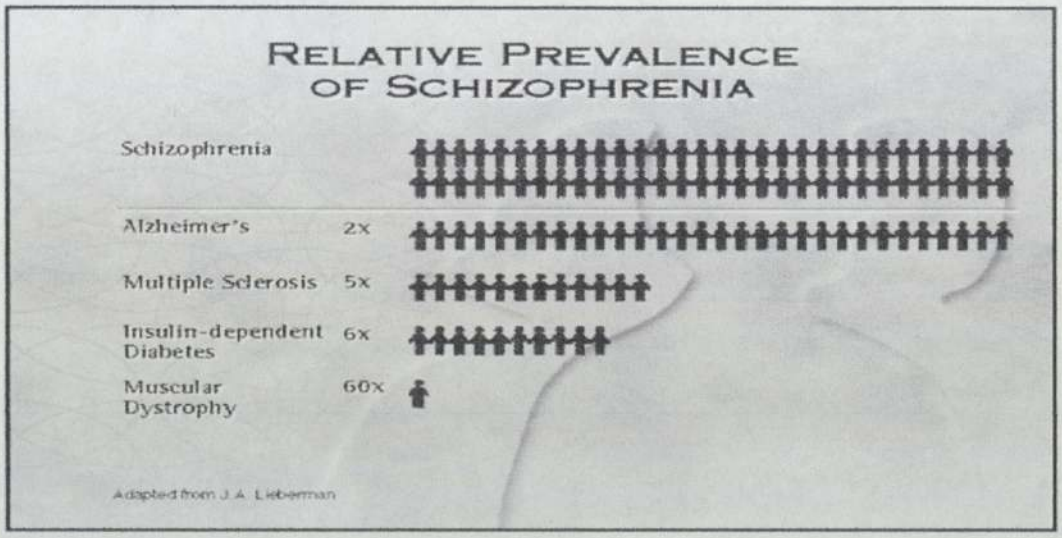

Fig 1: shows the relative prevalence of schizophrenia, when compared to other diseases. (www.chovil.com)

1.4 – Aetiology

Schizophrenia is a complex disorder of the brain, and although the precise cause remains unclear, it seems to involve a combination of genetic and environmental factors (Mueser 2004). However it is interesting to note that the risk of developing schizophrenia between identical twins (share identical genomes) is only 48 % (Gottesman 2001) and this shows that the disorder is not entirely a genetic disease and must have other factors which contribute. Other factors which may also be involved include, stress, trauma and viral infection at an early age (Rehn 2005).

- Genetic factors:

There are a number of reasons why genetic factors have been implicated in the aetiology of schizophrenia. Rates of schizophrenia have been shown to be higher among relatives of sufferers rather than in the general population. Monozygotic twins who share 100% of the same genes were the most at risk at 48%, while first degree relatives such as parents (who share 50% of the same genes) were at 6-17% risk of getting schizophrenia. The risk reduced with the amount of genes shared, with second degree relatives only at a 2-6% risk while the general population has a risk of only 1% (see fig 2) (Gottesman 2001).

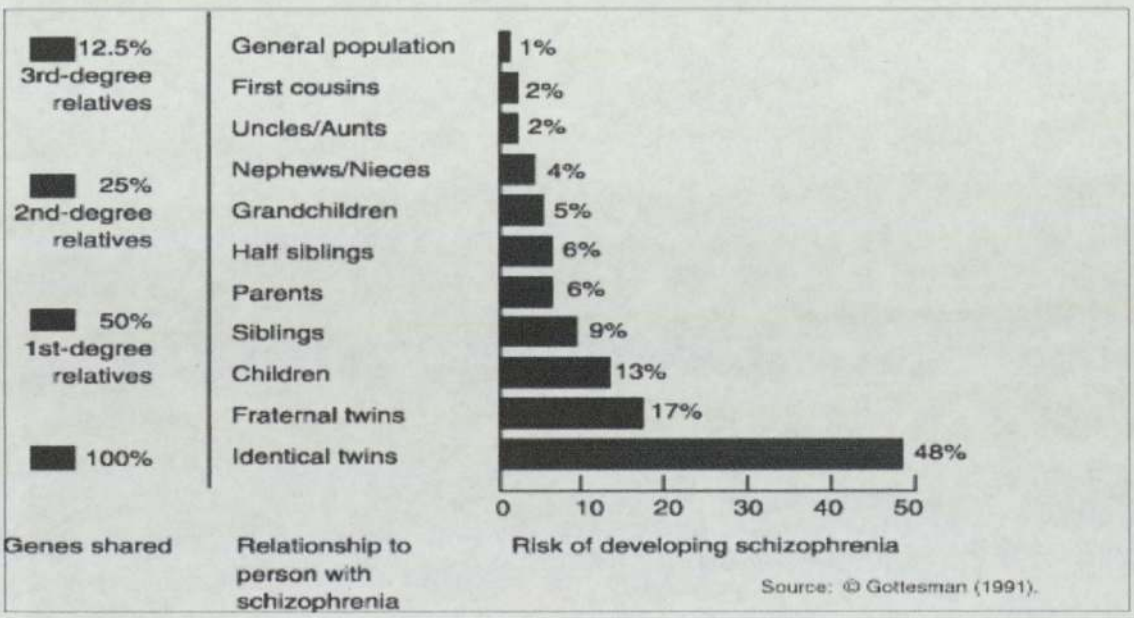

Fig 2: shows the risk of developing of schizophrenia

The current thinking is that genetic transmission does not follow simple Mendelian inheritance patterns, which involve single genes, and is more likely to involve multiple genes, each with a small effect (Mueser 2004, Harrison 2003 and Thaker 2001).

- Environmental factors:

A number of environmental risk factors have been identified including biological and psychosocial factors. The risk of developing schizophrenia is made greater by a variety of prenatal and perinatal events, such as rubella, malnutrition (Levav 1995a,b), smoking during pregnancy and obstetric complications (Susser 1992, Takei 1996 and Thomas 2001). Obstetric complications associated with hypoxia are especially linked to increased risk, which may be mediated by excitotoxic effects of hypoxia on the brain of newborn infants (Cannon 2002). The majority of cases involving obstetric complications do not lead to schizophrenia (Ordonez 2005) and therefore it is possible that such complications may interact with the genetic vulnerability, to increase the risk of schizophrenia (Thomas 2001). It remains unclear, whether the elevated frequency of obstetric complications associated with schizophrenia is the result of abnormal brain development, that is itself associated with genetic vulnerability, or is the consequence of an additional environmental factor.

Many sociodemographic factors have also been linked to increased risk of developing schizophrenia (van Os 1998). Poverty (Mueser 2004) and lower social class are two factors that have long been recognized as possible links to increased rates of schizophrenia. There are currently two hypotheses explaining this link. Social causation, which means that stressful environmental conditions increase the risk of developing schizophrenia and downward social drift, which explains how symptoms of schizophrenia reduce social and occupational functioning. Both of these theories have received support (Fox 1990, Dohrenwend 1998). Another possible factor, is location. It has been found that individuals born in urban areas have a greater probability of developing schizophrenia, compared to those born in rural areas

(Peen 1997).

Even though, the prevalence of this disorder is similar across different ethnic groups, there are increased rates in some ethnic minority groups, such as second generation Afro-Caribbean individuals living in the UK (Boydell 2001) and African-American individuals (Rabkin 1979). These differences may reflect stressful effects which link to being an ethnic minority in the social environment.

1.5 – Pathophysiology

The most frequently recognized neurobiological finding among schizophrenia patients is the enlargement of the ventricular system, in particular of the lateral and third ventricles when compared to healthy controls (Syvalahti 1994). The enlargement of the ventricles also causes an overall reduction in brain volume and cortical grey matter (Andreasen 1994). Decreased volumes in regions such as the frontal lobes (Syvalahti 1994), amygdala, hippocampus, parahippocampus, thalamus, medial temporal lobe cingulated gyrus (Clinton 2004) and superior temporal gyrus have been identified in schizophrenic patients compared with healthy controls (Byne 2002, Choi 2005 and Wright 2000). Ventricular enlargement and reduced brain volume have only been seen to be evident in newly diagnosed patients (Fannon 2000) and may occur in unaffected relatives who are at risk of the disorder. Therefore these signs cannot be attributed to the chronic effect of the illness or to treatment (McDonald 2002).

PET (Positron Emission Tomography) (Gur 1993) is a commonly used technique, that has been used to identify different and possible dysfunctional neural circuitry used in cognitive tasks. This technique allows examination of cerebral blood flow and receptor function in vivo. PET studies have shown (Holzmann 1996) that

schizophrenia sufferers had abnormalities in blood flow to frontal regions, thalamus and cerebellum in the brain (Miller 1997) while performing tasks that involve executive functions such as memory and sustained attention (see fig 3). This reduction in blood flow to the prefrontal region of the brain (Weinberger 1986, Danos 2004) while completing cognitive tasks has been linked to reduced dopamine activity, which plays a role in the pathology of schizophrenia.

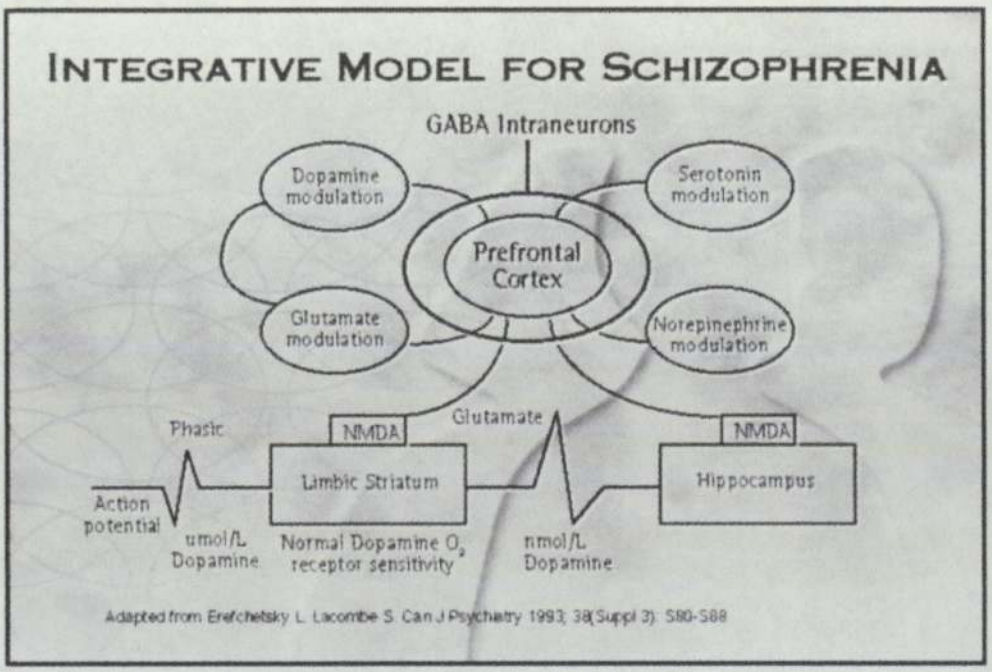

Fig 3: shows an integrative model for schizophrenia.

Functional imaging techniques are another approach used to understand schizophrenia. One of which is functional magnetic resonance imaging (MRI) (Cho 2005, Gur 1993),which allows the assessment of activity in particular parts of brain while the patient completes cognitive tasks. This technique uses deoxygenated haemoglobin as an endogenous tracer. Abnormalities in neural activity in the frontal and temporal areas of the brain have been identified in schizophrenia patients compared to controls (Yurgelun-Todd 1996) (see fig 4). So far findings from fMRI

studies suggest that a disruption in functional circuits could be the cause for such abnormalities (Benes 1998, Danos 2004), rather than localized dysfunction in single brain regions. Neuroimaging studies which show functional and structural irregularities in first-episode (Whitford 2005) never treated patients, suggest that these irregularities are not secondary to treatment or chronicity of the disorder. Losses in social cognition capabilities that involve the ability to accurately process social information such as emotions, are a key characteristic of schizophrenia (Penn 1997) is linked to abnormalities in the left prefrontal cortex (Kaiser 2005).

Another use of fMRI is for longitudinal assessment of psychopharmacological effects on cerebral physiology. A study by Honey and co-workers (Honey 1999) found that after substituting a conventional antipsychotic agent for risperidone, a novel aypical antipsychotic agent, patients performing memory tasks showed significantly improved frontal functioning. This was attributed to raised dopaminergic transmission to the frontal cortex.

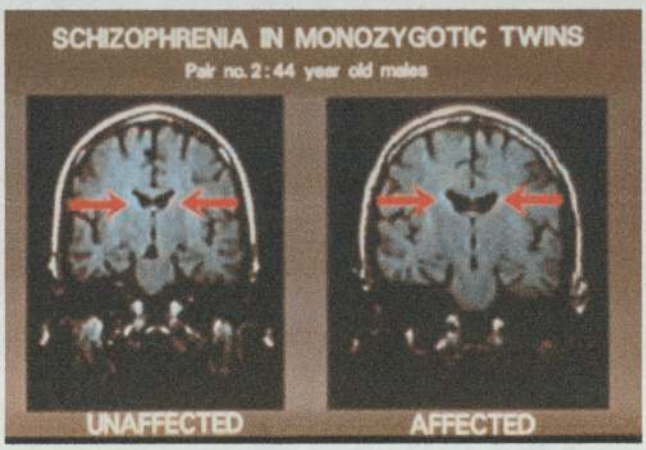

Fig 4: shows an MRI image of monozygotic twins, one affected by schizophrenia, and one not. The arrows seen in the image, point to the ventricles, which are much larger in the affected twin.

1.6 – Diagnosis

Modern concepts about schizophrenia are based on the work of Kraeplin (Kraepelin 1971, Musalek 2005), whose research mainly focused on the long-term deterioration of individuals with this illness, and of Bleuler (Bleuler 1950), who recognized the main symptoms of this disorder as impairments in thinking, loss of directional behaviour, and retreating into an inner world (autism) (Mueser 2004). Two main diagnostic systems used in this illness are the Tenth Revision of the International Classification of Diseases (ICD –10) (WHO 1992) and the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV). Both systems are similar in the way they objectively define symptoms and characteristic impairments experienced by sufferers. As a result, both systems have improved reliability (McCormick 2005, Peralta 2003) and accuracy of diagnosis over more subjective diagnostic methods or approaches. Although similar, there are some important differences between the two systems. The primary one is that in the DSM system there is a requirement for social / occupational dysfunction in order to make a diagnosis of schizophrenia which is not found in ICD-10. Consequently the DSM-IV (American Psychiatric Association 1994) gives a more precise definition of this disorder (Mueser 2004).

When making a diagnosis, it is important to rule out other possible illnesses because patients sometimes may suffer from severe mental symptoms or even psychosis due to undetected conditions. Therefore, before finally concluding that the patient has schizophrenia, a medical history should be taken and a physical examination and laboratory tests should be conducted to eliminate any other possible causes of the symptoms. A number of commonly abused drugs can produce symptoms very similar to that of schizophrenia (Kosten 1997) and for this reason blood and/or urine samples

must be taken and tested for the presence of such drugs.

In some cases it is difficult to tell one mental illness from another. For example, some individuals with symptoms of schizophrenia show prolonged extremes of raised or depressed mood. It is essential to determine whether such an individual has schizophrenia or a manic-depressive (or bipolar) illness. Other individuals, whose symptoms cannot be clearly identified, are sometimes diagnosed as suffering from a 'schizoaffective disorder' (Pope 1980).

As mentioned previously, schizophrenia is a complex disorder that has a wide range of clinical presentations. Criterion-based diagnostic systems, such as the ICD-10 (WHO 1992) and the DSM-III-R / DSM-IV (American Psychiatric Association 1994), describe characteristic symptoms that an individual suffering from schizophrenia should exhibit. For example, the ICD-10 (WHO 1992) states that severe symptoms should be present for a month, whereas the DSM-IV (American Psychiatric Association 1994), states that severe symptoms should be present for six months .The DSM-IV refers to the diagnosis of schizophrenia being based on a constellation of signs and symptoms, which are present for a sufficient period of time, are not caused by another medical condition / substance and which cause substantial impairment in role functioning.

In order to diagnose schizophrenia, all the following criteria should be present: (DSM)

- **Criterion A**: includes hallucinations, disorganized speech, delusions, disorganized / catatonic behaviour and negative symptoms (see below). Of these symptoms, two or more need to be present, during a one month period, in the active phase of the illness. If a patient, however describes strange delusions or auditory hallucinations, consisting of voices, only one of these symptoms is required.

- **Criterion B**: focuses on the deterioration of social and occupational function, for a significant length of time, since the beginning of the disturbance.

- **Criterion C**: any sufferers, with less than 6 months of continued disturbance are excluded.

- **Criterion D**: eliminates sufferers whose illness has a mood aspect, and therefore may be diagnosed as having schizoaffective disorder or a mood disorder.

- **Criterion E**: reinforces the fact that individuals, diagnosed as having schizophrenia, do not suffer from any other medical condition, which may produce similar symptoms to that of schizophrenia.

- **Criterion F**: recognizes that schizophrenia may be diagnosed in patients with an autistic or developmental disorder as long as there has been prominent delusions / hallucinations that have lasted for at least one month.

Individuals with schizophrenia usually exhibit premorbid manifestations of the disorder during their teenage years. These manifestations include low academic achievement, mild social symptoms and disruption to language, thought and perception (Strous 2004). Often at this early stage, these symptoms are not recognizable as the first signs of schizophrenia. However, symptoms may progressively worsen over time to include psychotic manifestations (Tamminga 1998). Once, the symptoms have developed into the first psychotic episode, several further symptoms are associated with the disorder. These symptoms are classified as being either, positive or negative symptoms (Andreasen 1985, Andreasen 1990 and Chang 1990). Positive symptoms are defined as those which show the presence of abnormal behaviour, whereas negative symptoms are those symptoms which show the absence of normal behaviour (see table 1 and figure 5).

Table 1: shows positive and negative symptoms of schizophrenia (see fig 5)

Positive symptoms of Schizophrenia	**Negative symptoms of Schizophrenia**
- Hallucinations	- Social withdrawal
- Delusions	- Isolation
- Disorganised speech and/or thinking	- Poor self care
- Grossly disorganized behaviour	- Blunted mood and facial expression
- Catatonic behaviour	- Lack of spontaneous thinking

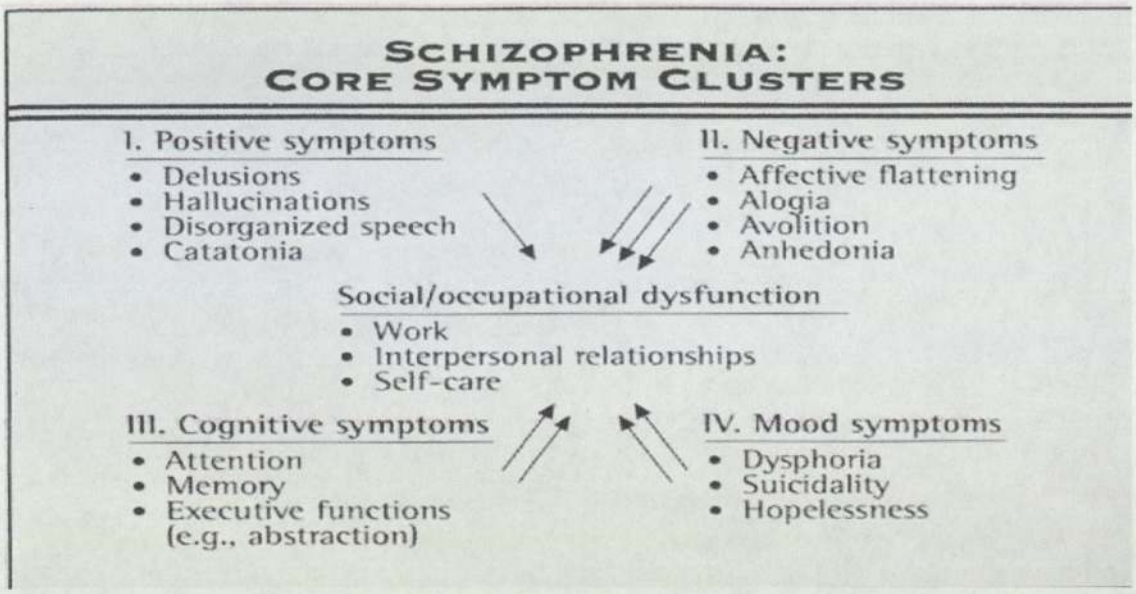

Fig 5: shows the subtypes of symptoms, associated with schizophrenia.

1.6.1 - Common types of schizophrenia include:

Bleuler categorized the following 3 types of schizophrenia (Ban 2004):

- **Paranoid schizophrenia**: (ICD-10)

This is the most common form of schizophrenia where the individual is stable, but usually paranoid with delusional symptoms such as hearing controlling voices and hallucinations. This type of schizophrenia may present in episodes or it can be chronic.

- **Hebephrenic schizophrenia:** (ICD-10)

In this type of schizophrenia, the individual shows mainly negative symptoms such as disorganized speech and thought, unpredictable behaviour and transient hallucinations. This category includes disorganized schizophrenia.

- **Catatonic schizophrenia**: (ICD-10)

In this type the individual primarily exhibits psychomotor disturbances that may alternate between the two extremes eg. hyperkinesis and stupor. Episodes of violence are also characteristic of this type of schizophrenia.

The above types of schizophrenia may overlap at some point, and to variable degrees. Other types of schizophrenia, that are less widespread than those mentioned above, include undifferentiated schizophrenia, post-schizophrenic depression, residual schizophrenia and simple schizophrenia.

1.6.2 - Common Outcome Measures / Rating Scales

The use of rating scales in clinical psychiatric research became increasingly popular in the late 1950's with the introduction of antipsychotics. The main aim of rating scales was to evaluate effectiveness of new drugs when compared with placebo. To conduct accurate ratings, it became essential to develop instruments with a high degree of reliability and validity. Early scales were symptom-based.

The AIMS (Abnormal Involuntary Movement Scale) is the only scale among the ones being described to look at the involuntary movements caused by antipsychotic drugs. The Brief Psychiatric Rating Scale (BPRS) was one of the most commonly used scales in the 1960's and 70s (Ventura 2000) for rating the effectiveness of antipsychotic drugs. This scale was originally designed to measure the outcome effectiveness rather than as a diagnostic scale. The CGI (Clinical Global Impression) scale refers to the doctors impression of the patient. The scale is broken down into 3 parts, with a lower overall score indicating greater improvement. The next scale GAF (Global Assessment of Functioning) is an updated version of the older GAS (Global

Assessment Scale), as the name suggests it rates the patients overall functioning. The PANSS (Positive and Negative Syndrome Scale) is a standard scale used to rate the severity of symptoms. There are sub-scales within this scale, PANSS-N and PANSS-P. A further scale assessing the symptoms associated with schizophrenia is SANS (Scale for the Assessment of Negative Symptoms). All these scales are described in more detail below.

Symptom rating scales:

The content of the items in the scales is similar in both the symptom rating scales and in the later DSM-III (DSM-IV and ICD-10) systems, but the main difference is the way in which the symptoms are quantified and combined.

The symptom rating scales such as the scale used to rate symptoms of AIMS typically quantifies individual symptoms using the Likert scale:

Table 2: shows the Likert scale of rating symptoms.

Point on scale	Symptom rating
0	Not present
1	Mild
2	Moderate
3	Marked
4	Severe

This is different to the way the diagnostic systems rate their symptoms, which is as present (1) or not present (0), rather than breaking down each symptom (DSM 1994).

Further methods of scaling symptoms include clinician-rated scales and patient rated scales (Lindenmayer 1992), where clinician rated scales are those commonly

performed by the therapist, and usually consist of observer rating scales, whereas patient or self rating scales, are questionnaires which are filled in by the patient themselves (Lindenmayer 1992).

The following are observer rating scales:

- Brief Psychiatric Rating Scale (BPRS)
- Positive and Negative Syndrome Scale (PANSS)

The following are commonly used rating scales in psychiatry.

- **AIMS** (Abnormal Involuntary Movement Scale)

This is a standardized physical examination for the assessment of medicine-induced abnormal movements such as tardive dyskinesia. The AIMS scale is particularly used for the evaluation of this condition. The rating scale identifies seven different parts of the body and the most common abnormal movements associated with them (see fig 6). Assessments are made using a 12 point scale (Guy 1976)' with severity ranging from 0-4 (none – severe).

How a patient is examined using the AIMS scale

- Either before or after completing the examination procedure, the patient is observed unobtrusively at rest.
- The patient is to sit in a chair that is firm and without arms.

The clinician will:

1. Ask the patient whether there is anything in his or her mouth (such as candy or gum) and, if so, to remove it.
2. Ask about the current condition of the patient's teeth. Ask if he or she wears dentures. Ask whether teeth or dentures are bothering the patient now.
3. Ask whether the patient notices any movements in his or her mouth, face, hands, or feet. If yes, ask the patient to describe them and indicate to what extent they currently bother the patient.
4. Have the patient sit in the chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at the entire body for movements while the patient is in this position.)
5. Ask the patient to sit with hands hanging unsupported—if male, between his legs, if female and wearing a dress, hanging over her knees. (Observe hands and other body areas.)
6. Ask the patient to open his or her mouth. (Observe the tongue at rest within the mouth.) Do this twice.
7. Ask the patient to protrude his or her tongue. (Observe abnormalities of tongue movement.) Do this twice.
8. Ask the patient to tap his or her thumb with each finger as rapidly as possible for 10 to 15 seconds, first with right hand, then with left hand. (Observe facial and leg movements.)
9. Flex and extend the patient's right and left arms, one at a time.
10. Ask the patient to stand up. (Observe the patient in profile. Observe all body areas again, including the hips.)
11. Ask the patient to extend both arms out in front, palms down. (Observe trunk, legs, and mouth.)
12. Have the patient walk a few steps, turn, and walk back to the chair. (Observe hands and gait.) Do this twice.

The observer will need to conduct the examination prior to scoring the patient. For the movement ratings (the first three categories on the AIMS form), rate the highest severity observed. 0 = none, 1 = minimal (may be extreme normal), 2 = mild, 3 = moderate, and 4 = severe. In general, TD is considered present if a rating of a 2 (mild) or above on the AIMS, on any of the categories, was observed.

Fig 6: shows how the AIMS scale is used, when examining a patient.

- **BPRS** (Brief Psychiatric Rating Scale)

This is a standardized rating scale used to assess the severity of symptoms, particularly psychotic symptoms. The scale consists of 18 items each of which are assessed on a 1-7 scale where 1 denotes that symptoms are not present and 7 denotes symptoms are extremely severe.The higher the score the more severe the disorder. This scale covers both positive and negative symptoms. This was initially published as a 16 item scale in 1962 (Overall 1962). Since then an 18 item scale (known as anchored version) has been developed (Woerner 1988) and this has been in use since 1967. An expanded version is now also available which covers 24 items (Lukoff 1986). This frequently revised form is widely used and is considered to be just as good as the more recently developed scales.

Table 3: shows the points scale used to rate the symptoms in the BPRS scale.

Measure	**Points**
Not present	1
Very mild	2
Mild	3
Moderate	4
Moderate to severe	5
Severe	6
Extremely severe	7

Table 4: shows the expanded 24 item symptom scale for BPRS (- indicates those included in the 18 item scale, * indicates those included in the 16 item scale)

1.	**Somatic concern**	- *	NA	1	2	3	4	5	6	7
2.	**Anxiety**	- *	NA	1	2	3	4	5	6	7
3.	**Depression**	- *	NA	1	2	3	4	5	6	7
4.	**Suicidality**		NA	1	2	3	4	5	6	7
5.	**Guilt**	- *	NA	1	2	3	4	5	6	7
6.	**Hostility**	- *	NA	1	2	3	4	5	6	7
7.	**Elated mood**		NA	1	2	3	4	5	6	7
8.	**Grandiosity**	- *	NA	1	2	3	4	5	6	7
9.	**Suspiciousness**	- *	NA	1	2	3	4	5	6	7
10.	**Hallucinations**	- *	NA	1	2	3	4	5	6	7
11.	**Unusual thought content**	- *	NA	1	2	3	4	5	6	7
12.	**Bizarre behaviour**		NA	1	2	3	4	5	6	7
13.	**Self-neglect**		NA	1	2	3	4	5	6	7
14.	**Disorientation**	-	NA	1	2	3	4	5	6	7
15.	**Conceptual disorganization**	- *	NA	1	2	3	4	5	6	7
16.	**Blunted affect**	- *	NA	1	2	3	4	5	6	7
17.	**Emotional withdrawal**	- *	NA	1	2	3	4	5	6	7
18.	**Motor retardation**	- *	NA	1	2	3	4	5	6	7
19.	**Tension**	- *	NA	1	2	3	4	5	6	7
20.	**Unco-operativeness**	- *	NA	1	2	3	4	5	6	7
21.	**Excitement**	-	NA	1	2	3	4	5	6	7
22.	**Distractibility**		NA	1	2	3	4	5	6	7
23.	**Motor hyperactivity**		NA	1	2	3	4	5	6	7
24.	**Mannerisms and posturing**	- *	NA	1	2	3	4	5	6	7

- **CGI** (Clinical Global Impression)

The title refers to the doctors clinical global impression of the patient (Guy 1976 a, b). The scale measures overall severity of the illness or the degree of improvement. This scale has three components – severity of illness, global improvement and efficacy index. The scale can only be used during or following treatment. Assessment using this scale requires previous experience. The lower the overall score the more signs of improvement. Any concept of improvement is linked to the clinical distance between the individuals current condition and that before the initiation of treatment. The scale is comprised of only 1 item (but with 3 parts), measured on a 7 point scale ranging from 1 which indicates normal or not ill, to 7 which indicates the patient is extremely ill, (0 can also be included which indicates that it was not assessed).

Severity of illness is the first component of the CGI scale. The rating is completed by the investigator at the initiation of the treatment. During this stage the other two components may be omitted by grading them 0, which shows they were not assessed. This item is rated on a 7 point scale where 1 means normal to 7 which means extremely ill (Guy 1976).

Global Improvement is the second component of the CGI scale. The total overall improvement is a judgment of the assessor, as to whether the improvement is entirely due to drug treatment. This component, like the first part, is measured on a weighted 7 point sale ranging from 0 (not assessed) to 7 (much worse) (Guy 1976).

Efficacy Index is the third and final component of the CGI scale. Rating of this component of the scale, involves the assessor selecting from a matrix of four terms for Side Effects (Y axis) and four terms for Therapeutic Effects (X axis). The Efficacy Index (EI) is then calculated by dividing the therapeutic score (TS) by the side effect score (SE).

For example: If TS = 4 and SE = 1 then,

$$\frac{TS \quad (=4)}{SE \quad (=1)} \text{ then } EI = 4$$

This third part of the CGI scale is rated on a four point scale from ' none ' to 'outweighs therapeutic effect' (Guy 1976).

Any success in treatment should result in an overall lower score in all the components of the scale. A consensus has been reached among experts that a reduction of 50 % in the total score is needed in order to consider the treatment as effective.

- **GAF** (Global Assessment of Functioning)

This is a revised version of GAS that was used as Axis V of the DSM-III to assess a patients overall functioning. GAF is a 100 point tool which rates the overall psychological, social and occupational functioning of an individual (over the age of 18). This scale excludes physical and environmental impairment.

This scale evaluates symptoms and functioning during the twelve weeks after treatment. The scale ranges from 1 (sickest) to 100 (healthiest).

Table 5: shows the breakdown of points on the GAF scale

91-100	Superior functioning in a wide rage of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many qualities. No symptoms.
90-81	Absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range or activities, socially effective, generally satisfied with life, no more than everyday problems or concerns.
80-71	If symptoms are present they are transient and expectable reactions to psychosocial stresses; no more than slight impairment in social, occupational, or school functioning
70-61	Some mild symptoms OR some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships.
60-51	Moderate symptoms OR any moderate difficulty in social, occupational, or school functioning.
50-41	Serious symptoms OR any serious impairment in social, occupational, or school functioning.
40-31	Some impairment in reality testing or communication OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood.
30-21	Behavior is considered influenced by delusions or hallucinations OR serious impairment in communications or judgment OR inability to function in all areas.
20-11	Some danger or hurting self or others OR occasionally fails to maintain minimal personal hygiene OR gross impairment in communication.
10-1	Persistent danger of severely hurting self or others OR persistent inability to maintain minimum personal hygiene OR serious suicidal act with clear expectation of death.

- **GAS** (Global Assessment Scale)

This scale has been modified and is now called the GAF scale (Global Assessment of Functioning scale) (Endicott 1976).

- **PANSS** (Positive and Negative Syndrome Scale)

This is a standard rating scale used to assess severity of symptoms (Kay 1987). The PANSS was created as a more thorough and objective method for the evaluation of both positive and negative symptoms as well as other symptoms associated with schizophrenia. The scale comprises of 30 items, each of which is rated on a scale of 1 (absent) – 7 (extreme). It is divided into sub-scales as to cover both positive (PANSS-P) and negative symptoms (PANSS-N). There are scales for both negative and positive symptoms, each made up of 7 items (7 positive symptoms and 7 negative symptoms), there is also a 16 item general psychopathology scale.

Table 6: shows the negative PANSS subscale, showing the negative symptoms of schizophrenia.

Negative symptoms scale item no.	**Item / Symptom**
N1	Blunted affect
N2	Emotional withdrawal
N3	Poor rapport
N4	Passive apathetic withdrawal
N5	Difficulty in abstract thinking
N6	Lack of spontaneity / flow of conversation
N7	Stereotyped thinking

Table 7: shows the positive PANSS subscale, showing the positive symptoms of schizophrenia.

Positive symptom scale item no.	**Item / Symptom**
P1	Delusions
P2	Conceptual disorganization
P3	Hallucinatory behaviour
P4	Excitement
P5	Grandiosity
P6	Suspiciousness / persecution
P7	Hostility

Table 8: shows the general psychological scale, part of the PANSS scale.

General symptom no.	Symptom
1	Somatic concern
2	Anxiety
3	Feelings of Guilt
4	Tension
5	Mannerisms & posturing
6	Depression
7	Motor retardation
8	Uncooperative
9	Unusual thought content
10	Disorientation
11	Poor attention
12	Lack of judgment & insight
13	Disturbance of volition
14	Impulse control
15	Pre-occupation
16	Active social avoidance

The PANSS scores should use all the information from a specified period of time (commonly the previous week). If the item is not present, it is usually given the score of 1. Raised levels of psychopathology are given scores from 2 (minimal) to 7 (extreme).

- **SANS** (Scale for the Assessment of Negative Symptoms)

This is a standardized scale used for the assessment of the negative symptoms associated with schizophrenia. Assessments are made using a six point scale, which cover a wide range of negative symptoms. This scale which evaluates symptoms which are linked to psychological deficits, was developed by Andreasen (Andreasen 1982). There are 30 symptoms in total, which are divided into 5 main symptom subgroups.

As mentioned in the table above (see PANSS), the negative symptoms of schizophrenia, include

1. Blunted Affect,
2. Alogia (poor speech and content of speech),
3. Avolition-Apathy (passive apathetic withdrawal),
4. Anhedonia-Asociality (the inability to feel pleasure, very few social contacts)
5. Attentional Impairments.

These are the main 5 subgroups.

Table 9: shows the breakdown of the six point scale used to grade each symptom.

Symptom	Points
None	0
Questionable	1
Mild	2
Moderate	3
Marked	4
Severe	5

Each symptom is graded using the above point system. The maximum total score is 150, which covers all 30 symptoms.

1.7 – Treatment

As yet there is no definite cure for schizophrenia and consequently the disease is often seen as incurable, severe and debilitating. This perception may hold true for 35% of patients (Kane 1987, see fig 7), but for the majority, the disorder can be less severe and given the correct treatment, sufferers may lead normal productive lives.

Treatment for schizophrenia is multi-faceted and while medication is the 1st line of treatment, counselling, social and family services are additional components that should be provided. Therefore, treatment of schizophrenia can be separated into pharmacological and psychosocial treatment (Mueser 2004).

Pharmacotherapy is the key approach to therapy of schizophrenia and antipsychotic agents are the primary drugs used. The main aim of treatment is to reduce symptoms and prevent relapse. Although, antipsychotics may have a significant effect on psychotic symptoms, the effect on negative symptoms and cognitive impairment is much less significant (Greden 1991).

Prior to the 1990's, the majority of treatment involved typical conventional agents, such as Chlorpromazine and Haloperidol, then the only readily available agents. Clozapine, an atypical agent, was first discovered in 1958 and introduced into Europe in 1975 but then withdrawn due to deaths from agranulocytosis (Hippius 1999). It was re-introduced in 1990 with strict monitoring (Lieberman 1998). Even though effective for the treatment of psychotic symptoms, conventional drugs produce many side effects (Prinssen 1999). The most notable are Parkinsonian and Extra pyramidial symptoms (EPS) which include muscle stiffness, akathisia and tardive dyskinesia.

After the 1990's, several other atypical agents were developed based on Clozapine, which gave effectiveness but with a reduced tendency to cause side effects. With this more favourable side-effect profile, evidence accumulated to suggest that atypical agents are also more clinically effective than typical agents (Davis 2003). However it has been suggested, that this could be due to the high doses of typical agents used in many trials (Lieberman 2003). Clozapine in particular, the prototype for the atypical drugs, has been identified as being unique, in its ability to provide benefit in the treatment of persistent psychotic symptoms, negative symptoms and suicidality. A weakness of Clozapine is that it can lead to agranulocytosis (a reduction in the number of white blood cells, which if undetected can be fatal) (Alvir 1995). Through mandoratory blood monitoring by the Clozaril National Registry, the incidence has

significantly reduced from premarketing values of approximately 1 to 2 % to a current value of 0.38 % (Lieberman 1998). Atypical agents, have been found to have a greater beneficial effect on cognitive functioning than typical antipsychotics (Harvey 2001).

Psychosocial treatment aims to improve the management of schizophrenia, which involves for example helping sufferers cope with the symptoms and to prevent any relapses. Specific interventions, have been found to improve the outcome of this disorder, these include, assertive community treatment, family psychoeducation, supported employment, social skills training, teaching illness management skills, cognitive-behaviour therapy for psychosis and integrated treatment for comorbid substance abuse (Mueser 2004).

Assertive community treatment:

Individuals suffering from severe schizophrenia, usually fail to follow up outpatient treatment. This results in lack of adherence to medication and as a consequence this may result in relapses. In a bid to solve this problem, several multidisciplinary assertive community treatment teams have been created to help those individuals having the most difficulty maintaining a balanced life (Stein 1998). These teams provide a lower staff to patient ratio, usually 1 to 10, as opposed to 1 to 30 (or higher) as it used to be. The majority of services will take place in surroundings suitable for the individual instead of in clinics and there is also 24 hour coverage. Research, from trials mainly carried out in the USA and Australia, has shown that this system reduces symptoms and hospitalizations and generally improves the individuals quality of life (Bond 2001). However, controlled research conducted on reduced staff to patient ratios as compared to traditional patient management ratios has not demonstrated any effect on reduced hospitalizations or improved functioning (Burns 1999, Muijen

1994). A study in England, which investigated intensive community services with typical treatment, was unsuccessful in finding better outcomes with the more intensive treatment (Thornicroft 1998) although this study has been criticized on methodological grounds (Marshall 1999).

Family Psychoeducation:

Since the majority of patients either live with family members, or have continuing contact with relations caring for them, schizophrenia has been linked to raised levels of burden for relatives. When difficulties arise between the patient and their family this may further destabilize the patient. Any additional strain could affect the patients biological vulnerability and induce future relapses and hospitalization (Butzlaff 1998). Family psychoedcuation programmes have been produced to help relieve the burden of care and so improve the management of this disorder. Programmes centre on teaching both patients and relatives about schizophrenia and its treatment with the aim of relieving stress and improving the ways in which individuals and their family can work together, to achieve both individual and shared aims. Research on this type of programme has indicated that it is effective in reducing both relapses and hospitalization rates and one study reported a fall in hospitalization rates fell from 60 % to less than 30 % (Pitschel-Walz 2001).

Supported Employment:

Employment rates for individuals with schizophrenia are low, commonly ranging from 10% - 20 %, even though most individuals want to work (Mueser 2001). To help address this problem, supported employment programmes have been created. The main aims of such programmes are to ensure rapid job search, work in community

surroundings, follow-up support once employment has been found and to pay particular attention to the individuals preferences regarding, for example, job type. Studies have found that this type of programme is more effective than other approaches at improving work outcomes (Bond 2001).

Social Skills Training:

Social dysfunction, is an important symptom of schizophrenia and is manifested by poor relationships with others and a lack of friends. This contributes to a poor quality of life (Erickson 1989). Social skills training, which focuses on social functioning by training patients to use new interpersonal skills, such as initiating conversations and conveying feelings has been shown to improve patients' social and leisure functionings (Heinssen 2001). Furthermore, trips out into the community to practice these skills has also been found to be beneficial (Glynn 2002).

Teaching illness-management skills:

It is widely recognized that nowadays patients may wish to become active in the management of their illness and programmes have been developed to accommodate this (Gingerich 2002, Hogarty 2002). Illness management is composed of several treatment areas, each of which improves knowledge or outcome. Firstly, patients learn about schizophrenia and its treatment so they can make educated choices about their own care (Atkinson 1996). Secondly, patients are taught how to recognize the early signs of relapse and how to prevent them in the future (Birchwood 1989). Thirdly, patients may be taught coping techniques, particularly for more persistent symptoms (Tarrier 1992). Teaching of coping techniques may involve analysis of the situations

that individuals find the most problematic and the use of the skills learnt to ease the situation.

Cognitive Behaviour Therapy for Psychosis:

Persistent psychotic symptoms, are experienced by 25 – 40 % of patients, even with optimal drug treatment (Curson 1988). Psychotic symptoms have been linked to raised levels of distress and may lead to functional impairment, which could mean a reduced ability to work. This type of therapy involves creating a mutual relationship with the patient to uncover under what circumstances these delusions / psychotic symptoms occur (Fowler 1995). Many trials, have shown that Cognitive Behaviour Therapy is effective in reducing both the severity of persistent psychotic symptoms and relapse rates (Gould 2001).

Integrated treatment for co-occurring substance misuse:

Substance misuse is the most common disorder that occurs with schizophrenia (Reiger 1990). Previous efforts to treat substance abuse in schizophrenia patients by referring them to specialists was unsuccessful, mainly because the hospitals had difficulty in maintaining patients in treatment (Ridgely 1990). Programmes in which both substance misuse and schizophrenia were treated concurrently by the same individuals have reported better outcomes (Mueser 2003).

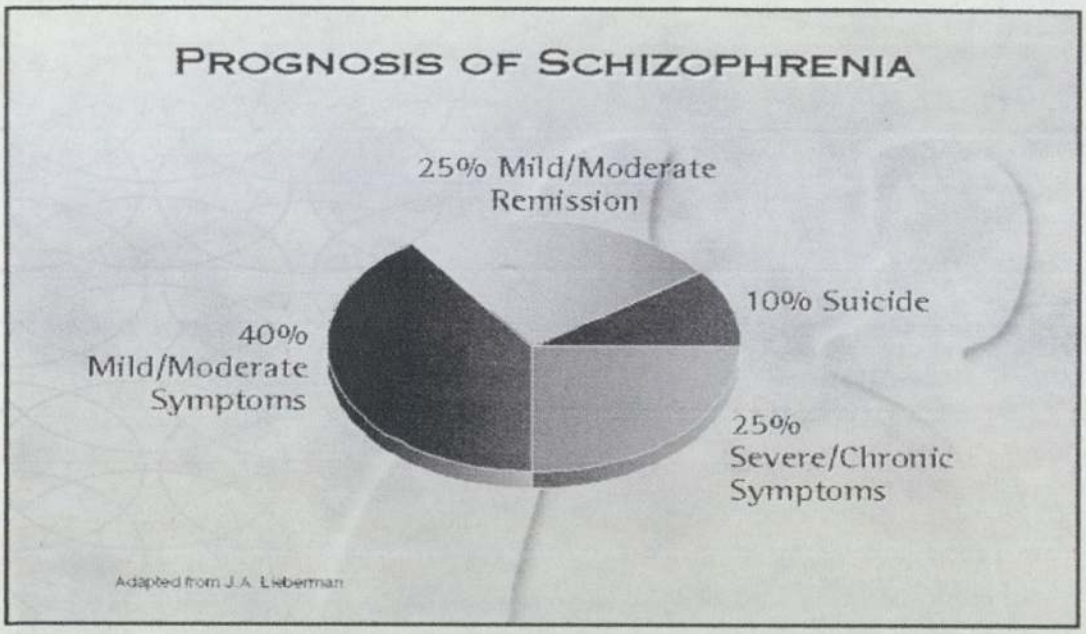

Fig 7: shows the amount of variation in outcome, among individuals diagnosed with schizophrenia. There are various outcomes, but the majority of people, lie in the area between complete recovery and mild symptoms. (www.chovil.com)

1.8 – Need for Evidence based medicine

Schizophrenia is one of the disorders that can still cause fascination even today. It affects 1% of the worlds population but the severity of the impairment experienced by patients, makes this one of the most serious and disabling of the mental illnesses.

The advent of Chlorpromazine, 50 years ago (1952) revolutionized psychiatric treatment. Since then newer drugs, termed 'atypicals', have superseded these older ' typical' drugs, that were then regarded as less effective and more prone to side effects. Now the general consensus is that atypicals and typicals are both equally effective, but atypicals produce fewer side effects. With the advantages that come with atypicals, there are associated costs, as atypicals are far dearer than typicals. So the clinician needs to make a choice about risk / benefit and cost effectiveness. Is the benefit that could be achieved worth the extra cost, they will have to pay. Also, is the

benefit that could be obtained worth the associated risks.

In order for clinicians to make these choices they must keep up-to-date with the latest research. Their main information sources are textbooks, clinical journals and reviews. As with everything, these sources of information will have the author's bias. For example, Slavin (Slavin 1995), stated 'traditional reviews maybe authorative, but subjective and lack rigorous scientific standards.' Sometimes clinicians maybe overwhelmed by the amount of information available, making it difficult for them to critically appraise their clinical importance. Most practicing non-specialists rely heavily upon those secondary sources mentioned above.

Sometimes clinical practice of psychiatry is affected by other factors such as public demand, financial pressures and government policy. For example, first world countries (such as USA and Britain) maybe able to afford these new atypical drugs but third-world countries will barely be able to afford typical drugs.

Also opinion about psychiatry and treatment will vary from psychiatrist to psychiatrist and therefore it is important that their decision about a patient's care is based on the best available evidence (Geddes 1997) and not their subjective views.

Even with the growing popularity of EBM, there still remains a huge gap between research and clinical practice (Geddes 1996). For example, there is still no consensus about optimum dosing for antipsychotic drugs (ie what dose produces the best results) (Marder 1991). Many studies have looked at this question but conflicting findings have been reported. There have been reports that low doses work better, contradictory findings have also been reported. There is debate about the value of low doses (Kane 1995). More replication studies are needed, to improve individual quality of life, and

generally improve standard of care, ultimately leading to individualized treatment, to end the 'trial and error' approach to treatment that is currently practiced.

1.9 – Focus of this thesis

The focus of this thesis concentrated on genetics to examine how this influences variability in response. This variability can range from benefit to extreme adverse effects, therefore it is crucial to identify the factors that control this variability. It is thought that this variability is linked to genetics. It is hoped that if a link between genetics and clinical response is found, patients will get individualized treatment based on their genotype.

CHAPTER 2

2.1 – Introduction

As mentioned earlier, (page 16) it was once thought that schizophrenia was caused by demons or evil spirits (Palha 1997, Mirsky 2005) and that the only treatment was exorcism or painful drilling into the skull to release the evil presence (Mirsky 2005). Treatment of schizophrenia was revolutionised by the introduction in 1952 of the first antipsychotic drug, Chlorpromazine (Wu 2005). Chlorpromazine was originally used as an anaesthetic but it was hoped that the calming effects seen with Chlorpromazine could be of benefit to schizophrenic patients (Jacobsen 1986). Now antipsychotics are the primary source of treatment for this disorder (Basile 2002) which has the main aim of reducing symptoms and preventing relapse (Davis 1975). With the success of Chlorpromazine, other antipsychotics were developed such as Haloperidol. The benefits of these drugs were, however, overshadowed by the many side-effects that the drugs produced (Kawanishi 2000). So these older 'typical', or more conventional drugs, which for a substantial length of time had been fore-runners in psychiatric drug treatment were superseded by newer antipsychotic drugs termed as 'atypicals' (Carpenter 1994). The typical drugs, are still being prescribed to patients today. These newer drugs promised to be as, if not more, effective than typicals with less side effects. Following success with Clozapine, other atypicals were created based on Clozapine such as Risperidone and Olanzapine. Side effects were still produced with atypicals but to a lesser extent (Kawanishi 2000). Clozapine in particular produces less side-effects than other atypicals, and this thesis will focus mainly on this agent. This chapter will discuss both typical and atypical antipsychotics in detail, particularly focussing on their mechanisms of action, their side effects and the properties that make atypicals atypical.

2.2 – Typical Antipsychotics

Antipsychotic drugs were first used in the 1950s (Delay 1952) with the introduction of Chlorpromazine. Following the clinical success of Chlorpromazine, other antipsychotics soon followed such as Haloperidol.

All these ' typical ' antipsychotics appear to have comparable clinical efficacy but differ from one another in their side-effect profile. This is thought to be linked to the drugs potency (Schwartz 1992, Brotman 1990). It is generally believed that antipsychotic drug action can be attributed to dopamine receptor antagonism (Carlson 1963, Seeman 1992) and specifically D2 receptor antagonism (Butcher 2000). This has given rise to the Dopamine theory of schizophrenia (Davis 1991). Amphetamines release dopamine into the brain, and can produce a behavioural syndrome similar to that of a schizophrenic episode (Bennett 1998). Potent dopamine agonists such as apomorphine have been shown to make schizophrenic symptoms worse whereas dopamine antagonists (for example resperine) have been shown to relieve the positive symptoms of schizophrenia (Davis 1991, Bennett 1998). Without exception, the typical antipsychotic agents are only effective in treating positive symptoms of schizophrenia (Kaplan 1998). It is thought that positive symptoms are linked to the mesolimbic pathway which links the mid brain to the nucleus accumbens in the limbic system (Lieberman 2004). In contrast, the negative symptoms are said to be linked to the mesocortical pathway, which links the mid-brain to the cortical areas in the frontal lobes (Lieberman 2004).

It is the binding of antipsychotic drugs to the D2 receptor, that is thought to induce EPS (extra pyramidal side effects) (Seeman 2004). These are movement disorders, the most serious of which is tardive dyskinesia (involuntary movements) (Dolder

2003). Other EPS include dystonia (involuntary muscle contractions) and akathesia (restlessness). It is thought that the nigrostriatal pathway, which links the substantia nigra to the striatum, is linked to tardive dyskinesia (Gordon 1989, Alao 2002) since the substantia nigra is involved with movement.

Other side effects which are also more common with 'typical' antipsychotics as opposed to atypical agents, include sedation and anticholinergic effects, such as dry mouth, and dizziness. So for some patients the scale of the side-effects produced, outweigh any of the benefits, which may have been gained. However, this does not take away from the fact that these typical antipsychotic drugs are still prescribed today, as a part of psychiatric drug treatment. This is despite the significant side effects they may produce.

2.3 - Atypical Antipsychotics

Newer antipsychotics were developed in response to the clinical limitations of the older 'typical' antipsychotics (Carpenter 1994). Clozapine was the prototype of these newer 'atypical' drugs and all the drugs that followed shared some of Clozapines pharmacological properties such as potent 5-HT2A antagonism and weaker D2 antagonism (Duggan 1999 and Leucht 1999).

Atypical antipsychotics are believed to work by antagonism of both D2 and 5-HT2A receptors (Ichikawa 1999, Lane 2003, Masellis 2000). Atypical drugs have a higher affinity for 5-HT receptors than Dopamine receptors. Evidence for involvement at 5-HT receptors (Leysen 1978) is that LSD (Lysergic Acid Diethylamide), a potent agonist at the 5-HT2A receptors, produces symptoms similar to that of schizophrenia (Glennon 1984). There is, however, controversy surrounding the issue of whether action at 5-HT2 receptors accounts for the antipsychotic effects or whether it just reduces undesirable side-effects of D2 antagonists. Other receptors systems (adrenergic, glutamatergic, histaminergic and muscarinic) have been implicated in the action of atypical drugs in schizophrenia, although these are not thought to play as big a role in drug response as dopamine or serotonin (Jibson 1998 and Moore 1999) . Adrenaline is a potential candidate because, antagonism of the adrenergic receptor subtypes α_{1A} and α_{2A} has been shown to produce antipsychotic effects. There is also considerable evidence linking the alpha adrenergic system to therapeutic response to clozapine (Tsai 2001). Glutamate is seen as a candidate for involvement in antipsychotic drug action (Hong 2001) for two reasons, firstly reduced concentrations of glutamate, and reduced receptor densities have been reported in post mortem brains of schizophrenic patients, and secondly the Glutamate NMDA receptor

antagonist ketamine (Cosgrove 1991) produces psychotic symptoms, such as hallucinations, which is a key symptom in schizophrenia. Histamines involvement is suspected (Mancama 2002), because reduced receptor density of the H1 receptor have been reported in the frontal cortex of schizophrenic patients. Furthermore, several atypical agents are known to have a high affinity for Histamine receptors (Mancama 2002).

The advantages of 'atypicals' over the 'typicals' has been attributed to 5-HT2 antagonism, and to the balance between the effects of 5-HT2 and D2 receptors. The foundation of all antipsychotic drug action is D2 receptor antagonism (Seeman 2004), but it has been found that atypicals have stronger 5-HT2 antagonism and weaker D2 antagonism. It is this binding to D2 receptors, that is thought to induce EPS (Seeman 2004). It has been hypothesised that the blockade of dopamine receptors is correlated with EPS. So a weak D2 blockade, as seen with atypical drugs, would correlate with a lower incidence of EPS. Whereas, typicals, which bind more tightly to D2 receptors have a higher incidence of EPS (Seeman 2002).

Although, atypicals are associated with a lower occurrence of EPS they may still induce some serious side effects. Examples are agranulocytosis with clozapine and weight gain which is a problem with all atypicals although this is variable between agents (Allison 1999). An increase in body weight may reduce general health and lead to other illnesses such as diabetes, and respiratory problems (Allison 1999).

The overall consensus is that both typicals and atypicals are equally effective clinically, but that atypicals cause far fewer side effects and EPS.

2.3.1 – Clozapine

This thesis will primarily focus on the atypical prototype drug Clozapine. Clozapine was discovered in 1958 but not introduced into Europe until 1975. It was then immediately withdrawn in the same year due to deaths from agranulocytosis (Hippius 1999). In 1990 it was re-introduced but with strict monitoring of patients (Lieberman 1998). Clozapine is mainly used for treatment-resistant patients who do not respond to other antipsychotics. Studies have found that Clozapine is 40-60% effective in these patients (Lieberman 1994 and Kane 1992). Clozapine is a useful antipsychotic drug as not only is it a D2 and 5-HT2A antagonist, but also a D4 antagonist (Cohen 1999). Others atypicals, do not antagonise D4. D4 is thought to be important in schizophrenia as it is abundant in the frontal cortex (Van Tol 1991), an area of the brain associated with cognitive dysfunction, a key symptom of this disease. As well as being an antagonist at D4, Clozapine is also a potent antagonist at serotonergic, muscarinic and alpha-adrenergic receptors (Richelson 2000). Clozapine like, other atypicals, has a weak affinity for D2 but a higher affinity for D1 and D4 (Van Tol 1991). As with other atypicals, Clozapine only causes minimal EPS (Tandon 2002), but most importantly, Clozapine does not induce Tardive Dyskinesia, a serious EPS, which is common in other antipsychotics (Basile 2002). Therefore, in some aspects Clozapine has a different pharmacological profile, from other atypical agents.

2.4 – What makes atypicals, atypical?

Although the term ' atypical ' was adopted by clinicians (Meltzer 2004) there is still some controversy over naming (Emilien 1999, Meltzer 1999 and Sawa 2002) with some still referring to them as 'novel' or 'second-generation' antipsychotics. These labels would in some cases be inaccurate, for example when discussing atypical antipsychotics such as clozapine, which was first discovered in the early stages of the first-generation antipsychotics time period (Muller 2004 see table 10).

Table 10: shows the years of introduction for various antipsychotic drugs (Muller 2004). Clozapine was discovered in 1958, but not introduced into Europe till 1975, withdrawn then re-introduced in 1990.

Drug	**Classification**	**Year of release**	**Country of release**
Chlorpromazine	Typical	1952	Europe
Chlorpromazine	Typical	1954	U.S.A
Fluphenazine	Typical	1959	U.S.A
Thioridazine	Typical	1959	U.S.A
Haloperidol	Typical	1967	U.S.A
Clozapine	Atypical	1975	Europe
Clozapine	Atypical	1990	U.S.A
Risperidone	Atypical	1994	U.S.A
Olanzapine	Atypical	1997	U.S.A
Quetiapine	Atypical	1997	U.S.A
Ziprasidone	Atypical	2001	U.S.A

There are some important differences between the two classes. Firstly in terms of their mechanisms of action (Meltzer 2004), typicals involve antagonism of the D2 receptor while the mechanism of action for atypicals is more complex. This is thought to involve a multi-target profile, which includes, adrenergic, histaminergic, glutamatergic, muscarinic receptors, aswell as dopaminergic and serotonergic receptors (Richelson 2000). It is believed that most atypical drug action is as a result

of a balance between potent 5-HT2 antagonism and weaker D2 antagonism (Meltzer 2004). Newer 'atypical' antipsychotics are currently being developed, called partial dopamine antagonists (PDA), but often they are just categorised as atypical, an example of these drugs is Aripiprazole (Burris 2002).

The mechanisms of action for antipsychotic drugs are thought to be linked to EPS through binding to the D2 receptor. The strength of binding between the drug and the D2 receptor is therefore a major factor in the link between EPS and antipsychotics (Kapur 2000, Kapur 1999 and Seeman 1998). For example, typical antipsychotics bind more tightly to (have a higher affinity at) the D2 receptors and therefore there is a high incidence of EPS. In contrast, atypicals bind with lower affinity to the D2 receptors and so are less likely to induce EPS (Crow 1976). Therefore, a second method of distinguishing between typicals and atypicals, is the amount of EPS produced. Although atypicals may produce far fewer EPS, they can still produce some serious metabolic and cardiovascular side effects, such as weight gain, diabetes, prolongation of the QTc interval (Muller 2004). These side effects will vary between atypicals, for instance, clozapine and olanzapine are most likely to cause weight gain, while ziprasidone rarely does so (Allison 1999, Muller 2004 see table 11). Histamine H1 receptor affinity seems to be the best predictor of weight gain, among antipsychotics (Meltzer 2004). Therefore, the clinician must assess the risks with the associated benefits of each drug, before prescribing to patients.

Table 11: shows the risks of weight gain among different antipsychotic drugs (Muller 2004)

Risk of weight gain	**Typical antipsychotics**	**Atypical antipsychotics**
Very high / high		Clozpaine
		Olanzapine
High / moderate	Chlorpromazine	Quetiapine
		Risperidone
		Zotepine
Low	Haloperidol	Amisulpride
Very low		Ziprasidone

Another difference between typicals and atypicals that has now emerged as of major relevance by clinicians is how atypical antipsychotics improve cognition (Andreasen 1997 and Goldberg et al). This could lead to improvements in the patients life such as greater employment and improved social skills. More trials are needed to confirm this (Meltzer 2004).

As can be seen from above, there many variations between typicals and atypicals, that provide ways of differentiating between the two. With classification of antipsychotic drugs being done, based upon their different pharmacological actions and clinical effects and in some cases their time of introduction. From above, it is evident to see that 'atypical' is a dubious term in a lot of ways. It seems to be a very heterogeneous group, more like a number of subgroups, linked by some common properties, but all very much differ from the earlier typical agents.

CHAPTER 3

3.1 – Introduction

Although many drugs are now on the market for the treatment of schizophrenia interindividual differences in response remains one of the most challenging problems in clinical psychiatry (Ozaki 2004). This is a general problem and is not specific to any drug or area of therapy be it either schizophrenia or psychiatry. In terms of antipsychotics, it has been suggested that this variability in response may in part be attributed to genetics (Basile 2002, Kerwin 2001). Genetics is one of a number of factors that can influence drug response, others include age (Balant-Gorgia 1993) and gender (Masellis 2000). Age may be a potential factor in influencing response however this has been difficult to show due to the complications experienced with conducting phase 1 studies in healthy individuals with antipsychotic drugs, therefore any published data is not always complete (Balant-Gorgia 1993). If further studies are conducted the possible relationship between age and response may become more clinically significant. Gender does not seem to be significant predictor of response although general differences between the genders have been reported such as females achieving the same results as males but with lower doses (Masellis 2000). (Both are explained in more detail in chapter 6 page 158) This section reviews the ways in which genetics can influence variability in response.

3.2 – Pharmacogenetics

The developing field of Pharmacogenetics is concerned with genetically determined variations in drug pharmacological response in humans. The long term aim of pharmacogenetics is to identify the genetic components of the variation of drug response (Masellis 2000) in order to provide individualised treatment for patients

(Ozaki 2004). Although the area of Pharmacogenetics has been around for several years, the methods used in this field are relatively recent. Pharmacogenetic research into complex traits such as drug response, has proven a much harder task than previously thought .The difficulty begins when drug target sites are investigated for their influence on response. The majority of antipsychotic drugs have a multitarget profile indicating a complex mechanism of action. Even though individual genes have been found to influence response, as yet no single gene can account for the variability in response that has been observed (Kerwin 2001). Pharmacogenetic research of drugs in general can be separated into two main categories, Pharmacokinetics and Pharmacodynamics. The interindividual variability in response mentioned above, which in part is attributed to genetics, is also influenced by environmental and pathophysiological factors that have an effect on the pharmacokinetics and pharmacodynamics of the drugs (Dahl 2002). Recent studies have shown that both categories have an influence on response to antipsychotic drug treatment (Arranz 2001).

3.2.1 – Pharmacogenetics of Clozapine

As with all antipsychotic drugs, individuals taking clozapine show a great deal of variation in terms of their clinical response (Masellis 2000). It is this variability that limits the drug's therapeutic use. Since response can vary between two extremes, benefit and serious potentially fatal adverse effects (Masellis 1998). This is particularly true for agranulocytosis, which although rare in patients (0.38% of patients) can be potentially fatal if left untreated (Hippius 1999). Therefore it is important to identify sources of interindividual variation in order to improve the therapeutic use of clozapine as well as other antipsychotics. Over the past decade

several studies have been published looking at the pharmacogenetics of clozapine response. Most have focussed on genetic polymorphisms within the serotonin (5-HT) and Dopamine receptors (pharmacodynamics).

3.2.2 – Pharmacogenomics

Pharmacogenomics involves the compilation of comprehensive information about genomic sequences using techniques such as gene mapping, sequencing and statistical genetics. This information is then used to identify genomic targets and consequently the discovery of susceptibility loci, which contribute to the interindividual variation observed in drug response (Persidis 1998, Regalado 1999).

The aim of both pharmacogenetics and pharmacogenomics is to establish the impact of genetic polymorphisms on interindividual variability in response to in this case, clozapine. The primary objective of these studies was to predict a patient's response to a certain drug and their likelihood of developing side effects. What sets these two fields apart is their methodological approaches. For example, the basis of pharmacogenetics is to use known information about receptors and genes in order to search for candidate genes to research polymorphisms. Pharmacogenomics uses techniques that screen makers across the whole genome in order to identify chromosomal regions which may be of interest.

3.3 – Pharmacokinetics

Pharmacokinetics involves the functions of absorption, distribution, metabolism and elimination (Masellis 2000, Ozaki 2004) of a drug. The pharmacokinetic studies of antipsychotics have mainly focussed on the association between genetic

polymorphisms within the CYP gene and the metabolism of these drugs. Polymorphisms in the CYP2D6 gene provide a way of dividing individuals into three groups according to their metabolising rate, these are poor metabolisers (PM), extensive metabolisers (EM) and ultrarapid metabolisers (UM). Individuals with these phenotypes can sometimes experience difficulties in their treatment response, for example patients who are PM are likely to develop toxic reactions if administrated drugs that cannot be eliminated due to deficient enzymes. However, patients who are UM, rapidly eliminate the drug without gaining any therapeutic benefit. A satisfactory response could not even be guaranteed in those cases where the drug was correctly metabolised.

3.3.1 – Response Variability

It is well known that patients taking the same drug will show some degree of interindividual variability in response (Masellis 2000). Variability in response is usually linked to the intensity of response. One reason for this interindividual variation is a variation in the pharmacokinetic functions of absorption, distribution, metabolism and elimination (Ozaki 2004). Interindividual variability in drug response is largely due to variability of metabolism in the liver, whose enzyme activity is influenced by both genetic and environmental factors (Meyer 1994). Therefore, studies looking at the pharmacokinetics of antipsychotic drugs have mainly concentrated on finding a link between genetic polymorphisms and metabolism of antipsychotic drugs (Ozaki 2004).

3.3.2 – CYP Enzymes

The majority of antipsychotic drugs are highly lipophilic (Dahl 2002) and in order to be excreted are broken down by a group of enzymes known as the cytochrome P450 (CYP) family (Ozaki 2004, Scordo 2002). The CYP enzymes are involved in Phase 1 reactions including oxidation, reduction and hydrolysis, all of which are involved in the metabolism of antipsychotic drugs (Bertilsson 1996). The genes which code for these enzymes are highly polymorphic, so creating the potential for interindividual variability related to the ability to metabolise various drugs (Masimirembwa 1997). Polymorphisms of drug metabolising enzymes (DMEs) can lead both to toxicity or to therapeutic failure (see chapter 3.3 PM and UM) (Kerwin 2001). The most studied genetic polymorphisms were found in CYP2D6 and CYP2C19 metabolic enzymes (Masimirembwa 1997). CYP2D6 is mainly responsible for metabolising antipsychotic drugs (Ozaki 2004), although some studies suggest that CYP1A2 may also contribute (Dahl 2002).

3.3.3 – CYP2D6

There are over 70 variants of the CYP2D6 gene of which approximately 20 encode for non-functional proteins (Ozaki 2004). This enzyme is involved in the metabolism of many antipsychotic drugs. Polymorphisms of CYP2D6 result, in 3 phenotypes, poor, extensive and ultrarapid metabolisers, which show how an individual metabolises a certain drug (Ingelman-Sundberg 2005). Individuals with two copies of non-functional alleles are described as poor metabolisers (PM), and will have higher plasma concentrations and are more prone to adverse effects of drug metabolism by the enzymes (Kerwin 2001, Ozaki 2004).

At the other end of the scale are the ultra-rapid metabolisers (UM) who normally have several copies of a particular CYP gene. In these individuals, normal doses are inadequate as the drug is broken down too rapidly (Kerwin 2001, Ozaki 2004). It is possible that the UM genotype of CYP2D6, where there is more than one active gene on one allele, maybe attributed to selective dietary choices within certain populations in North East Africa (Masimirembwa 1997, Ingelman-Sundberg 2005).

The polymorphisms of CYP2D6 greatly affect the pharmacokinetics of approximately 50% of the drugs, in clinical use today (Ingelman-Sundberg 2005). Being able to predict CYP 2D6 genotypes, has been found to be beneficial for treatment in about 30-40% of CYP2D6 substrates, which equates to 7-10 % of all clinically used drugs (Ingelman-Sundberg 2005). When comparing extensive metabolisers (EM) and poor metabolisers (PM), poor metabolisers show decreased or no CYP2D6 activity, which causes potentially increased concentrations of metabolised drugs. Whereas ultra rapid metabolisers (UM), who are found in 1% of the Caucasian population, usually do not reach therapeutic concentrations and therefore need to have an increased dose (Ozaki 2004). Distinct ethnic differences have been found in terms of the frequency of both the PM and UM phenotypes, for instance, the occurrence of the PM phenotype is 5-10 % among the Caucasian population, 7 – 8% among the African population and approximately 2 % among the Asian population (Berg 1998).

3.3.4 – Other CYPs

Other CYPs such as CYP1A2 and 3A4 (Scordo 2002), also influence interindividual variation in kinetics and occurrence of drug reactions. CYP1A2 has been linked to the metabolism of antipsychotic drugs (Basile 2002, Van der Weide 2003), in in-vivo studies in healthy controls, which have suggested that CYP1A2 may be involved in

variance of the disposition of clozapine (Masellis 2000). A further study has suggested that ultra rapid CYP1A2 activity may account for an inadequate response to clozapine (Ozdemir 2001). As yet no association has been found between the CYP2D6 genotype and therapeutic effects of clozapine.

3.3.5 - Clozapine

Now to focus on Clozapine, there is conflicting evidence regarding the role of CYP2D6, in the metabolism of Clozapine. Functional variants in the CYP2D6 gene, which have been previously investigated have been found not to be important for response to clozapine, however those variants in the CYP1A2 and CYP3A4 enzymes have yet to be investigated (Mancama 2002(b)). Some in-vivo studies have suggested slight involvement of CYP2D6 with clozapine response (Fischer 1992, Linnet 1997), while others have found no involvement at all (Pirmohamed 1995, Eiermann 1997). In contrast, the involvement of CYP1A2 is suspected since Fluvoxamine, a potent CYP1A2 inhibitor, significantly increases the plasma concentration of clozapine (Hiemke 1994, Jerling 1994). In-vitro studies have confirmed that both CYP1A2 and CYP3A4 catalyse the metabolism of clozapine (Eiermann et al 1997). One study also suggested the involvement of CYP2C19 (Linnet et al 1997), but there has been contradictory findings suggesting no such involvement (Dahl et al 1994).

In conclusion, therefore, there is evidence that CYP2D6 does account for the metabolism of the majority of typical antipsychotics as well as atypical drugs. However, for most antipsychotic agents, studies of a link between genotype and steady-state concentrations are still missing. As mentioned earlier, PM have a higher plasma concentration, and are more at risk of developing adverse effects (Kerwin 2001, Ozaki 2004), when treated with CYP2D6 substrates, unless the dose is adjusted.

The majority of studies that have showed a lack of association between CYP2D6 genotype and drug effects have been retrospective studies and have relied on case record data. The involvement of other CYPs particularly, CYP1A2 and 3A4 (Eiermann 1997), is increasingly gaining more support as a cause of interindividual variability in terms of the pharmacokinetics of antipsychotic drugs. The metabolism of clozapine as seen from above is complex and not fully understood. Research has shown it involves CYP2D6, 1A2 and maybe 3A4. Therefore, the pharmacokinetics of clozapine requires further attention and investigation.

3.4 – Pharmacodynamics

Pharmacodynamics is the biochemical and physiological consequences of a drug and its mechanism of action (Ozaki 2004). As previously mentioned (page 61), antipsychotic drug response behaves like a complex trait, it is unlikely to be determined by only one metabolic enzyme, or a simple combination of genes, but rather multiple genes (Kerwin 2001). This point has gained further support, through studies reporting the influence of genetic variants in the dopaminergic, serotonergic and other neurotransmitter systems on treatment response. We will look at these variants more closely below and their association with predicting response to clozapine.

3.4.1 – Candidate receptors

Selecting a good candidate gene is more difficult, since the mechanism of action for antipsychotics is not known. Association studies have looked at the link between genetic polymorphisms and clinical response to investigate whether a polymorphism in a particular candidate gene can predict response. The studies conducted so far have

used previous knowledge about the genes to identify which would be suitable candidates to investigate further (Ozaki 2004). To date, the Dopamine and 5-HT systems have been the ones that have been explored the most, in terms of polymorphisms in their subtypes being associated with the prediction of clinical response. Other neurotransmitter receptors, such as Adrenaline (Bolonna et al 2000, Tsai et al 2001), Glutamate (Hong et al 2001) and Histamine (Mancama et al 2002) have also been investigated for their influence on response.

3.4.2 – Clinical response

Response to clozapine can range from total remission to no effect (Masellis 1998). Also there can be a large degree of variation between patients who experience benefit and those who are affected by potentially fatal agranulocytosis. This is why it is crucial to identify what controls this variation. As to date, there is no way of predicting who will have a favourable response and who will not. The nature of schizophrenia makes any rating of symptoms (in order to classify response) difficult, due to subjectivity of grading symptoms. This is very much different from other diseases, for example heart disease that has a clinical measurement, with definite outcome measures such as blood pressure. Therefore, as well as choosing an appropriate candidate gene, it is important to evaluate clinical response, since there is still no biological marker which reveals the severity of the disorder (Masellis 2000, Ozaki 2004). Therefore, it is critical that reliable and valid rating scales are used to assess clinical symptoms. Rating scales are very much a qualitative issue. Common rating scales, that are currently used, include the BPRS (Brief Psychiatric Rating Scale) (Overall 1962, Lukoff 1986) and the PANSS (Positive and Negative Syndrome Scale) (Kay 1987) (see chapter 1 p33-42). Among the pharmacogenetic studies that

have been conducted, there is no consensus on, which rating scale should be used for all trials (Kerwin 2001). At the moment the scales, particularly the observer rating scale and others that use an individuals judgement to grade symptoms, are very subjective causing variation in findings and bias. Furthermore, scales tend to differ in terms of their level of complexity. A difficulty with scales being too complicated is that not many people will attempt them. Therefore it is made harder to identify if the scale is actually reliable. If one rating scale is used in all trials this would aid comparison among trials and give a more standardised result, so producing more reliable results. It is unlikely that variation in response is due to variation in assessment.

3.4.3 – Clozapine

Pharmacodynamic studies of clozapine response have mainly concentrated on polymorphisms within the dopamine and 5-HT systems. The Dopamine D4 receptor has been shown particular importance, due to the affinity that clozapine has for the receptor. Dopamine D2 and D3 have also been investigated for that reason. From the 5-HT system, the 5HT2A receptor has been explored the most partly due to the high affinity clozapine has for this receptor, but also because of the links that this receptor has with the pathophysiology of hallucinations. Clozapine has also been shown to bind with high affinity to the 5-HT2A and 5-HT2C receptors when therapeutic levels are reached (Masellis 1998). At therapeutic concentrations there is 84-90% occupancy of the 5-HT2 receptors with only approximately 20% D2 receptor occupancy (Masellis 1998). For these reasons it is thought that 5-HT2A and 2C may influence antipsychotic drug action (Meltzer 1991).

3.4.4 – Dopamine Involvement

Dopaminergic receptors were clear choices for candidate genes because D2 receptor antagonism is considered to be the foundation of all antipsychotic drug action (Seeman 2004, Butcher 2000). Dopamine involvement has been confirmed through the Dopamine theory (Davis 1991) (see chapter 2 page 52). So subsequently, receptors of this system became instant candidates in pharmacogenetic studies linking these receptors to clozapine response.

3.4.4.1 – Dopamine D4

The first dopaminergic receptor gene to be investigated for its link with clozapine response was the D4 receptor (see Fig 8) (Ozaki 2004). Some reasons for this are, firstly the high affinity that clozapine has for D4 (Van Tol 1991) and secondly the fact that D4 is abundant in the prefrontal cortex area (Van Tol 1991) of the brain, the region responsible for the cognitive dysfunction experienced by sufferers of schizophrenia (Joyce 1997). In relation to the D4 receptor gene, the polymorphism most examined is the 48bp variable number of tandem repeats (VNTR). Varying affinities for clozapine among the alleles of this polymorphism, were also noted (Rao 1994).

Another polymorphism within the D4 receptor gene, is the 12bp repeat found in exon 1 (Catalano 1993). Further polymorphisms were also found in exon 1, Gly11Arg and 13bp Ins/Del. These have not been examined as extensively as the 48bp repeat.

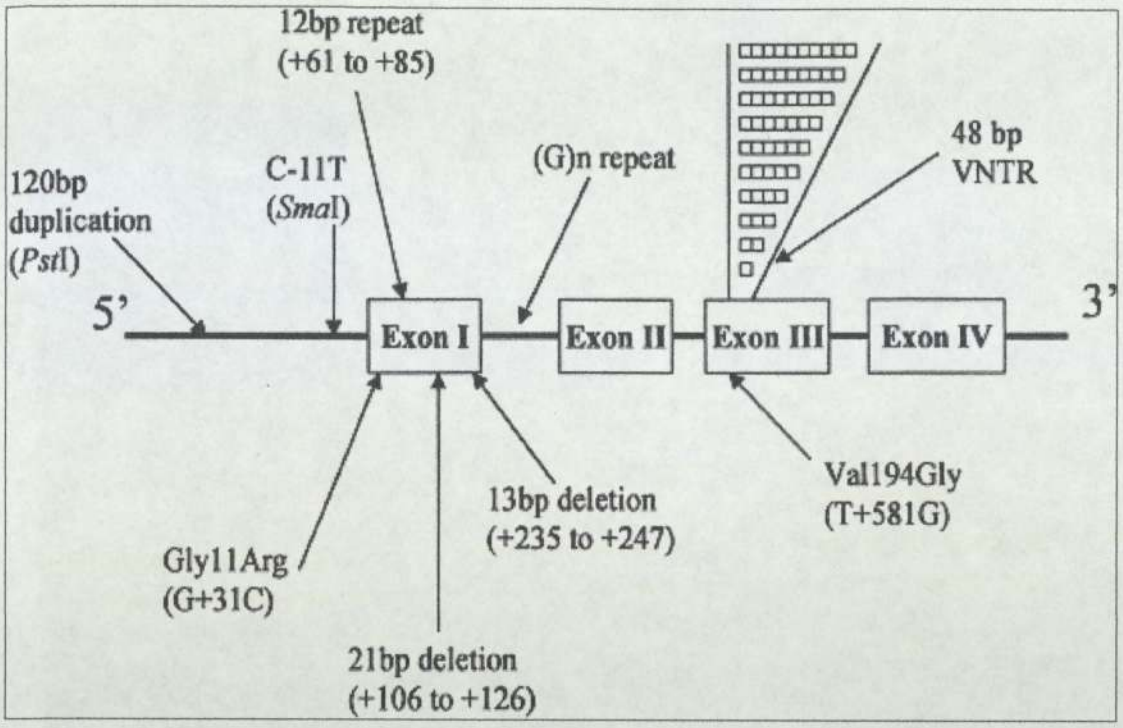

Fig 8: shows the structure of the D4 receptor gene, polymorphic sites on the gene are also shown. D4 has been identified as having four exons (I-IV) and 9 polymorphisms, the nucleotide positions of these polymorphisms are given in brackets (Paterson 1999).

3.4.4.2 – Dopamine D3

Interest was generated by researchers in the Dopamine D3 receptor gene as a potential candidate in pharmacogenetic studies because a polymorphism within this gene, Ser9Gly, was shown to influence dopamine binding (Lundstrom 1996). This polymorphism involves a mutation that causes a serine to glycine amino acid substitution, in the N-terminal extracellular part of the D3 receptor (Durany 1996). Also the D3 receptor has been shown to have a high affinity for clozapine, higher than D2 although not as high as D4 (Scharfetter 1999). A further reason for interest in this receptor system is that expression of the D3 receptor gene appears to be restricted to the limbic regions of the brain (Sokoloff 1992) and both typical and atypical drugs are thought to affect this expression (Buckland 1993).

3.4.4.3 – Dopamine D2

The D2 receptor gene was always going to be an obvious candidate for a link with response since all antipsychotic drugs exert their effects through D2 antagonism. It is this binding of antipsychotic drugs to D2 that induces EPS, which affects more than 60 % of patients (Meltzer 1999, Kerwin 2000 see fig 9). Several polymorphisms have been identified within this receptor gene, including (-) 141C Ins/Del, which is the polymorphism that has been studied the most, (found in the promoter region), Ser311Cys and the intronic variant Taq IA. The (-) 141C Del allele has been linked to altered D2 expression in *in-vitro* studies (Arinami1997) and it has also been shown to be linked to increased D2 densities in the striatum region of the brain in healthy subjects, the area of the brain involved with motor function (Jonsson 1999, Pohjalainen 1999). This polymorphism has also been implicated in the regulation of D2 expression in the mesocorticolimbic regions of the brain, thought to be involved with processes such as cognition, psychosis, and negative symptoms. While the A1 allele of the Taq 1A polymorphism has been associated with reduced gene expression in in-vitro studies (Ritchie 2003, Thompson 1997).

Other polymorphisms have also been shown to produce an opposite effect to that of the (-) 141C Del allele on D2 density in the striatum. These polymorphisms cause a reduction of D2 density compared to an increase produced with the (-)141C Del allele (Hwang 2005). These polymorphisms are the T allele of the C957T polymorphism (Hirvonen 2004) and the B1 allele of the Taq1B polymorphism (Ritchie 2003). A recent study has looked at 12 SNP within the D2 receptor and compared them in two ethnicities. This is the first study to look at 12 polymorphisms (Hwang 2005).

3.4.5 – 5-HT Involvement

5-HT receptors seem to be ideal candidates for pharmacogenetic / pharmacodynamic studies because of the evidence that 5-HT mediated receptor antagonism is vital to atypical antipsychotic drug action (Meltzer 1991, Ozaki 2004). Eighteen serotonin receptors have been identified so far, fourteen of which have already been cloned (Meltzer 1995).

3.4.5.1 – 5-HT2A

The 5-HT2A receptor subtype has received the most attention in terms of its relation with pharmacogenetics studies of antipsychotics (Ozaki 2004). This interest is due to the receptor being linked to sleep, mood, motor control (Hoyer 1994), perception and cognition. These functions are all located on the pyramidal neurons in the frontal cortex (Masellis 1998) and parts of the limbic system (Masellis 1998) including the basal ganglia (Hoyer 1994). More importantly, a further reason for the implication of 5-HT2A is that it is thought that this receptor might be linked to the pathophysiology of hallucinations (Ozaki 2004). It has been reported that the 5-HT2A agonist LSD produces hallucinogenic symptoms in humans (Glennon 1984). Furthermore, atypicals have a high affinity for 5-HT receptors, particularly 5-HT2A. With atypical drugs, the affinity is higher for 5-HT2A than D2 (Meltzer 1991, Meltzer 1999, Kapur 1996). Position Emission Tomography (PET) studies have shown that all atypical drugs, share this particular feature (Kapur 1998).

The first polymorphism within the 5-HT2A receptor to be investigated for its link to clozapine response was T102C (Arranz 1995). It involves a silent substitution of cytosine for thymine at the 102 position. Another common polymorphism found in

this receptor is (-) 1438 A/G which is located in the promoter region of the receptor and is in linkage disequilibrium with T102C. As T102C is a silent substitution, it cannot influence the function of the receptor, therefore the variant that it is in linkage disequilibrium with must have an effect on response. One such variant is (-) 1438 A/G. A further polymorphism in this receptor is His452Tyr, a histidine to tyrosine amino acid substitution at the 452 position.

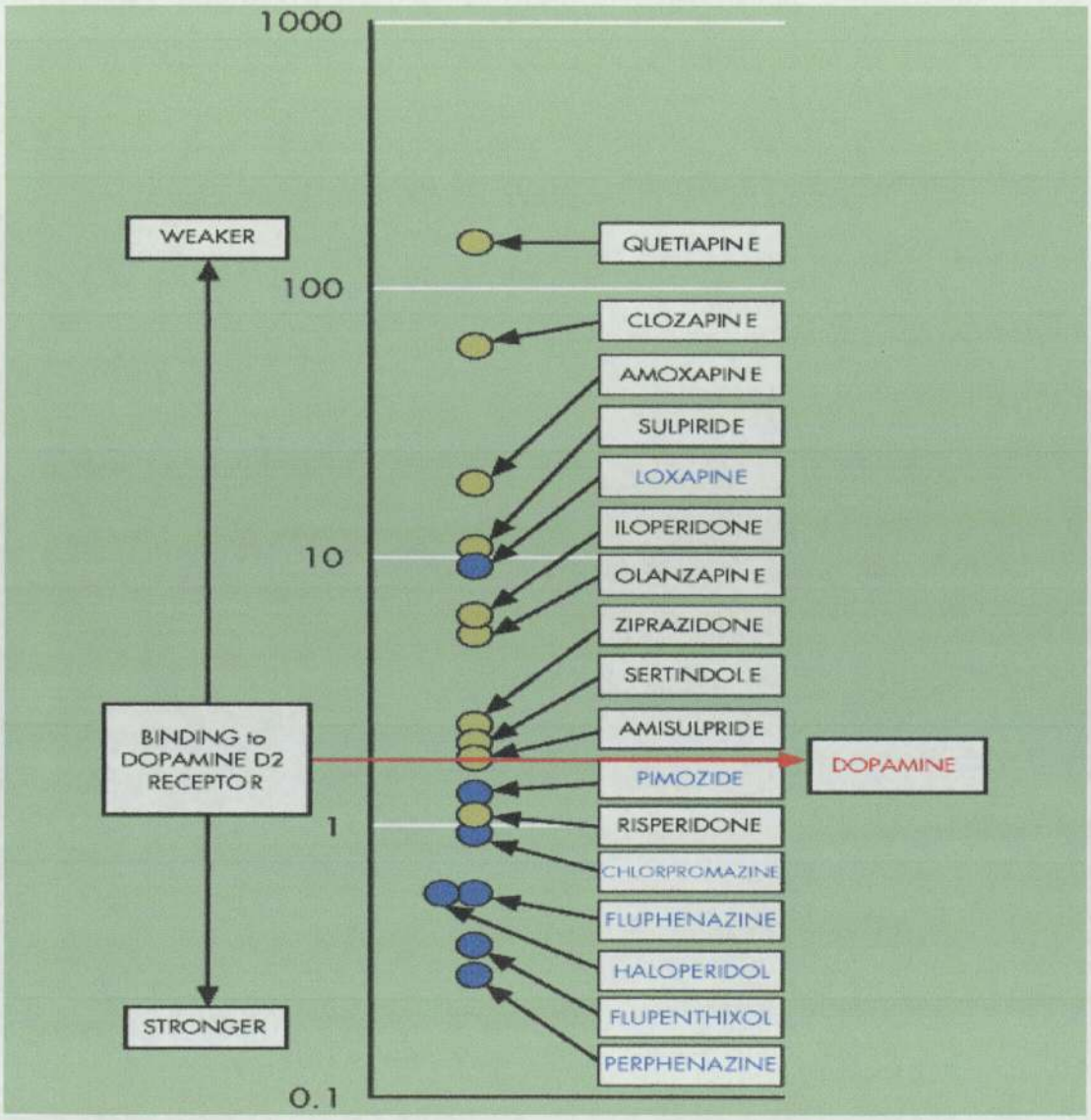

Fig 9: shows how tightly different antipsychotic drugs, bind to the D2 receptor. The lower the number, the tighter the binding. The atypical drugs, shown in the lighter circles (green circles), can be seen as binding less tightly, while the typical drugs (darker blue circles) bind more tightly.

3.4.5.2 – 5-HT2C

The 5-HT2C receptor has been implicated, firstly due to the high affinity that clozapine has for this receptor (Masellis 2001), but also because of the high density of this receptor found in the area of the brain which is involved in the pathophysiology of schizophrenia (Malhotra 1996). A commonly examined polymorphism at this receptor, is Cys23Ser. This receptor was seen as an interesting candidate due to its location on the X chromosome.

3.4.5.3 – 5-HT6

The 5-HT6 receptor has been linked to response due to the high affinity that clozapine has for this receptor (Masellis 2001). The most investigated polymorphism at this receptor is the thymidine to cytosine substitution at position 267 (C267T).

3.4.5.4 – Other receptors

There has been less attention on other receptors such as 5-HT3 and 5-HT5. With very few studies on the link between these receptors and clinical response. The most likely reason for this is that the affinity of clozapine for these receptors, is not as high as for those receptors mentioned previously. The 5- HT3 receptor has gained some attention because clozapine is a potent antagonist at this receptor (Hermann 1996). Also the location of this receptor (11q23.1-23.2), is in an area, that is linked with schizophrenia. Interest in the 5-HT5A receptor has developed since reports that the receptor may be involved in higher cortical and limbic functions. Further studies are needed for both 5-HT3 and 5-HT5 receptors.

3.4.6 – Other Neurotransmitters

As mentioned earlier, other receptor systems may also be involved in antipsychotic drug action. These are namely, Adrenergic, Glutamergic, Histaminergic and Muscarinic (Richelson 2000). As these systems have been implicated in drug action, their influence on genetic polymorphisms and clozapine response was also investigated.

Adrenaline has been investigated because antagonism of adrenergic receptor subtypes has been shown to produce antipsychotic effects. Despite this evidence only a couple of studies have been conducted, looking into the association between polymorphisms in the adrenaline receptors and clozapine response (Bolonna 2000, Tsai 2001).

Glutamate is implicated in antipsychotic drug action since the Glutamate NMDA antagonist, ketamine, induces hallucinations, a key symptom of schizophrenia, but also reduced concentrations and receptor densities have been reported for Glutamate in the post-mortem brains of schizophrenic patients. There is limited data, regarding polymorphisms in the Glutamate system and their link to the prediction of response. In fact, at the time of writing this thesis, only one study had been published looking at this association (Hong 2001).

Another receptor gene to be examined for its involvement, is Histamine (Mancama 2002), its reasons for involvement, include, reduced receptor density, particularly of the H1 receptor, in the frontal cortex of schizophrenic patients (Nakai 1991). Also, numerous atypical drugs, have a high affinity for Histamine receptors (Ellenbroek 2000). As with Glutamate, limited data also exists for Histamine.

As yet, there does not seem to be any data looking at polymorphisms within the muscarinic receptors and their link with response. It is thought that inhibition of muscarinic receptors, can lead to cognitive impairment (Crook 2001). Other receptors also thought to be involved include acetylcholinergic receptors (Meltzer 1991, Meltzer 1989).

CHAPTER 4

4.1 – Introduction

The question of interindividual variability in response is one that has fascinated clinicians for a long time. It has been well observed that the response to any drug will show some degree of interindividual variability and that this variability may be influenced by a number of factors such as age, gender and genetics (Ozaki 2004). This study has focussed upon the genetic aspect of response variability and in particular upon the question as to whether polymorphisms within receptor genes predict how well an individual will respond to the drug clozapine. This chapter covers the methods used to investigate evidence of a link between genetic polymorphisms and clozapine response.

4.2 – Objectives

When investigating the association between genetic polymorphisms and clozapine response, the majority of the studies examined the Dopamine and 5-HT systems. Therefore the project had two primary objectives:

- Firstly, whether polymorphisms within the dopamine system can influence clozapine response.
- Similarly whether polymorphisms within the 5-HT system influence clozapine response.

These primary objectives can be broken down further for each subtype within these systems, for example, can polymorphisms in the Dopamine D2 receptor influence clozapine response.

4.3 – Outcome measures

The main outcome measure used in this study was clinical response. For schizophrenia, clinical response is taken by defining patients as either responders or non-responders to treatment, through use of symptom rating scales. A number of scales are in use (see chapter 1 p33-42). Each scale has different criteria for the definition of response. No single scale was used in all the studies and therefore comparisons are complicated by the lack of standardisation and by the subjective nature of the scale assessments.

4.4 – Search Terms

Search terms were derived after the completion of a 'mind map' (see appendix C p219) to fully exhaust all the terms linked to the research question. Table 12 shows the terms used in the searches. Searches were conducted using various databases, such as PubMed (P), Cochrane, Medline (M) and Science Direct (SD). Search terms were adapted according to the database used, although all combinations of each term were tried.

In the case of the dopaminergic and serotonergic receptors subtypes, the number of the subtype was replaced in the search and then the search was repeated.

Table 12: shows a list of the search terms used and their variations

Search Term	**Variations of search term**
Dopamine D2	Dopamine D(2), D2, dopamine D2
Dopamine D3	Dopamine D(3), D3, dopamine D3
Dopamine D4	Dopamine D(4), D4, dopamine D4
5-HT2A	5HT2A, Serotonin 2A
5-HT2C	5HT2C, Serotonin 2C
5-HT3	5HT3, Serotonin 3
5-HT5	5HT5, Serotonin 5
5-HT6	5HT6, Serotonin 6
Adrenaline	Adrenoceptor, Adrenergic, Epinephrine
Glutamate	Glutamatergic, NMDA
Histamine	Histaminergic, H1
Polymorphism	Polymorphisms, mutations, mutation
Response	Response
Clozapine	Clozaril
Genetics	Genetic, Pharmacogenetic, Pharmacogenetics

4.5 – Search strategy

References were located through electronic searches of the PubMed, Medline and Science Direct databases. The Cochrane database was also searched but no studies were identified. This database is particularly valuable for reviews rather than studies. All the studies used to extract data were case-control studies. Because of the ethical issues in the use of randomised controlled trials on schizophrenic patients, the majority of the studies were retrospective. The diagram below shows a generic search strategy (fig 10).

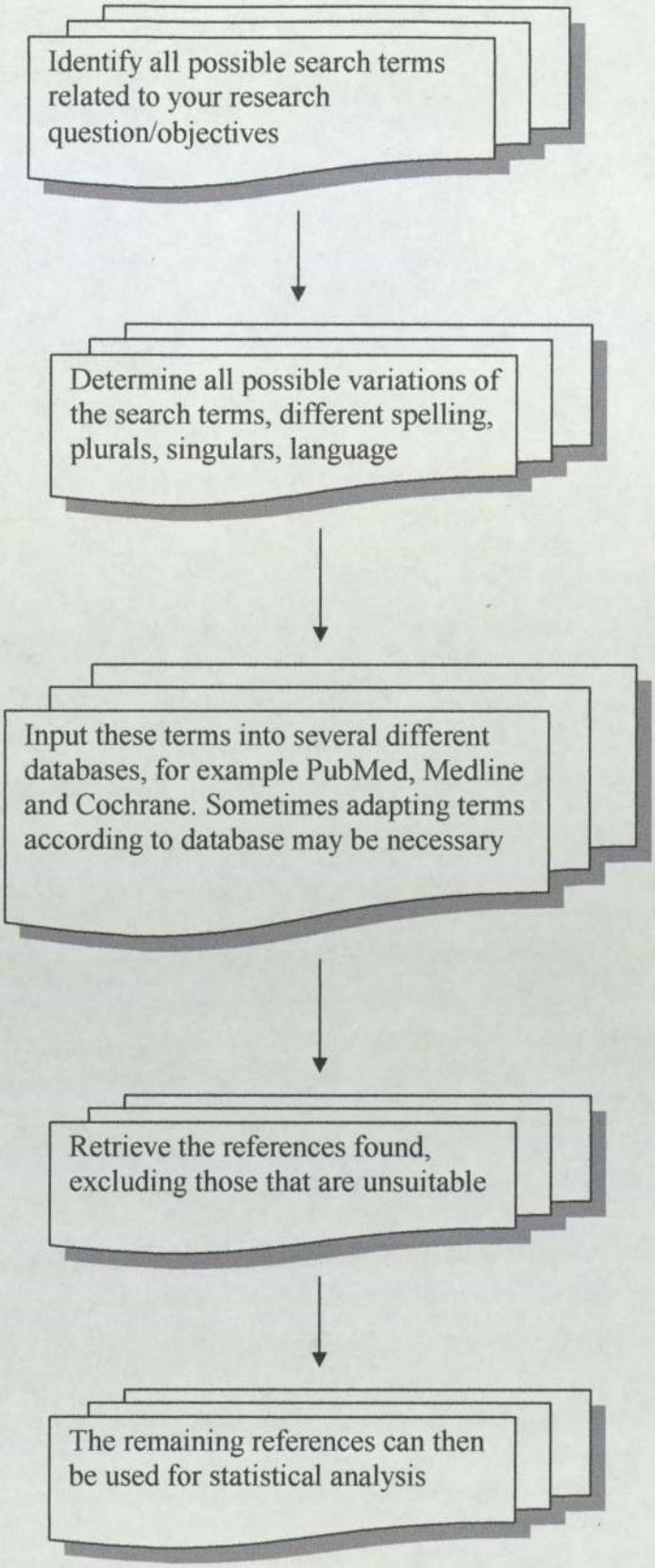

Fig 10: shows a generic search strategy

4.6 – Inclusion / Exclusion Criterias

The search terms were derived from the research question and study objectives. Therefore any reference which did not discuss these terms was excluded (polymorphism, clozapine, response, and the receptor subtype). Further reasons for exclusion, when the reference was a comment, and therefore did not contain any data, and also if the data was in a format that could not be used for analysis (not genotypes of responders and non-responders). The PubMed and Medline databases identified the same references, whereas the Science Direct database was not as specific, sometimes not identifying references retrieved by the other two databases. No restrictions on age, ethnicity or gender were applied. In addition, there were no language limitations.

4.7 – Data extraction

The following section shows the results of searches that were conducted. The actual search strategy used is also given for each receptor (number of references found are shown in brackets). Thorough searches were conducted using variations for words, such as using '5-HT2A' as well as, '5HT2', but also using both plural and singular words, for example, 'genetic' and 'genetics'. The same search strategy was employed in all the database searches. The PubMed database has been abbreviated to P, while Medline is M and Science Direct SD. It was found that the strategy did not need to be adapted according to the database being used, as the same references were usually identified by all three databases. This is contrary to what was previously thought (see page 79). The total number of references found, was reduced after application of exclusion criteria.

4.7.1 – Articles retrieved which identify polymorphisms in the D2 receptor and their link to clozapine response

Search strategy:	P	M	SD
Dopamine D2+response+clozapine+polymorphism	(13)	(13)	(5)
Dopamine D(2)+response+clozapine+polymorphism	(2)	(2)	(0)
dopamine D2+ response+clozapine+polymorphism	(13)	(13)	(5)
D2+response+clozapine+polymorphism	(13)	(13)	(6)
Dopamine D2+response+clozaril+polymorphism	(11)	(11)	(0)
D2+response+clozaril+polymorphism	(11)	(11)	(0)
dopamine D2+response+clozapine+polymorphisms	(9)	(9)	(5)
dopamine D2+response+clozapine+mutation	(3)	(3)	(3)
dopamine D2+response+clozapine+mutations	(3)	(3)	(3)
dopamine D2+response+clozapine+mutation+genetic	(0)	(0)	(1)
dopamine D2+response+clozapine+mutations+genetic	(0)	(0)	(1)
dopamine D2+response+clozapine+mutation+genetics	(3)	(3)	(1)
dopamine D2+response+clozapine+mutations+genetics	(3)	(3)	(1)
dopamine D2+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(0)
dopamine D2+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
dopamine D2+response+clozapine+polymorphism+genetic	(10)	(10)	(1)
dopamine D2+response+clozapine+polymorphisms+genetics	(7)	(7)	(1)
dopamineD2+response+clozapine+polymorphism+pharmacogenetic	(3)	(3)	(1)
dopamine D2+response+clozapine+polymorphisms+pharmacogenetics	(1)	(1)	(1)

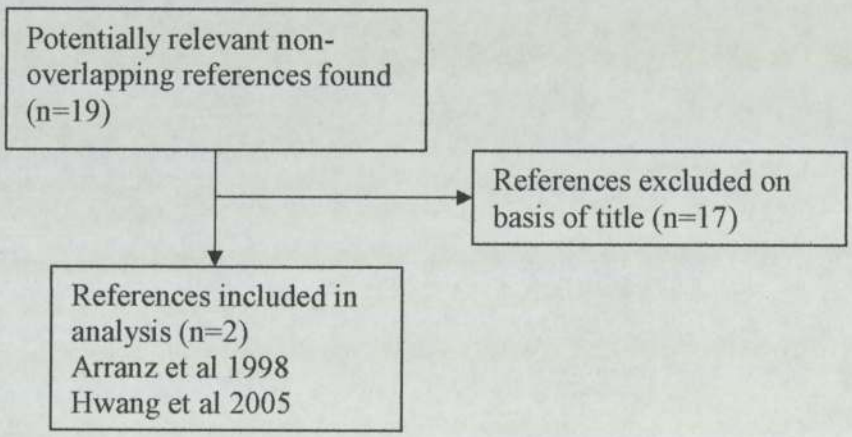

Fig 11: shows the search strategy for identifying references regarding polymorphisms in the D2 receptor and its association with clozapine response. (The numbers in brackets equals the number of references retrieved using the PubMed (P), Medline (M) and Science Direct (SD) databases).

4.7.2 – Articles retrieved which identify polymorphisms in the D3 receptor and their link to clozapine response

Search strategy :

	P	M	SD
Dopamine D3+response+clozapine+polymorphism	(6)	(6)	(3)
Dopamine D(3)+response+clozapine+polymorphism	(1)	(1)	(0)
dopamine D3+ response+clozapine+polymorphism	(6)	(6)	(3)
D3+response+clozapine+polymorphism	(6)	(6)	(5)
Dopamine D3+response+clozaril+polymorphism	(5)	(5)	(0)
dopamine D3+response+clozapine+polymorphisms	(4)	(4)	(3)
dopamine D3+response+clozapine+mutation	(1)	(1)	(1)
dopamine D3+response+clozapine+mutations	(1)	(1)	(1)
dopamine D3+response+clozapine+mutation+genetic	(0)	(0)	(1)
dopamine D3+response+clozapine+mutations+genetic	(0)	(0)	(1)
dopamine D3+response+clozapine+mutation+genetics	(1)	(1)	(1)
dopamine D3+response+clozapine+mutations+genetics	(1)	(1)	(1)
dopamine D3+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(0)
dopamine D3+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
dopamine D3+response+clozapine+polymorphism+genetic	(5)	(5)	(2)
dopamine D3+response+clozapine+polymorphisms+genetics	(3)	(3)	(2)
dopamine D3+response+clozapine+polymorphism+pharmacogenetic	(1)	(1)	(1)
dopamine D3+response+clozapine+polymorphisms+pharmacogenetics	(2)	(2)	(1)

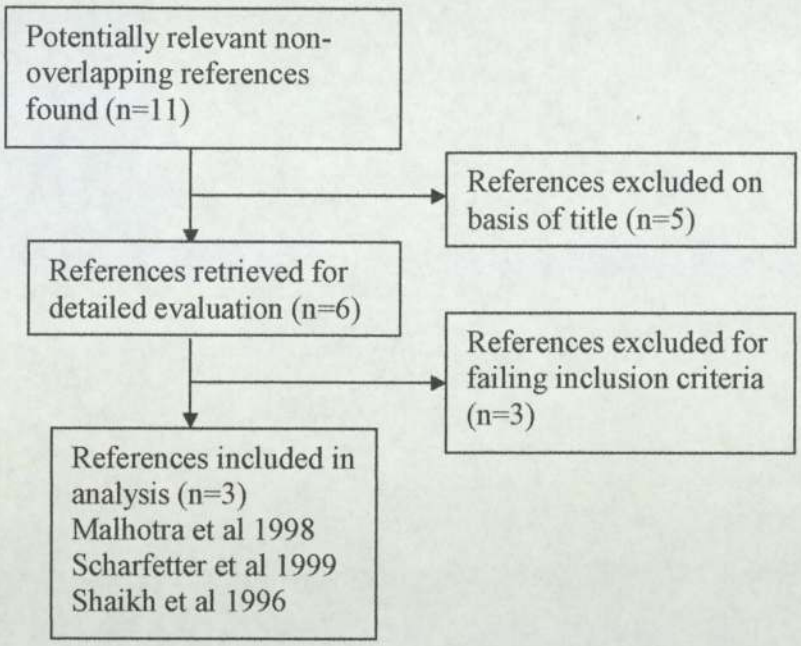

Fig 12: shows the search strategy for identifying references regarding polymorphisms in the D3 receptor and its association with clozapine response. (The numbers in brackets equals the number of references retrieved using the PubMed (P), Medline (M) and Science Direct (SD) databases).

4.7.3 – Articles retrieved which identify polymorphisms in the D4 receptor and their link to clozapine response

Search strategy :	P	M	SD
Dopamine D4+response+clozapine+polymorphism	(8)	(8)	(6)
Dopamine D(4)+response+clozapine+polymorphism	(2)	(2)	(1)
dopamine D4+ response+clozapine+polymorphism	(8)	(8)	(6)
D4+response+clozapine+polymorphism	(8)	(8)	(8)
Dopamine D4+response+clozaril+polymorphism	(7)	(7)	(0)
dopamine D4+response+clozapine+polymorphisms	(6)	(6)	(6)
dopamine D4+response+clozapine+mutation	(0)	(0)	(3)
dopamine D4+response+clozapine+mutations	(0)	(0)	(3)
dopamine D4+response+clozapine+mutation+genetic	(0)	(0)	(2)
dopamine D4+response+clozapine+mutations+genetic	(0)	(0)	(2)
dopamine D4+response+clozapine+mutation+genetics	(0)	(0)	(2)
dopamine D4+response+clozapine+mutations+genetics	(0)	(0)	(2)
dopamine D4+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(0)
dopamine D4+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
dopamine D4+response+clozapine+polymorphism+genetic	(7)	(7)	(5)
dopamine D4+response+clozapine+polymorphisms+genetics	(8)	(8)	(4)
dopamine D4+response+clozapine+polymorphism+pharmacogenetic	(1)	(1)	(2)
dopamine D4+response+clozapine+polymorphisms+pharmacogenetics	(1)	(1)	(2)

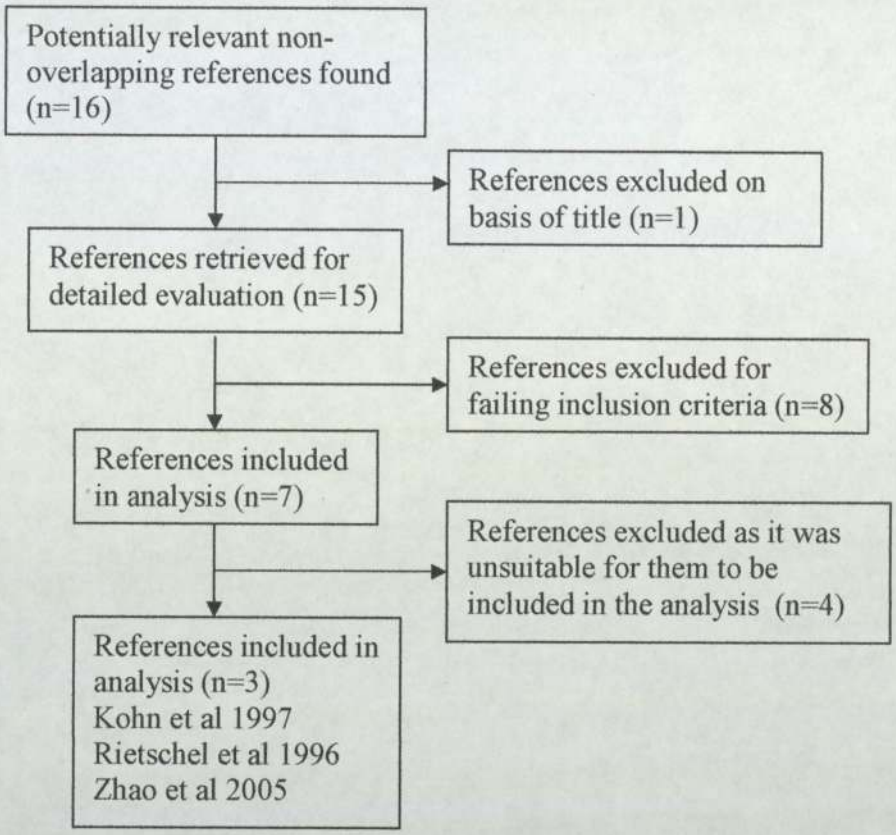

Fig 13: shows the search strategy for identifying references regarding polymorphisms in the D4 receptor and its association with clozapine response. (The numbers in brackets equals the number of references retrieved using the PubMed (P), Medline (M) and Science Direct (SD) databases).

4.7.4 - Articles retrieved which identify polymorphisms in the 5-HT2A receptor and their link to clozapine response

Search strategy :	P	M	SD
5-HT2A+response+clozapine+polymorphism	(20)	(20)	(8)
5HT2A+response+clozapine+polymorphism	(3)	(3)	(3)
Serotonin 2A+ response+clozapine+polymorphism	(7)	(7)	(1)
5-HT2A+response+clozaril+polymorphism	(11)	(11)	(0)
5-HT2A+response+clozapine+polymorphisms	(10)	(10)	(8)
5-HT2A+response+clozapine+mutation	(4)	(4)	(2)
5-HT2A+response+clozapine+mutations	(4)	(4)	(2)
5-HT2A+response+clozapine+mutation+genetic	(4)	(4)	(2)
5-HT2A+response+clozapine+mutations+genetic	(4)	(4)	(2)
5-HT2A+response+clozapine+mutation+genetics	(4)	(4)	(2)
5-HT2A+response+clozapine+mutations+genetics	(4)	(4)	(2)
5-HT2A+response+clozapine+mutation+pharmacogenetic	(1)	(1)	(0)
5-HT2A+response+clozapine+mutations+pharmacogenetic	(1)	(1)	(0)
5-HT2A+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
5-HT2A+response+clozapine+polymorphism+genetic	(17)	(17)	(4)
5-HT2A+response+clozapine+polymorphisms+genetics	(9)	(9)	(4)
5-HT2A+response+clozapine+polymorphism+pharmacogenetic	(2)	(2)	(2)
5-HT2A+response+clozapine+polymorphisms+pharmacogenetics	(1)	(1)	(2)

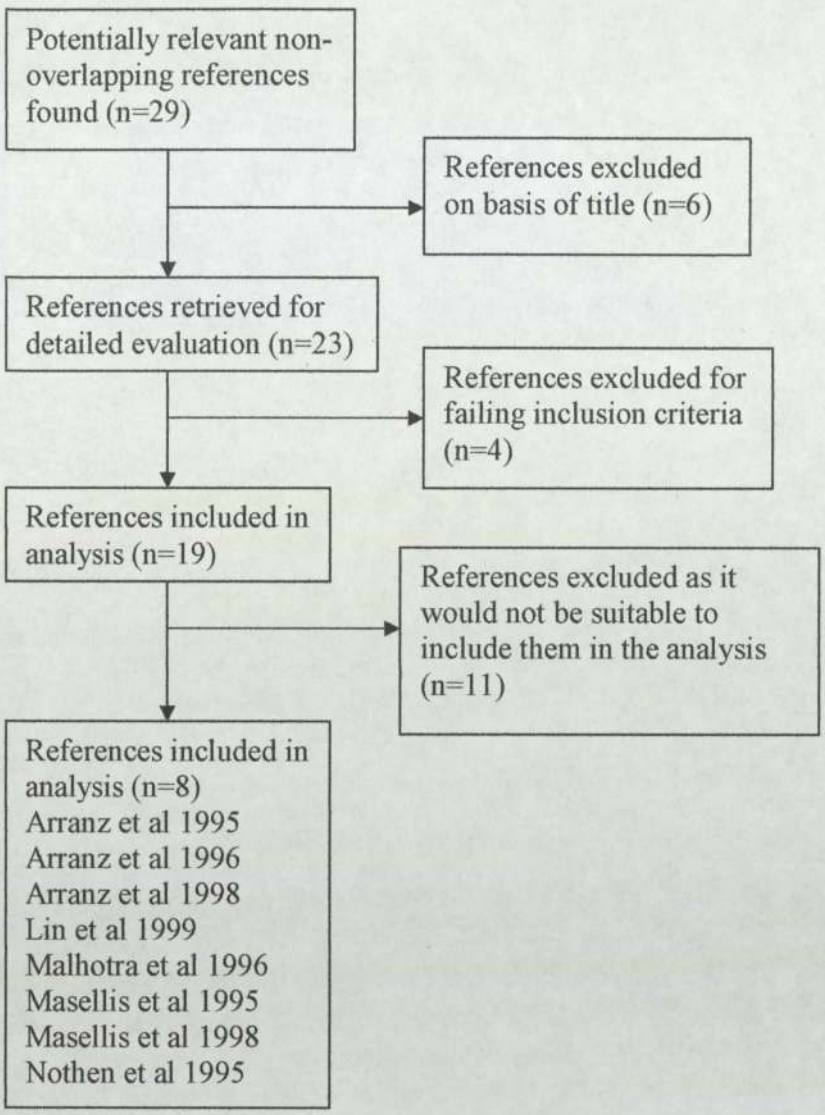

Fig 14: shows the search strategy for identifying references regarding polymorphisms in the 5-HT2A receptor and its association with clozapine response. (The numbers in brackets equals the number of references retrieved using the PubMed (P), Medline (M) and Science Direct (SD) databases).

4.7.5 - Articles retrieved which identify polymorphisms in the 5-HT2C receptor and their link to clozapine response

Search strategy :	P	M	SD
5-HT2C+response+clozapine+polymorphism	(9)	(9)	(3)
5HT2C+response+clozapine+polymorphism	(3)	(3)	(2)
Serotonin 2C+response+clozapine+polymorphism	(1)	(1)	(0)
5-HT2C+response+clozaril+polymorphism	(4)	(4)	(0)
5-HT2C+response+clozapine+polymorphisms	(4)	(4)	(3)
5-HT2C+response+clozapine+mutation	(3)	(3)	(1)
5-HT2C+response+clozapine+mutations	(3)	(3)	(1)
5-HT2C+response+clozapine+mutation+genetic	(3)	(3)	(0)
5-HT2C+response+clozapine+mutations+genetic	(2)	(2)	(0)
5-HT2C+response+clozapine+mutation+genetics	(3)	(3)	(0)
5-HT2C+response+clozapine+mutations+genetics	(2)	(2)	(0)
5-HT2C+response+clozapine+mutation+pharmacogenetic	(1)	(1)	(0)
5-HT2C+response+clozapine+mutations+pharmacogenetic	(1)	(1)	(0)
5-HT2C+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
5-HT2C+response+clozapine+polymorphism+genetic	(7)	(7)	(1)
5-HT2C+response+clozapine+polymorphisms+genetics	(3)	(3)	(1)
5-HT2C+response+clozapine+polymorphism+pharmacogenetic	(3)	(3)	(2)
5-HT2C+response+clozapine+polymorphisms+pharmacogenetics	(1)	(1)	(2)

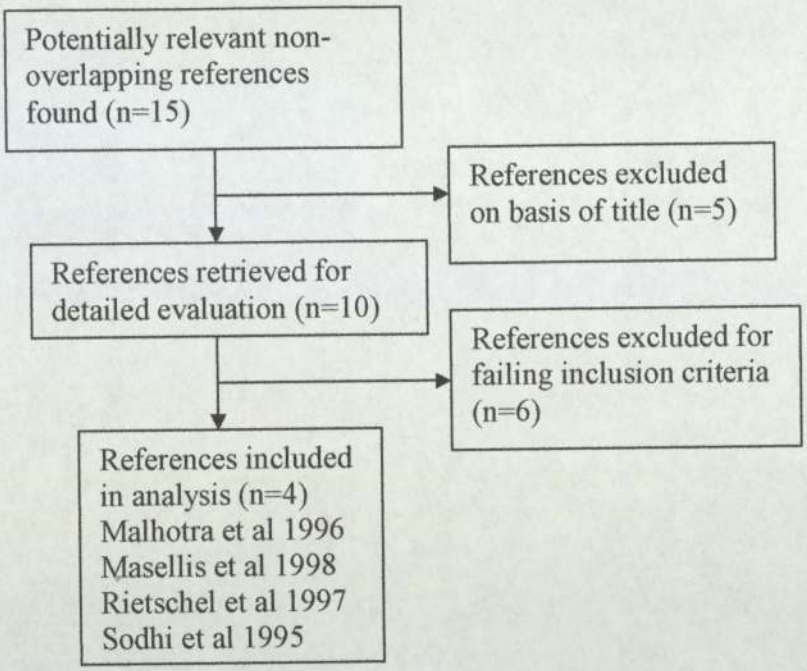

Fig 15: shows the search strategy for identifying references regarding polymorphisms in the 5-HT2C receptor and its association with clozapine response. (The numbers in brackets equals the number of references retrieved using the PubMed (P), Medline (M) and Science Direct (SD) databases).

4.7.6 - Articles retrieved which identify polymorphisms in the 5-HT3 receptor and their link to clozapine response

Search strategy :	P	M	SD
5-HT3+response+clozapine+polymorphism	(1)	(1)	(1)
5HT3+response+clozapine+polymorphism	(0)	(0)	(0)
Serotonin 3+response+clozapine+polymorphism	(4)	(4)	(1)
5-HT3+response+clozaril+polymorphism	(1)	(1)	(0)
5-HT3+response+clozapine+polymorphisms	(1)	(1)	(1)
5-HT3+response+clozapine+mutation	(1)	(1)	(1)
5-HT3+response+clozapine+mutations	(1)	(1)	(1)
5-HT3+response+clozapine+mutation+genetic	(1)	(1)	(0)
5-HT3+response+clozapine+mutations+genetic	(1)	(1)	(0)
5-HT3+response+clozapine+mutation+genetics	(1)	(1)	(0)
5-HT3+response+clozapine+mutations+genetics	(1)	(1)	(0)
5-HT3+response+clozapine+mutation+pharmacogenetic	(0)	(0)	(0)
5-HT3+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(0)
5-HT3+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
5-HT3+response+clozapine+polymorphism+genetic	(1)	(1)	(0)
5-HT3+response+clozapine+polymorphisms+genetics	(1)	(1)	(0)
5-HT3+response+clozapine+polymorphism+pharmacogenetic	(0)	(0)	(0)
5-HT3+response+clozapine+polymorphisms+pharmacogenetics	(0)	(0)	(0)
Serotonin 3+clozapine+response+mutation	(1)	(1)	(1)
Serotonin 3+clozapine+response+mutations	(1)	(1)	(1)
Serotonin 3+clozapine+response+mutation+genetic	(1)	(1)	(0)
Serotonin 3+clozapine+response+mutations+genetic	(1)	(1)	(0)
Serotonin 3+clozapine+response+mutation+genetics	(1)	(1)	(0)
Serotonin 3+clozapine+response+mutations+genetics	(1)	(1)	(0)
Serotonin 3+clozapine+response+mutation+pharmacogenetic	(1)	(1)	(0)
Serotonin 3+clozapine+response+mutations+pharmacogenetic	(1)	(1)	(0)
Serotonin 3+clozapine+response+mutations+pharmacogenetics	(0)	(0)	(0)
Serotonin 3+response+clozapine+polymorphism+genetic	(4)	(4)	(0)
Serotonin 3+response+clozapine+polymorphisms+genetics	(3)	(3)	(0)
Serotonin 3+response+clozapine+polymorphism+pharmacogenetic	(1)	(1)	(0)
Serotonin 3+response+clozapine+polymorphisms+pharmacogenetics	(0)	(0)	(0)

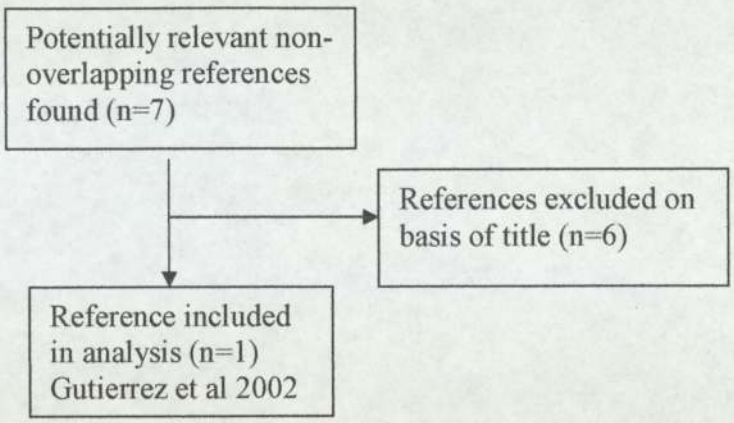

Fig 16: shows the search strategy for identifying references regarding polymorphisms in the 5-HT3 receptor and its association with clozapine response. (The numbers in brackets equals the number of references retrieved using the PubMed (P), Medline (M) and Science Direct (SD) databases).

4.7.7 - Articles retrieved which identify polymorphisms in the 5-HT5A receptor and their link to clozapine response

Search strategy :	P	M	SD
5-HT5+response+clozapine+polymorphism	(0)	(0)	(0)
5HT5+response+clozapine+polymorphism	(0)	(0)	(0)
Serotonin 5+response+clozapine+polymorphism	(28)	(28)	(9)
5-HT5+response+clozaril+polymorphism	(0)	(0)	(0)
5-HT5+response+clozapine+polymorphisms	(0)	(0)	(0)
5-HT5+response+clozapine+mutation	(0)	(0)	(0)
5-HT5+response+clozapine+mutations	(0)	(0)	(0)
5-HT5+response+clozapine+mutation+genetic	(0)	(0)	(0)
5-HT5+response+clozapine+mutations+genetic	(0)	(0)	(0)
5-HT5+response+clozapine+mutation+genetics	(0)	(0)	(0)
5-HT5+response+clozapine+mutations+genetics	(0)	(0)	(0)
5-HT5+response+clozapine+mutation+pharmacogenetic	(0)	(0)	(0)
5-HT5+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(0)
5-HT5+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
5-HT5+response+clozapine+polymorphism+genetic	(0)	(0)	(0)
5-HT5+response+clozapine+polymorphisms+genetics	(0)	(0)	(0)
5-HT5+response+clozapine+polymorphism+pharmacogenetic	(0)	(0)	(0)
5-HT5+response+clozapine+polymorphisms+pharmacogenetics	(0)	(0)	(0)
Serotonin 5+clozapine+response+mutation	(8)	(8)	(2)
Serotonin 5+clozapine+response+mutations	(8)	(8)	(2)
Serotonin 5+clozapine+response+mutation+genetic	(8)	(8)	(2)
Serotonin 5+clozapine+response+mutations+genetic	(7)	(7)	(2)
Serotonin 5+clozapine+response+mutation+genetics	(8)	(8)	(2)
Serotonin 5+clozapine+response+mutations+genetics	(7)	(7)	(2)
Serotonin 5+clozapine+response+mutation+pharmacogenetic	(2)	(2)	(0)
Serotonin 5+clozapine+response+mutations+pharmacogenetic	(2)	(2)	(0)
Serotonin 5+clozapine+response+mutations+pharmacogenetics	(0)	(0)	(0)
Serotonin 5+response+clozapine+polymorphism+genetic	(25)	(25)	(6)
Serotonin 5+response+clozapine+polymorphisms+genetics	(12)	(12)	(6)
Serotonin 5+response+clozapine+polymorphism+pharmacogenetic	(3)	(3)	(3)
Serotonin 5+response+clozapine+polymorphisms+pharmacogenetics	(0)	(0)	(0)

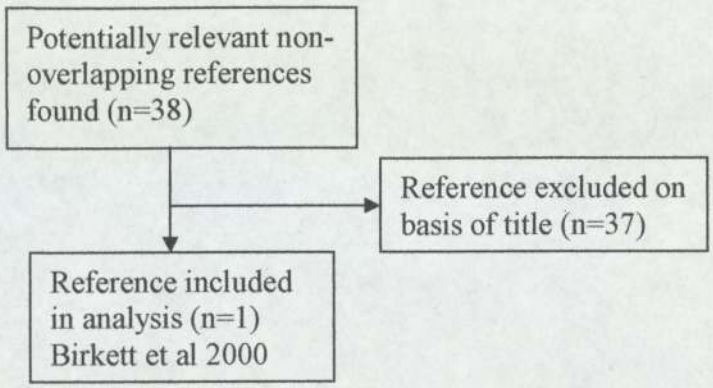

Fig 17: shows the search strategy for identifying references regarding polymorphisms in the 5-HT5A receptor and its association with clozapine response. (The numbers in brackets equals the number of references retrieved using the PubMed (P), Medline (M) and Science Direct (SD) databases).

4.7.8 - Articles retrieved which identify polymorphisms in the 5-HT6 receptor and their link to clozapine response

Search strategy :	P	M	SD
5-HT6+response+clozapine+polymorphism	(2)	(2)	(1)
5HT6+response+clozapine+polymorphism	(1)	(1)	(1)
Serotonin 6+response+clozapine+polymorphism	(6)	(6)	(0)
5-HT6+response+clozaril+polymorphism	(1)	(1)	(0)
5-HT6+response+clozapine+polymorphisms	(2)	(2)	(1)
5-HT6+response+clozapine+mutation	(0)	(0)	(0)
5-HT6+response+clozapine+mutations	(0)	(0)	(0)
5-HT6+response+clozapine+mutation+genetic	(0)	(0)	(0)
5-HT6+response+clozapine+mutations+genetic	(0)	(0)	(0)
5-HT6+response+clozapine+mutation+genetics	(0)	(0)	(0)
5-HT6+response+clozapine+mutations+genetics	(0)	(0)	(0)
5-HT6+response+clozapine+mutation+pharmacogenetic	(0)	(0)	(0)
5-HT6+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(0)
5-HT6+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
5-HT6+response+clozapine+polymorphism+genetic	(2)	(2)	(1)
5-HT6+response+clozapine+polymorphisms+genetics	(2)	(2)	(1)
5-HT6+response+clozapine+polymorphism+pharmacogenetic	(1)	(1)	(1)
5-HT6+response+clozapine+polymorphisms+pharmacogenetics	(1)	(1)	(1)
Serotonin 6+clozapine+response+mutation	(2)	(2)	(0)
Serotonin 6+clozapine+response+mutations	(2)	(2)	(0)
Serotonin 6+clozapine+response+mutation+genetic	(2)	(2)	(0)
Serotonin 6+clozapine+response+mutations+genetic	(2)	(2)	(0)
Serotonin 6+clozapine+response+mutation+genetics	(2)	(2)	(0)
Serotonin 6+clozapine+response+mutations+genetics	(2)	(2)	(0)
Serotonin 6+clozapine+response+mutation+pharmacogenetic	(1)	(1)	(0)
Serotonin 6+clozapine+response+mutations+pharmacogenetic	(1)	(1)	(0)
Serotonin 6+clozapine+response+mutations+pharmacogenetics	(0)	(0)	(0)
Serotonin 6+response+clozapine+polymorphism+genetic	(6)	(6)	(0)
Serotonin 6+response+clozapine+polymorphisms+genetics	(4)	(4)	(0)
Serotonin 6+response+clozapine+polymorphism+pharmacogenetic	(2)	(2)	(0)
Serotonin 6+response+clozapine+polymorphisms+pharmacogenetics	(0)	(0)	(0)

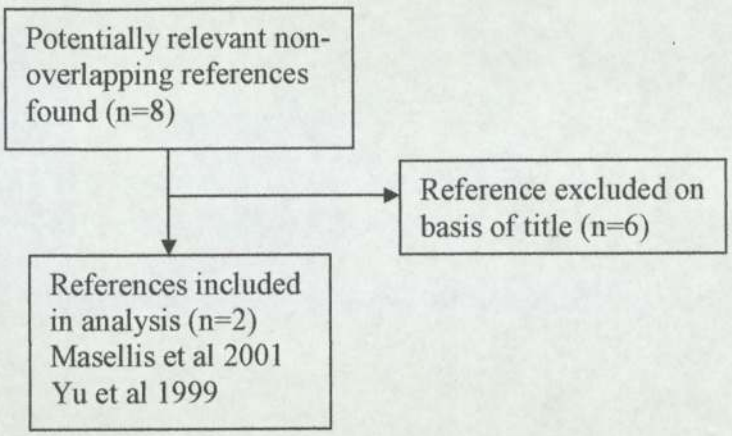

Fig 18: shows the search strategy for identifying references regarding polymorphisms in the 5-HT6 receptor and its association with clozapine response. (The numbers in brackets equals the number of references retrieved using the PubMed (P), Medline (M) and Science Direct (SD) databases).

4.7.9 – Articles retrieved which identify polymorphisms in the Adrenaline receptors and their link to clozapine response

Search strategy :	P	M	SD
Adrenaline+response+clozapine+polymorphism	(0)	(0)	(0)
Adrenergic+response+clozapine+polymorphism	(4)	(4)	(2)
Adrenoceptor+response+clozapine+polymorphism	(2)	(2)	(2)
Epinephrine+response+clozapine+polymorphism	(0)	(0)	(0)
Adrenergic+response+clozaril+polymorphism	(3)	(3)	(0)
Adrenergic+response+clozapine+polymorphisms	(2)	(2)	(2)
Adrenergic+response+clozapine+mutation	(0)	(0)	(1)
Adrenergic+response+clozapine+mutations	(1)	(1)	(1)
Adrenergic+response+clozapine+mutation+genetic	(0)	(0)	(1)
Adrenergic+response+clozapine+mutations+genetic	(1)	(1)	(1)
Adrenergic+response+clozapine+mutation+genetics	(0)	(0)	(1)
Adrenergic+response+clozapine+mutations+genetics	(1)	(1)	(1)
Adrenergic+response+clozapine+mutation+pharmacogenetic	(0)	(0)	(1)
Adrenergic+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(1)
Adrenergic+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(1)
Adrenergic+response+clozapine+polymorphism+genetic	(4)	(4)	(1)
Adrenergic+response+clozapine+polymorphisms+genetics	(2)	(2)	(1)
Adrenergic+response+clozapine+polymorphism+pharmacogenetic	(0)	(0)	(1)
Adrenergic+response+clozapine+polymorphisms+pharmacogenetics	(1)	(1)	(1)
Adrenoceptor+response+clozaril+polymorphism	(2)	(2)	(0)
Adrenoceptor+response+clozapine+polymorphisms	(0)	(0)	(2)
Adrenoceptor+response+clozapine+mutation	(0)	(0)	(2)
Adrenoceptor+response+clozapine+mutations	(0)	(0)	(2)
Adrenoceptor+response+clozapine+mutation+genetic	(0)	(0)	(1)
Adrenoceptor+response+clozapine+mutations+genetic	(0)	(0)	(1)
Adrenoceptor+response+clozapine+mutation+genetics	(0)	(0)	(1)
Adrenoceptor+response+clozapine+mutations+genetics	(0)	(0)	(1)
Adrenoceptor+response+clozapine+mutation+pharmacogenetic	(0)	(0)	(0)
Adrenoceptor+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(0)
Adrenoceptor+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
Adrenoceptor+response+clozapine+polymorphism+genetic	(2)	(2)	(1)
Adrenoceptor+response+clozapine+polymorphisms+genetics	(0)	(0)	(1)
Adrenoceptor+response+clozapine+polymorphism+pharmacogenetic	(0)	(0)	(0)
Adrenoceptor+response+clozapine+polymorphisms+pharmacogenetics	(0)	(0)	(0)

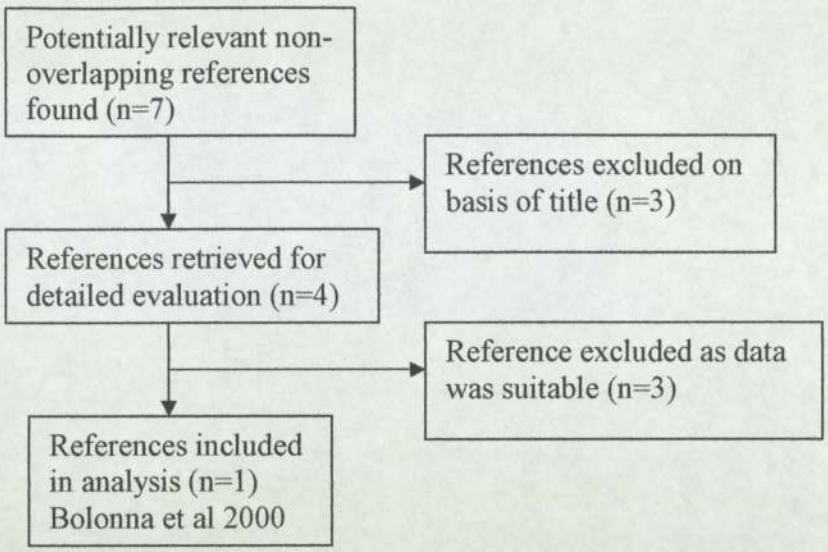

Fig 19: shows the search strategy for identifying references regarding polymorphisms in the Adrenaline receptor and its association with clozapine response. (The numbers in brackets equals the number of references retrieved using the PubMed (P), Medline (M) and Science Direct (SD) databases).

4.7.10 – Articles retrieved which identify polymorphisms in the Glutamate receptors and their link to clozapine response

Search strategy :	P	M	SD
Glutamate+response+clozapine+polymorphism	(1)	(1)	(1)
Glutamatergic+response+clozapine+polymorphism	(0)	(0)	(0)
NMDA+response+clozapine+polymorphism	(1)	(1)	(1)
Glutamate+response+clozaril+polymorphism	(1)	(1)	(0)
Glutamate+response+clozapine+polymorphisms	(0)	(0)	(1)
Glutamate+response+clozapine+mutation	(0)	(0)	(1)
Glutamate+response+clozapine+mutations	(0)	(0)	(1)
Glutamate+response+clozapine+mutation+genetic	(0)	(0)	(1)
Glutamate+response+clozapine+mutations+genetic	(0)	(0)	(1)
Glutamate+response+clozapine+mutation+genetics	(0)	(0)	(1)
Glutamate+response+clozapine+mutations+genetics	(0)	(0)	(1)
Glutamate+response+clozapine+mutation+pharmacogenetic	(0)	(0)	(0)
Glutamate+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(0)
Glutamate+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
Glutamate+response+clozapine+polymorphism+genetic	(0)	(0)	(1)
Glutamate+response+clozapine+polymorphisms+genetics	(0)	(0)	(1)
Glutamate+response+clozapine+polymorphism+pharmacogenetic	(0)	(0)	(0)
Glutamate+response+clozapine+polymorphisms+pharmacogenetics	(0)	(0)	(0)
NMDA+response+clozaril+polymorphism	(1)	(1)	(0)
NMDA+response+clozapine+polymorphisms	(0)	(0)	(1)
NMDA+response+clozapine+mutation	(0)	(0)	(0)
NMDA+response+clozapine+mutations	(0)	(0)	(0)
NMDA+response+clozapine+mutation+genetic	(0)	(0)	(0)
NMDA+response+clozapine+mutations+genetic	(0)	(0)	(0)
NMDA+response+clozapine+mutation+genetics	(0)	(0)	(0)
NMDA+response+clozapine+mutations+genetics	(0)	(0)	(0)
NMDA+response+clozapine+mutation+pharmacogenetic	(0)	(0)	(0)
NMDA+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(0)
NMDA+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
NMDA+response+clozapine+polymorphism+genetic	(0)	(0)	(0)
NMDA+response+clozapine+polymorphisms+genetics	(0)	(0)	(0)
NMDA+response+clozapine+polymorphism+pharmacogenetic	(0)	(0)	(0)
NMDA+response+clozapine+polymorphisms+pharmacogenetics	(0)	(0)	(0)

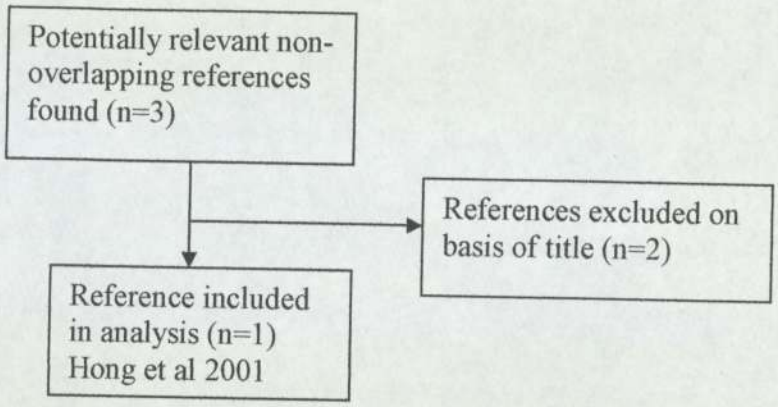

Fig 20: shows the search strategy for identifying references regarding polymorphisms in the Glutamate receptor and its association with clozapine response. (The numbers in brackets equals the number of references retrieved using the PubMed (P), Medline (M) and Science Direct (SD) databases).

4.7.11 – Articles retrieved which identify polymorphisms in the Histamine receptors and their link to clozapine response

Search strategy :	P	M	SD
Histamine+response+clozapine+polymorphism	(1)	(1)	(2)
Histaminergic+response+clozapine+polymorphism	(0)	(0)	(0)
H1+response+clozapine+polymorphism	(1)	(1)	(1)
Histamine+response+clozaril+polymorphism	(1)	(1)	(0)
Histamine+response+clozapine+polymorphisms	(2)	(2)	(2)
Histamine+response+clozapine+mutation	(0)	(0)	(0)
Histamine+response+clozapine+mutations	(0)	(0)	(0)
Histamine+response+clozapine+mutation+genetic	(0)	(0)	(0)
Histamine+response+clozapine+mutations+genetic	(0)	(0)	(0)
Histamine+response+clozapine+mutation+genetics	(0)	(0)	(0)
Histamine+response+clozapine+mutations+genetics	(0)	(0)	(0)
Histamine+response+clozapine+mutation+pharmacogenetic	(0)	(0)	(0)
Histamine+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(0)
Histamine+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
Histamine+response+clozapine+polymorphism+genetic	(1)	(1)	(0)
Histamine+response+clozapine+polymorphisms+genetics	(2)	(2)	(0)
Histamine+response+clozapine+polymorphism+pharmacogenetic	(0)	(0)	(0)
Histamine+response+clozapine+polymorphisms+pharmacogenetics	(1)	(1)	(0)
H1+response+clozaril+polymorphism	(1)	(1)	(0)
H1+response+clozapine+polymorphisms	(2)	(2)	(1)
H1+response+clozapine+mutation	(0)	(0)	(0)
H1+response+clozapine+mutations	(0)	(0)	(0)
H1+response+clozapine+mutation+genetic	(0)	(0)	(0)
H1+response+clozapine+mutations+genetic	(0)	(0)	(0)
H1+response+clozapine+mutation+genetics	(0)	(0)	(0)
H1+response+clozapine+mutations+genetics	(0)	(0)	(0)
H1+response+clozapine+mutation+pharmacogenetic	(0)	(0)	(0)
H1+response+clozapine+mutations+pharmacogenetic	(0)	(0)	(0)
H1+response+clozapine+mutations+pharmacogenetics	(0)	(0)	(0)
H1+response+clozapine+polymorphism+genetic	(1)	(1)	(0)
H1+response+clozapine+polymorphisms+genetics	(2)	(2)	(0)
H1+response+clozapine+polymorphism+pharmacogenetic	(0)	(0)	(0)
H1+response+clozapine+polymorphisms+pharmacogenetics	(1)	(1)	(0)

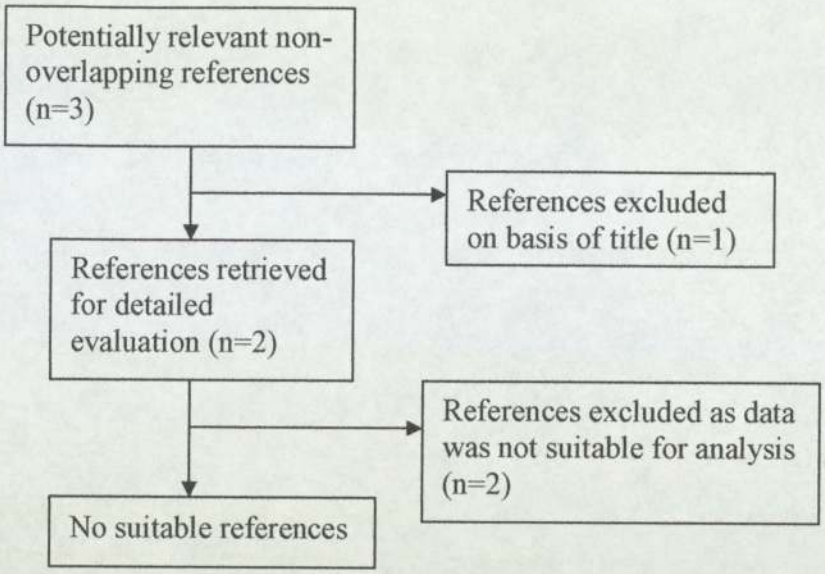

Fig 21: shows the search strategy for identifying references regarding polymorphisms in the Histamine receptor and its association with clozapine response. (The numbers in brackets equals the number of references retrieved using the PubMed (P), Medline (M) and Science Direct (SD) databases).

CHAPTER 5

5.1 – Introduction

This study has analysed all the available data on the pharmacogenetics of clozapine response. The overall aim was to determine the importance of pharmacogenetics in the response variability to atypical antipsychotics. Most of the available studies have looked at polymorphisms within the dopamine and serotonin receptor genes.

5.2 – Dopamine Receptor Genes

There is a long established link between the Dopamine system and the pathophysiology of schizophrenia (Widschwendter 2005). The dopamine theory of schizophrenia (Davis 1991), states that dopamine agonists, such as apomorphine, made symptoms of schizophrenia worse while dopamine antagonists (antipsychotic drugs), for example resperine, were effective in treating positive symptoms (Bennett 1998, Davis 1991). As a result, dopamine receptors are prime candidates in the investigation of the clinical response to clozapine.

5.2.1 – Dopamine D2

Since, all antipsychotic drugs, are D2 antagonists, this made the D2 receptor gene an important candidate for further investigation (Butcher 2000, Seeman 2004). As yet, only 2 studies have been conducted on this receptor, its polymorphisms and their link with clozapine response (Arranz 1998 and Hwang 2005). Findings from both studies have been summarised in table 13.

There are various similarities and differences between the two studies. Both studies, used two ethnic groups for comparison. Arranz and co-workers, used British and Chinese samples while Hwang and co-workers used Caucasian and African-American. However, whilst Arranz and co-workers used a similar number of patients from both ethnicities (151 of British origin and 146 of Han Chinese origin), in the study by Hwang and co-workers, there was a significant difference between the number of patients from either ethnicity (183 of Caucasian origin and 49 of African-American origin). This difference in sample sizes may contribute to the eventual findings, of whether there is an association between polymorphisms in this receptor and clozapine response. Also the Hwang study, is not comparing like with like, for example, if a comparison between Caucasians with African-Americans is done, then the term Negroids should be used. However, the term African-American was most likely used because the black US population is highly differentiated from the world wide black African population. As Hwang is comparing a race (Caucasians) with an ethnicity (African-American). Then again, if patients from African-American origin are being compared, then the Caucasian population, needs to be more specified, as to its origin. If the study by Arranz, has data based on the patients origin , and the Hwang study has data based on race , then the two studies in theory cannot be compared.

The two studies used different response criterias to find whether a patient could be classified as a responder or a non-responder. Arranz and co-workers used a 20 point

Table 13: shows the studies that have investigated polymorphisms in the D2 receptor gene and its link to clozapine response

Author	Year	Polymorphism	Receptor	Location	Notes	Code - key	N responders			Responders			N non-responders			Non-responders			Criteria response	Result
								Allele 1	Allele 2	Ins/Ins	Ins/Del	Del/Del		Allele 1	Allele 2	Ins/Ins	Ins/Del	Del/Del		
Arranz	1998	141C Ins/Del	D2	11q22-q23	British origin		94			67	27	0	57			45	12	0	20 point improvement in GAS , treatement length not defined .	NS
					Chinese origin		85			71	13	1	61			55	6	0	Personal interview, treatment length 6 wks	NS
								Allele 1	Allele 2	Genotype 1 / 1	Genotype 1 / 2	Genotype 2 / 2		Allele 1	Allele 2	Genotype 1 / 1	Genotype 1 / 2	Genotype 2 / 2		
Hwang	2005	(-) 241 A/G	D2	11q22-q23	Caucasian	A = 1 , G = 2	93	167	19	76	15	2	81	145	17	65	15	1	20% reduction in BPRS score after 6 months	NS
					African-American		24	36	12	15	6	3	23	36	10	14	8	1		NS
		(-) 141C Ins/Del			Caucasian	Del = 1 , Ins = 2	93	17	169	0	17	76	83	19	147	1	17	65		NS
					African-American		25	24	26	4	16	5	24	22	26	4	14	6		NS
		rs4648317 C/T			Caucasian	C = 1 , T = 2	92	162	22	73	16	3	82	144	20	64	16	2		NS
					African-American		24	44	4	21	2	1	23	38	8	15	8	0		S
		rs1125394 A/G			Caucasian	A = 1 , G = 2	92	151	33	64	23	5	82	134	30	56	22	4		NS
					African-American		24	45	3	21	3	0	23	36	10	15	6	2		S
		Taq IB C/T			Caucasian	C = 1 , T = 2	92	28	156	3	22	67	82	26	138	3	20	59		NS
					African-American		24	0	48	0	0	24	23	4	42	0	4	19		S
		Taq ID C/T			Caucasian	T = 1 , C = 2	84	91	97	25	41	28	84	76	92	18	44	24		NS
					African-American		24	21	27	5	11	8	23	18	28	6	6	11		NS
		NcoI C/T			Caucasian	C = 1 , T = 2	93	127	59	46	35	12	82	108	56	36	36	10		NS
					African-American		24	15	33	2	11	11	23	17	29	3	11	9		NS
		C957T			Caucasian	C = 1 , T = 2	89	89	89	24	41	24	81	82	80	17	48	16		NS
					African-American		24	37	11	15	7	2	24	40	8	16	8	0		NS
		rs2242591 A/G			Caucasian	A = 1 , G = 2	93	149	37	62	25	6	82	128	36	51	26	5		NS
					African-American		24	44	4	20	4	0	23	37	9	15	7	1		NS
		rs2242592 C/T			Caucasian	T = 1 , C = 2	90	53	127	9	35	46	79	47	111	6	35	38		NS
					African-American		23	24	22	7	10	6	23	29	17	11	7	5		NS
		rs2242593 A/G			Caucasian	A = 1 , G = 2	92	152	32	64	24	4	82	137	27	58	21	3		NS
					African-American		24	47	1	23	1	0	23	42	4	19	4	0		NS
		TaqIA C/T			Caucasian	T = 1 , C = 2	95	36	154	4	28	63	83	33	133	4	25	54		NS
					African-American		25	9	41	1	7	17	24	20	28	5	10	9		S
		S- Significant	NS- not significant																	

improvement in the GAS (Global Assessment Scale) as a cut-off for response while Hwang and co-workers used a > 20 % reduction in the overall BPRS score (Brief Psychiatric Rating Scale). These assessment methods are very subjective, but as yet there is nothing better. So here the key issue is the difficulty of comparison. However, the two studies had comparable findings, Arranz and co-workers found no statistically significant association between the –141C Ins/Del polymorphism in the D2 receptor and clozapine response, in either population. Hwang and co-workers had similar findings, of no significant association between that polymorphism and response in either of their sample populations. Arranz and co-workers only investigated the –141C Ins/Del polymorphism whereas the study by Hwang and co-workers was much wider looking at 12 polymorphisms within the D2 receptor. Referring back to the –141C Ins/Del polymorphism both the sample sets from the study by Arranz and co-workers and the Caucasian sample in the study by Hwang and co-workers found the Ins/Ins genotype to be most common in responders, however this was not the case in the African-American sample (from the study by Hwang and co-workers) which found that the Ins/Ins genotype was not as common, with the Ins/Del genotype being shown to be more frequent. The African-American sample in the study by Hwang and co-workers found 3 polymorphisms (Taq 1A, Taq 1B and rs1125394) to be statistically significant for an association with clozapine response. For approximately half of the 12 polymorphisms investigated by Hwang and co-workers similar results were found among both populations for instance both samples sets would find a certain genotype was the most common, for example in the –241 A/G polymorphism both populations found the A/A genotype was most common in both responders and non-responders . Although it was found to a lesser extent in the African-American sample due to the smaller sample size. More studies are needed on the lesser known

polymorphisms in order to confirm these findings. This result of African-American patients responding differently to drugs is not uncommon; studies have found that Africans and African-Americans needed much higher doses of antipsychotic drugs than other populations to achieve the same result (Pearlman 1984, Strickland 1991). Contradictory results have also been reported (Adams 1984, Sramek 1991).

Although both are association studies, the study by Hwang and co-workers, is far more exploratory since it examines 12 polymorphisms, some of them unknown. In contrast, Arranz and co-workers focussed on the already known polymorphism in the D2 receptor gene (-) 141C Ins/Del ; although this polymorphism has not been investigated by itself before. Therefore both are original studies.

5.2.2 – Dopamine D3

The D3 receptor gene has been seen as a potential candidate for the investigation of the pharmacogenetics of clozapine because one of its polymorphisms (Ser9Gly) is thought to be linked to dopamine binding (Lundstrom 1996).To date, 3 studies have looked at the association between the Ser9Gly polymorphism in the D3 receptor gene and clozapine response, (Malhotra 1998), (Scharfetter 1999) and (Shaikh 1996) (see table 14).

The studies by Malhotra and co-workers and Scharfetter and co-workers, were similar in the way they described the ethnicity of their samples. Instead of describing a race or an area of origin, both defined participants on a geographical basis. The studies stated, patients were from the U.S (Malhotra) or from Pakistan (Scharfetter). In comparison, Shaikh and co-workers gave a more specific definition stating that the

sample consisted of patients who were of white European Caucasian origin. Although, all of the studies will exhibit some degree of ethnic heterogeneity, the study by Scharfetter and co-workers, stated that recruited patients were from similar ethnic communities and social backgrounds, and so would be from the same or similar ethnicity / race / region. All three studies, just looked at one sample group. This is different to the D2 receptor studies, which looked at two different ethnic samples and compared the findings .

Table 14: shows studies that have investigated the Ser9Gly polymorphism in the D3 receptor gene and its link to clozapine response

Author	Year	Polymorphism	Notes	N Responders	S/S	S/G	G/G	N Non-responders	S/S	S/G	G/G	Response	Result
Malhotra	1998	Ser9Gly	68 patients US Americans	19	5	11	3	49	21	20	8	20% decrease in BPRS score after 10 wks	NS
Scharfetter	1996	Ser9Gly	32 patients, from Pakistan	21	5	12	4	11	8	3	0	At least 50 % decrease in BPRS after 6 months	S
Shaikh	1996	Ser9Gly	133 patients , all of white european caucasian origin	79	28	46	5	54	29	23	2	A 20 point improvement in GAS after at least 3 months	NS

S/S – Ser/Ser genotype
SG – Ser/Gly genotype
G/G – Gly/Gly genotype

NS – Not significant
S - Significant

There was a large variation in the sample sizes of these studies. The Malhotra study used 68 patients while the Scharfetter study enrolled 32 patients and the Shaikh study included 133 patients. However, on the whole all these sample sizes were small. A potentially significant finding reported by Malhotra and co-workers was that the Ser9/Ser9 genotype was particularly found in non-responders. However this is not evident in any of the other studies, even though it was reported by Malhotra and co-workers.

In terms of sample size, the largest study, by Shaikh and co-workers, is better, even though all the studies had a small sample size, but the study by Malhotra and co-workers, is also a HRR (haplotype relative risk) study, the gold standard for association studies. The HRR study was done to establish a link between allele and genotype frequencies and the transmission of schizophrenia . The clozapine association section of this study was a double-blind trial. Malhotra and co-workers and Scharfetter and co-workers both used the BPRS for defining response while Shaikh used the GAS. Among the three studies, there were several occasions when results were similar in two of the studies, but different in the third. In other results, a different two studies would find similar findings for instance in the number patients with similar genotypes, both Shaikh and co-workers and Scharfetter and co-workers found that a greater number of responders had the Ser/Gly genotype. While Malhotra and co-workers and Scharfetter and co-workers both reported that a greater number of non-responders had the Ser/Ser genotype. Also from the rating scales used, two studies using the same scale and the third being different.

5.2.3 – Dopamine D4

There are 2 main reasons why the D4 receptor gene has been implicated in pharmacogenetic studies of clozapine response. Firstly, because clozapine has been shown to have a 10 times higher affinity for D4 when compared to D2 and D3 (Van Tol 1991) and secondly, because an increased level of D4 receptors were found in the brains of schizophrenic patients when compared to controls (Van Tol 1991). Several studies have been conducted on the association of polymorphisms in the D4 receptor and their link to clozapine response. A range of polymorphisms within the D4 receptor have been investigated. Some studies have had to be excluded (see chapter 4-Methods). The remaining ones have been evaluated; Kohn and co-workers 1997 (Kohn 1997), Rietschel and co-workers 1996 (Rietschel 1996) and Zhao and co-workers 2005 (Zhao 2005) (see tables 15, 16, 17 and 18).

Both Kohn and co-workers and Rietschel and co-workers investigated the exon I 12bp polymorphism, Rietschel and co-workers also looked at the exon I 13bp polymorphism as well as the Gly11Arg polymorphism. The exon III 48bp repeat polymorphism was investigated by Kohn and co-workers, Rietschel and co-workers and also Zhao and co-workers.

The study by Kohn and co-workers involved 98 patients who were Israeli Jews. Subjects were then further subdivided as being either Ashkenazi Jews, those whose origin or parents origin was in European countries, other than the Balkans or Non-Ashkenazi, those whose origin was in North Africa or Asia. The study by Rietschel and co-workers involved 231 patients of German descent only. The study by Zhao and co-workers was the smallest with 81 patients, from the Han Chinese population, of the Hu Nan province.

The three studies employed different methods of defining response. Kohn and co-workers assessed response to clozapine retrospectively by interviewers using a symptom assessment with a 3 point scale, marked, partial or absent. Patients who exhibited marked symptomatic improvement and definite progress in terms of hospitalisation and functioning were classed as definite responders. Those who showed an unchanged or worse symptomatic status were classed as non-responders while those patients who showed partial or definite symptomatic improvement, but no additional change in hospitalisation status or functioning, were classed as minimal responders. The study by Rietschel and co-workers assessed response by placing patients into 4 groups. Those in Group 0 showed worsening or no change and those in Group 1 patients exhibited slight improvement . Subjects in these two groups, were viewed as non-responders. Patients in Group 2 showed a marked improvement while those in Group 3, had an almost total reduction in symptoms. Subjects in Groups 2 and 3, were viewed as responders. Finally, the study by Zhao and co-workers, defined response as a 50% reduction in PANSS score. This type of definition, using a rating scale is what is most often clinically used to assess outcome, although sometimes other scales may be used, such as BPRS, CGI and GAS. Kohn and co-workers found that by subdividing their subjects into groups according to their ethnicities and response to clozapine, the power of the study was reduced because of relatively small numbers in each group (ranging from 0 – 44 when looking at values for the exon I polymorphism).This was also a problem with the study by Rietschel which grouped according to side-effects and which resulted in limited numbers in each group . No mention of power was found in the study by Zhao.

These studies did not show an association between polymorphisms in either exon I, Gly11Arg (tables 15, 16 and 17) or exon III (table 18) and clozapine response.

Though studies by both Kohn and co-workers and Rietschel and co-workers found that the 2/2 genotype in the exon I 12bp polymorphism was the most common in both responders and non-responders. The 1/1 genotype was the rarest. No definite conclusions can be made about the exon I 13bp deletion polymorphism and clozapine response since only one study has been conducted (Rietschel 1996). In this study the non deletion/non deletion genotype seems to be the most frequent among both responders and non-responders, therefore it is unlikely to affect interindividual variability. Rietschel and co-workers are again the onlyindividuals to have examined the Gly11Arg polymorphism for its link to clozapine response. The Gly11Gly11 genotype was the most common among studied patients. Like with the other polymorphisms examined by Rietschel and co-workers(exon I 12bp and exon I 13bp deletion) the defintion of response in this study was defined by placing patients into 4 groups according to efficacy. Finally the exon III 48 bp repeat polymorphism, this was more complex as a greater number of genotypes were involved, as compared to the previous polymorphisms. The 4/4 genotype was shown to be the most common in studies by both Kohn and coworkers and Rietschel and coworkers, Zhao and co-workers found the 5/5 genotype to be more frequent. However all the studies, suggested that it was not possible to exclude D4's involvement in response, on the basis of their findings . Some of these studies may be more useful than others, in terms of sample size, the Kohn and Zhao studies were limited, while the Rietschel study has a somewhat larger sample size. The study by Zhao, primarily focused on the exon III 48 bp polymorphism, while the other studies, looked at polymorphisms within exon I as well.

Table 18 may look more complex than table 15, 16 and 17 this is due to the exon III 48bp polymorphism having many more genotypes, as opposed to the 2 or 3 shown in tables 15, 16 and 17. The study by Zhao and co-workers was the only one to use a rating scale. Rietschel and co-workers did not class their subjects too rigorously, as Kohn and co-workers found that this reduced the power of their study. Although, the study by Kohn, is the only study, to compare response, among two populations, Ashkenazi Israeli Jews and Non-Ashkenazi Israeli Jews.

Table 15: shows studies that have investigated the polymorphisms in exon 1 of the D4 receptor gene and its link to clozapine response

Author	Year	Polymorphism	Notes	N responders	11	12	22	N Non-responders	11	12	22	Response	Result
Kohn	1997	Exon I 12bp	Ashkenazi patients 98 patients , Israeli Jews	54	0	9	45	49	0	13	36	Symptomatic response on 3 point scale, change in patients , hospitalisation , and functioning status	NS
			Non-Ashkenazi patients	50	3	5	42	3	0	0	3		
Rietschel	1996	Exon I 12bp	Responder Group 0 231 patients of German descent					72	0	7	33	Defined 4 groups in terns of efficacy . Groups 0 &1 – non-responders , Groups 2 & 3 – responders	NS
			Responder Group 1						1	7	24		
			Responder Group 2	77	0	9	36						
			Responder Group 3		0	3	29						

NS – Not significant

11 – 1-fold / 1-fold genotype
12 – 1-fold / 2-fold genotype
22 – 2-fold / 2-fold genotype

Table 16: shows a study that has investigated the exon 1 13bp deletion polymorphism in the D4 receptor gene and its link to clozapine response

Author	Year	Polymorphism	Notes	N Responders	Del / non-del	Non-del / non-del	N Non-responders	Del / non-del	Non-del / non-del	Response	Result
Rietschel	1996	Exon I 13bp deletion	Responder Group 0 231 patients of German descent				72	1	39	Defined 4 groups in terns of efficacy . Groups 0 &1 – non-responders , Groups 2 & 3 – responders	NS
			Responder Group 1					1	31		
			Responder Group 2	77	2	43					
			Responder Group 3		2	30					

NS – Not significant

Table 17: shows a study that has investigated the Gly11Arg polymorphism in the D4 receptor gene and its link to clozapine response

Author	Year	Polymorphism	Notes	N Responders	Gly11-Arg11	Gly11-Gly11	N Non-responders	Gly11-Arg11	Gly11-Gly11	Response	Result
Rietschel	1996	Gly11Arg substitution	Responder Group 0 231 patients of German descent				72	2	38	Defined 4 groups in terns of efficacy . Groups 0 &1 – non-responders , Groups 2 & 3 – responders	NS
			Responder Group 1					0	32		
			Responder Group 2	77	0	45					
			Responder Group 3		1	31					

Table 18: shows the studies that have investigated the exon III 48 bp polymorphism in the D4 receptor and its link to clozapine response

Author	Year	Polymorphism	Receptor	Location	Notes	N responders	responders														N non-responders	non-responders							Design	Criteria response	Result
							33	34	37	44	45	46	47	48	67	77	79	Others		24	44	47	77	Others							
Kohn	1997	exon III 48bp repeat	D4	11p15.5	Ashkenazi patients	40		2		21			13			4		0.12	49	0	40	9	0	0	Retrospect	Symptomatic response on 3 point scale - change in patients hospitalisation & functioning status	Not significant					
					Non-Ashkenazi patients	46		7		29			10			0		0.05	43	3	26	14	0	0.12									
Rietschel	1998	exon III 48bp repeat	D4	11p15.5	Responder Group 0	72	0	6	4	1	1	14	0	0	12	1	1	0	0											Patients put into 4 grs to measure efficacy 0 - worse / no change 1 - slight improvement 2 - marked improvement 3 - total reduction	Not significant	
					Responder Group 1		0	5	1	3	1	14	1	0	7	0	0	1	1												
					Responder Group 2	77	0	8	1	1	0	29	1	1	5	0	0	1	0												
					Responder Group 3		1	3	1	2	1	16	0	0	8	0	0	0	0												
							3_3	3_4	2_5	3_5	5_5	5_6	6_6							3_3	3_4	2_5	3_5	5_5	5_6	6_6	6_6				
Zhao	2005	exon III 48 bp repeat	D4	11p15.5		62	4	1	0	25	27	4	1							19	1	0	1	3	14	0	0		50% reduction in PANSS score after at least 6 wks	Found that the 5_5 genotype and 5 allele was significantly less frequent in responders than non-responders

Rietschel 95 : Group 0 - increasing / no change ,
Group 1 - slight improvement ,
Group 2 - marked improvement and
Group 3 - almost total reduction in symptoms

Group 0 and 1 - Non - responders (n = 72)
Group 2 and 3 - Responders . (n = 77)

The numbers in bold refer to genotypes eg: 3_3 is the genotype 3/3 etc

Kohn 97 - numbers were given as frequencies , therefore need to multiply frequencies by number of subjects . Therefore numbers given in this table will have been rounded up or down

5.3 – Serotonin (5-HT) Receptor Genes

Interest in the serotonin system in pharmacogenetic studies of clozapine response has arisen because the 5-HT2A receptor agonist LSD has been shown to produce hallucinations (Glennon 1984, Ozaki 2004), a key symptom of schizophrenia. In addition, 5-HT2 and 5-HT6 receptors have been found to have a high affinity for clozapine; (Meltzer 1991, Meltzer 1999, Kapur 1996). Because of the general interest in the 5-HT receptors and antipsychotics, other receptors in this family have also been studied. This section repeats pharmacogenetic searches on 5-HT2, 5-HT3, 5-HT5 and 5-HT6 and clozapine.

5.3.1 – Serotonin 5-HT2A

The 5-HT2A receptor has received the most attention, both because it may be involved in the pathophysiology of hallucinations (Glennon 1984, Ozaki 2004), and also because clozapine has a high affinity for this receptor (Meltzer 1991, Meltzer 1999, Kapur 1996). Many more studies have looked at this receptor and its association with clozapine response than any other receptor subtype. These studies are, Arranz and co-workers 1995 (Arranz 1995), Arranz and co-workers 1996 (Arranz 1996), Arranz and co-workers 1998 (Arranz 1998), Lin and co-workers 1999 (Lin 1999), Malhotra and co-workers 1996 (Malhotra 1996), Masellis and co-workers 1995 (Masellis 1995), Masellis and co-workers 1998 (Masellis 1998) and Nothen and co-workers 1995 (Nothen 1995).

To review these studies it is necessary to divide them according to the polymorphisms examined . Consequently they have separated into two groups according to whether they have looked at one polymorphism or several.

5.3.1.1 – T102C

There are three studies that have focussed on one polymorphism (Arranz 1995, Lin 1999 and Masellis 1995) (see table 19). All have looked at the T102C polymorphism.

The study by Lin, was the only study to use controls and this was only done to investigate whether there was an association between this polymorphism and schizophrenia. The controls were not involved in the investigation of a link between polymorphisms and clozapine response. The study by Masellis differed from the others in that it enrolled patients of two different populations. However, the patients were not recruited in similar numbers, in fact there was a marked difference. It is unclear whether or not Masellis and co-workers attempted to recruit similar sample numbers in both populations, or if they were just looking at both populations as a whole sample. Also, the two populations, are very diverse, as one is described, by colour, while the other by origin. A common characteristic of all three studies was the vagueness of their description of their patients ethnicities.

The study by Lin and the study by Masellis both defined response using the BPRS, while the study by Arranz 1995 used the GAS. Lin and co-workers, who assessed therapeutic response directly from the patients BPRS score rather than separating the subjects into responders and non-responders, suggested that this may have reduced the power of their study. The decision to assess using BPRS as opposed to separating patients into responders / non-responders, was because of concerns about dichotomising. In this case the responder / non-responder information shown in table 19 was obtained directly from the author of the study, since it was not provided in the published article. Only the study by Lin and co-workers (1999) makes reference to the power of their study. The remaining two studies, Masellis and co-workers (1995) and

Arranz and co-workers (1995) did dichotomise patients, as responders and non-responders.

Both Lin and coworkers and Masellis and coworkers found the T/C genotype to be the most common among both responders and non-responders. The study by Arranz and coworkers found the T/C genotype to most common in responders but the C/C genotype was the most frequent in non-responders. Only Arranz and co-workers 1995, showed an association between the T102C polymorphism and clozapine response. There is no obvious reason, why this study should have found an association when the other studies failed to do so.

5.3.1.2 – Remaining Studies on T102C

Three other studies have investigated the T102C polymorphism and clozapine response: Malhotra and co-workers (1996), Masellis and co-workers (1998) and Nothen and co-workers (1995). These, unlike the studies above, investigated two or three different polymorphisms within the 5-HT2A receptor subtype and its link with response to clozapine (see table 19).

The study by Malhotra and co-workers recruited 70 patients but no information about ethnicity was given . The study by Masellis and co-workers enrolled 185 patients from a mixture of ethnicities: 144 Caucasians, 40 African-Americans and 1 Asian. The Nothen and co-workers study enrolled 146 patients, all of German descent. As with other studies that have employed two or more different population groups, this study does not have an equal number in each ethnic group, making this an unreliable comparison . The authors of this study stated that this diversity of ethnic backgrounds may have created a type II error.

As mentioned previously, sample size is linked to power of the study. The study by Malhotra, indicated that their study has an effect size of 0.13, which means that 700 additional patients would be needed to achieve a power of 80 %, their current power was 61%. This indicates that their failure to replicate the findings of Arranz and co-workers, may not be a question of power, since the Arranz sample only included 149 patients. The Masellis study, does not mention power of their study.

Like the other studies looking at the T102C polymorphism mentioned above in 5.3.1.1 these studies also found the T/C genotype to be the most frequent among both responders and non-responders.

Table 19: shows studies that have investigated the T102C polymorphism in the 5-HT2A receptor gene for its link to clozapine response

r	Year	Polymorphism	Notes	N Responders	T/T	T/C	C/C	N Non-responders	T/T	T/C	C/C	Response	Result
z	1995	T102C	149 patients, West European	92	15	54	23	57	9	18	30	20 point improvement in GAS after 12 weeks	S
	1999	T102C	97 patients & 101 controls, Chinese	58	20	31	7	39	16	16	7	20% reduction in BPRS score after 8 wks	NS
tra	1996	T102C	70 patients no information about ethnicity given	21	2	14	5	49	9	27	13	20% reduction in BPRS score after 10 wks .	NS
lis	1995	T102C	126 patients, 25 Afr-Am and 101 'whites'	72	13	40	19	54	6	31	17	20% reduction in BPRS score after 6 months	NS
lis	1998	T102C	185 patients , 144 Caucasians, 40 Afr-Ams and 1 Asian	95	19	48	28	86	18	43	25	20% reduction in BPRS (or 1 category of CGI) after 6 months .	NS
n	1995	T102C	Responder Group 0 146 patients of German descent					41	5	18	18	Split into 4 groups according to efficacy, corresponds to GAS	NS
			Responder Group 1					32	7	15	10		
			Responder Group 2	38	9	15	14						
			Responder Group 3	35	6	18	11						

5.3.1.3 – His452Tyr

A number of studies have investigated this polymorphism, Malhotra and co-workers 1996, Arranz and co-workers 1996, Arranz and co-workers 1998, Masellis and co-workers 1998, and Nothen and co-workers 1995. Malhotra and co-workers and Nothen and co-workers both employed the same sample sets to investigate this polymorphism as they used when examining the T102C polymorphism (results shown in table 19). The data for His452Tyr is summarised in table 20.

Table 20: shows studies that have investigated the His452Tyr polymorphism in the 5-HT2A receptor gene and its link to clozapine response

r	Year	Polymorphism	Notes	N Responders	H/H	H/T	T/T	N Non-responders	H/H	H/T	T/T	Response	Result
:	1996	His452Tyr	153 patients , 178 controls all European Caucasians	99	87	11	1	54	45	6	3	20 point improvement in GAS after 6 wks	S
:	1998	His452Tyr	Sample I 160 patients, 178 controls all white Caucasians of British origin	102	90	11	1	58	48	7	3	20 point improvement in GAS after 3 months	S
			Sample II 114 patients all white Caucasians of British origin	79	63	16	0	35	25	9	1		
ra	1996	His452Tyr	70 patients no ethnicity info. given	21	17	4	0	49	39	9	1	20% reduction in BPRS score after 10wks	NS
lis	1998	His452Tyr	185 patients , 144 Caucasians, 40 Afr-Ams and 1 Asian	95	82	13	0	86	63	20	3	20% reduction in BPRS score , or 1 category of CGI after 6 months	S
n	1995	His452Tyr	Responder Group 0 146 patients of German descent					41	37	4	0	Split into 4 groups according to efficacy , corresponds to GAS	NS
			Responder Group 1					32	26	5	1		
			Responder Group 2	38	34	4	0						
			Responder Group 3	35	30	5	0						

H – His/His genotype
T – His/Tyr genotype
T – Tyr / Tyr genotype

Two studies, Arranz and co-workers 1996 and Arranz and co-workers 1998, both used GAS, while Malhotra and co-workers and Masellis and co-workers utilised the BPRS scale. Although Nothen and co-workers assessed response by dividing patients according to their efficacy to treatment, the groups did correspond to responders / non-responders and the GAS.

Power was not mentioned in the study by Arranz and co-workers (1996). The Malhotra study, had a power of 61%. In their 1998 study, Arranz and co-workers, stated that the cut-off, for response was chosen to minimise error without losing any power, although no actual figure for the power was provided. Masellis and co-wokers, stated that the power of their study, 0.80 was enough to identify allelic variations in the genes which may affect the variation in response to clozapine. However, this power was not enough to detect the effects of the genes which may play a more minor role in clozapine response. Nothen and co-workers did not state power.

Arranz and co-workers 1996 and 1998, found a significant association, between the His452Tyr polymorphism and clozapine response , similar findings were collated by Masellis and co-workers 1998. However, Malhotra and co-workers and Nothen and co-workers have reported contradictory findings . A common finding among all the studies was that the His/His genotype was the most frequent among both responders and non-responders. Arranz and co-workers 1996, found that the Tyr452 allele was linked to poor response . So, the overall conclusions are that 3 studies found significant associations while 2 studies did not. Here, there may be a possible link with the rating scale used, since both studies by Arranz and co-workers used the GAS scale, and found some link. While the Malhotra study, used the BPRS , and found no association. However this pattern is not followed by Masellis and co-workers, who

also found an association, but used the BPRS. Nothen and co-workers used GAS, but did not report any link, this may be attributed to the way their patients were divided according to efficacy .

5.3.1.4 - G[-1438]A

The final polymorphism, investigated in the 5-HT2A receptor, is –1438 G/A (see table 21). This polymorphism was investigated by Arranz and co-workers 1998 and Masellis and co-workers 1998. Arranz and co-workers 1998 used the same sample group, to investigate both this polymorphism and the previous His452Tyr polymorphism. Masellis and co-workers also used the same sample set to investigate this polymorphism, as was used for the earlier polymorphisms (T102C and His452Tyr). Arranz et al used two independent samples of 160 and 114 patients, sample I also had 178 controls, these patients were all white Caucasians, of British origin. While, the Masellis and co-workers sample, used 185 patients, from a variety of ethnic backgrounds, 144 Caucasians, 40 African-Americans and 1 Asian.

Table 21: shows studies that have investigated the G[-1438]A polymorphism in the 5-HT2A receptor gene and its link to clozapine response

Author	Year	Polymorphism	Notes	N Responders	G/G	G/A	A/A	N Non-responders	G/G	G/A	A/A	Response	Result
Arranz	1998	G[-1438]A	Sample I 160 patients, 178 controls white Caucasians of British origin	99	28	52	19	57	32	17	8	20 point improvement in GAS score after 3 months	S
			Sample II 114 patients white Caucasians of British origin	79	25	42	12	35	15	14	6		
Masellis	1998	G[-1438]A	185 patients, 144 caucasians, 40 Afr-Ams and 1 Asian	No Genotype data				No Genotype Data				20% or more reduction in BPRS score after 6 months or if close to 20% 1 category of CGI scale.	NS

G/G- G-1438/G-1438 genotype
G/A- G-1438/A-1438 genotype
A/A- A-1438/A-1438 genotype

For the study by Masellis the power value of 0.80 still applies. While the study by Arranz stated that the cut-off for response was chosen to minimise error without losing any power, no actual value for power was mentioned.

The study by Arranz and co-workers (1998), found a significant association between this polymorphism and clozapine response, whereas, the study by Masellis failed to find such an association. No genotype data was given in the study by Masellis and co-workers. The G/A genotype was more common among responders while the G/G genotype was more common among non-responders. There are two important differences between the studies that might account for the different findings: the outcome measure and sample ethnicity. Arranz and co-workers used the GAS (Global Assessment Scale) as an outcome measure, while the Masellis study used the BPRS. The study by Arranz and co-workers had white Caucasians of British origin while the study by Masellis focussed more on subjects from North America .

There are two other differences which may give some support to the study by Arranz and co-workers. This study used 2 independent samples, so that sample 2 can be used to confirm findings of sample 1 and unlike the study by Masellis and co-workers, it provided genotype data.

5.3.2 – Serotonin 5-HT2C

Interest in this receptor also arises because clozapine has been shown to have a high affinity for this receptor (Masellis 2001) and high densities of this receptor have been demonstrated in areas of the brain that are linked to the pathophysiology of schizophrenia (Malhotra 1996). Any associations found between polymorphisms of this receptor and response would be extremely beneficial since this receptor is located on the X chromosome. If a gender effect were found this could aid the individualisation of treatment .

There have been four studies that have investigated the association between the Cys23Ser polymorphism in the 5-HT2C receptor and clozapine response (Malhotra 1996), (Masellis 1998), (Rietschel 1997) (Sodhi 1995).

The patients recruited in these studies cover a diverse range of ethnicities (see table 22 below for further details). The study by Masellis 1998, used the same sample set to examine this polymorphism as they did to investigate the T102C polymorphism .

Table 22: shows studies that have investigated the Cys23Ser polymorphism in the 5-HT2C receptor gene and its link to clozapine response

-	Year	Polymorphism	Notes	N Responders	S/S	C/S	C/C	N Non-responders	S/S	C/S	C/C	Response	Result
tra	1996	Cys23Ser	66 patients from the USA	18	0	0	4	48	2	2	9	20% reduction in BPRS after 10wks	NS
is	1998	Cys23Ser	Caucasians 185 patients , 144 caucasians	72	13	4	55	67	5	4	58	20% reduction in BPRS after 6 months or 1 category of CGI	NS
			Afr-Ams (40 Afr-Ams)	20	8	3	9	19	6	3	10		
hel	1997	Cys23Ser	Responder Group 0 152 patients of German descent					74	0	3	12	Split into 4 groups according to efficacy	NS
			Responder Group 1						0	3	14		
			Responder Group 2	78	0	6	17						
			Responder Group 3		1	7	13						
	1995	Cys23Ser	162 patients Western European Caucasians	103	11	8	84	59	1	1	57	20 point improvement in GAS after 3 months	S

S/S – Ser/Ser genotype , C/S – Cys/Ser genotype
C/C – Cys/Cys genotype
Allele frequencies were not put in the table , due to space restrictions (see table 23).

Table 23: shows studies that have investigated the Cys23Ser polymorphism in the 5-HT2C receptor gene and its link to clozapine response (allele values)

Author	Year	Polymorphism	Receptor	Location	Notes	N responders		responders				N non-responders		non-responders				Design	Criteria response	Result
							Ser	SerSer	CysSer	Cys	CysCys		Ser	SerSer	CysSer	Cys	CysCys			
Malhotra	1996	Cys23Ser	5-HT2C	Xq24		18	3	0	0	11	4	48	9	2	2	26	9	Prospective	20% reduction in BPRS after 10 wks of treatment	Not significant
Masellis	1998	Cys23Ser	5-HT2C	Xq24	Caucasians	72	[13]	13	4	[55]	55	67	[5]	5	4	[58]	58	Prospective	20% reduction in BPRS score (will accept 15-20 %) or 1 category of CGI after 6 months or more of treatment	Not significant
					African Americans	20	[8]	8	3	[9]	9	19	[6]	6	3	[10]	10			
Rietschel	1997	Cys23Ser	5-HT2C	Xq24	Responder Group 0							74	4	0	3	23	12	Retrospective	Split into 4 groups according to efficacy	Not significant
					Responder Group 1								1	0	3	14	14			
					Responder Group 2	78	3	0	6	19	17									
					Responder Group 3		2	1	7	10	13									
Sodhi	1995	Cys23Ser	5-HT2C	Xq24		103	[11]	11	8	[84]	84	59	[1]	1	1	[57]	57		20 point improvement in GAS after at least 3 months treatment	Significant

Figures shown in brackets eg . [13] are the same as the numbers next to them eg. 13 . Those articles have said that eg. Ser or Ser/Ser are 13 , the figure must only be counted once for it to equal the no. of responders .

Rietschel 97 : Responder Group 0 - worsening / no change , Group 1 - slight improvement ,
Group 2 - marked improvement and Group 3 - almost total reduction in symptoms .

Group 0 and 1 - non responders , Group 2 and 3 - responders

As previously mentioned study power is one of the most significant factors when looking at complex traits. Malhotra and co-workers did not mention power in their study. Masellis and co-workers stated that their sample was likely to be genetically heterogeneous due to wide range of ethnicities they had recruited; this was thought to reduce their power to detect genes of small effect. Rietschel and co-workers indicated that the power of their study was 88.2%, based on their sample size. The study by Sodhi did not mention power.

Findings of these studies, strongly suggest that this polymorphism is not linked to clozapine response. Since 3 studies found a non-significant association, while only one reported a significant link (see tables 22 and 23, table 23 also shows allele values). However all the studies found the Cys/Cys genotype to be the most common among both responders and non-responders. Malhotra and co-workers and Masellis and co-workers both used the BPRS, while the Rietschel and co-workers study used the method of dividing their patients into 4 groups, according to efficacy of treatment, with Group 0 being worsening / no change, Group 1, slight improvement, these two groups can be viewed as non-responders, Group 2 is a marked improvement, and Group 3 an almost total reduction in symptoms, these two groups can be seen as responders. Sodhi and co-workers also used a different method of defining response by using the GAS. This difference in rating scales may be an important factor, as to why conflicting findings were found. The key point is that the study by Sodhi found a significant association and used the GAS, this could show a link between rating scales and significant links between polymorphisms and response.

All the studies were quite similar in the comparisons analysis used. For example, since this receptor is located on the X chromosome, males are hemizygous for Ser23 or Cys23 (only one copy), while females are either homozygous (Cys/Cys or Ser/Ser) or heterozygous (Cys/Ser). Therefore, separate comparisons had to be done for the two genders. No differences were found. This further supports the conclusion of no link between this polymorphism and clozapine response. However, there are also some important differences such as the criteria they used for defining response and the broad range of ethnicities used in the sample sets. There is always the possibility of false positives or negatives. The study by Masellis and co-workers was the first study to report differences between the Caucasian and African –American patients in terms of distribution of the cys23ser polymorphism. This study also differs from the others in that it measures response prospectively rather than retrospectively.

5.3.3 – Serotonin 5-HT3

This receptor has been associated with clozapine response, not only because clozapine is a potent antagonist at the 5-HT3 receptor (Hermann 1996), but also due to the location of this receptor in an area of the brain linked to schizophrenia .

As yet there has been little investigation of this receptor. Only 1 study has looked at polymorphisms within this receptor and its link with clozapine response (Gutierrez 2002) (see tables 24 and 25).

This study looked at both 5-HT3A and 5-HT3B. The polymorphisms found in the 5-HT3A receptor are, 178-C/T and 1596-A/G. While the polymorphism found in the 5-

HT3B receptor is a CA repeat. This study has recruited 266 patients, all of whom are British Caucasians (see tables 24 and 25).

Responses in this study were measured retrospectively using the GAS. The power of this study was stated as being 80%.

The finding of this study was that it would be unlikely for there to be any association between polymorphisms in this receptor and clozapine response since there were no clear differences in genotype frequencies between responders and non-responders. From the 5-HT3A receptor, the C/C genotype in the 178-C/T polymorphism seemed to be the most common, while in the 1596-A/G polymorphism the A/A genotype was the most frequent. Within the 5-HT3B receptor the 2/2 genotype in the CA repeat polymorphism was marginally more frequent than the 1/ 2 genotype in responders, whereas in non-responders the 1 / 2 genotype was clearly more common. However, more replication studies need to be conducted to confirm or deny these findings.

Table 24: shows a study that has investigated both the 178-C/T and 1596-A/G polymorphisms in the 5-HT3A receptor gene and its link to clozapine response

Author	Year	Polymorphism	Notes	N Responders	C/C	C/T	T/T	N Non-responders	C/C	C/T	T/T	Response	Result
Gutierrez	2002	178-C/T	266 patients, all British caucasians	119	71	42	6	72	47	23	2	20 point improvement in GAS after 3 months of treatment	NS
					A/A	A/G	G/G		A/A	A/G	G/G		
Gutierrez	2002	1596-A/G	266 patients , all British caucasians	159	93	57	9	89	49	36	4	20 point improvement in GAS after 3 months	NS

Table 25: shows a study that has investigated the CA repeat polymorphism in the 5-HT3B receptor gene and its link to clozapine response

Author	Year	Polymorphism	Notes	N Responders	2/2	1/2	1/1	N Non-responders	2/2	1/2	1/1	Response	Result
Gutierrez	2002	CA repeat	266 patients , all British caucasians	180	80	79	21	86	27	49	10	20 point improvement in GAS score after 3 months	NS

5.3.4 – Serotonin 5-HT5A

This receptor has gained attention in pharmacogenetic studies of clozapine response because it is thought that variations within this receptor may be linked to susceptibility to depression and other major psychoses (Birkett 2000).

However, as with the 5-HT3 receptor, only one study has been conducted on this subtype (Birkett et al 2000) (see table 26). This study enrolled 269 patients, all of whom were white Caucasians of British origin. Two polymorphisms have been found within this receptor ; -19 G/C and 12-A/T. Response was assessed retrospectively by the GAFS/GAS scales. The study had a power of 80%.

This study found that neither polymorphism was linked to clozapine response (see table 26). The G/C genotype in the –19G/C polymorphism was the most frequent among both responders and non-responders. In the 12A/T polymorphism the T/T genotype was the most common. Further studies need to be done on this and other lesser known receptors, such as 5-HT1 , 5-HT3 and 5-HT7.

Table 26: shows a study that has investigated both the 178-C/T and 1596-A/G polymorphisms in the 5-HT5A receptor gene and its link to clozapine response

Author	Year	Polymorphism	Notes	NResponders	G/G	G/C	C/C	N Non responders	G/G	G/C	C/C	Response	Result
Birkett	2000	(-) 19G/C	269 patients, all white Caucasians of British origin	176	67	93	16	90	28	49	13	GAFS independently assessed after 3 months .	NS
					A/A	A/T	T/T		A/A	A/T	T/T		
Birkett	2000	12A/T	269 patients , all white Caucasians of British origin	178	12	74	92	91	4	33	54	GAFS independently assessed after 3 months .	NS

5.3.5 – Serotonin 5-HT6

Due to the high affinity that clozapine has for this receptor, 5-HT6, has become an important receptor to examine further (Masellis 2001). These studies, examine the hypothesis that genetic variation within the 5-HT6 receptor may be linked to interindividual variability in response seen when taking clozapine.

As yet there have been only 2 published studies on this receptor (Masellis 2001) (Yu 1999).

Both these studies investigated the polymorphism C267T and its link to clozapine response. The study by Masellis and co-workers 2001 used the same patients sample that had been used in the earlier 1998 study. These being 185 patients, 144 Caucasians, 40 African-Americans and 1 Asian. While the study by Yu enrolled 99 patients all Chinese, these were the same patients, as used in the Lin 1999, which investigated polymorphisms in the 5-HT2A receptor .

Table 27: shows studies that have investigated the C267T polymorphism in the 5-HT6 receptor gene and its link to clozapine response

Author	Year	Polymorphism	Notes	N Responders	T/T	T/C	C/C	N Non-responders	T/T	T/C	C/C	Response	Result
Masellis	2001	C267T	185 patients , 144 caucasians, 40 African-American and 1 Asian	91	4	18	69	82	2	21	59	15-20% reduction in BPRS , or 1 category of CGI after 6 months treatment	NS
Yu	1999	C267T	99 patients, all Chinese	60	5	24	31	39	1	18	20	20 % reduction in BPRS score after 7 wks	S

These studies reported conflicting findings. Masellis and co-workers found no association between the C267T polymorphism and clozapine response whereas Yu and co-workers found an association. However both studies reported the C/C genotype to be the most common among both responders and non-responders. Various factors have been reported by the authors of these two studies to explain this discrepancy, such as methodological differences, however Masellis and co-workers, say this, would not have been significant. The power in the study by Masellis and co-workers was the same as in their previous studies (0.80). The power of the study was not given by the Yu and co-workers study. Another factor which could have influenced the eventual outcome is the ethnicity of the sample, for example the C267T polymorphism does not seem to alter the predicted amino acid sequence of the 5-HT6 receptor. However, an unidentified functional polymorphism of this receptor which changes response to clozapine to non-response, may be in linkage disequilibrium with this polymorphism. This theory can only explain findings in the sample population, of the Yu and co-workers study, but not in the Masellis and co-workers study. Also, the diversity in the ethnicities used in the study by Masellis and co-workers may have induced a type II error. The authors of this study tried to account for this by ensuring that the responder and non-responder groups were as similar as possible in terms of ethnicity. The two studies both used the BPRS to define response but the study by Masellis also used the CGI scale. Masellis and co-workers used this additional scale if the patient seemed to be clinically improved and also showed a $> 15\%$ but $< 20\%$ decrease in BPRS, and a reduction in at least one of the categories of the CGI scale.

As yet, the study by Yu and co-workers is the first study, to identify an association between the C267T polymorphism and clozapine response, further replication studies are needed to either confirm or deny, the findings reported by Yu and co-workers.

CHAPTER 6

Discussion

The treatment of schizophrenia has come a long way since before the advent of chlorpromazine (Wu 2005). Even after the introduction of chlorpromazine, significant breakthroughs have occurred, particularly in the form of the atypical antipsychotic drugs. The prototype of these drugs was Clozapine (Duggan 1999, Leucht 1999), it is still seen as the most effective of its category in that it can also be taken by treatment-resistant patients who do not benefit from other antipsychotic drugs. As well as being effective, it has a lower side-effect profile when compared to other antipsychotic drugs. Although the mechanism of action for atypical antispychotics has not been fully elucidated it is thought to involve antagonism of both the dopamine and serotonin receptors (Ichikawa 1999). Although, Clozapine is effective in treating 40-60% of treatment refractory patients, the remaining patients do not respond (Arranz 1995, Gutierrez 2002). This variability in response has prompted investigation into the predictors of response (Kerwin 2001).

There is some degree of variation in patients response with every drug. For example, some may not respond at all whereas others may have a total reduction in symptoms (Masellis 2001). There are a number of factors governing this variation, such as age, gender and genetics. The aspect of genetics that we will be looking at, is polymorphisms within the receptors. Recently published pharmacogenetic studies, have been focussing on the atypical prototype drug, clozapine. Our objective, is to investigate all the polymorphisms in all the receptor subtypes to establish if these polymorphisms are linked to the prediction of response to clozapine .

Pharmacogenetic research into complex traits such as antipsychotic drug response , has proven to be a difficult task (Kerwin 2001). The task becomes more complex when drug target sites are investigated for their influence in drug response . The majority of antipsychotic drugs have a multi-target profile and so a complex mode of action (Kerwin 2001). Individual genes have been reported to influence response, but as yet no single gene can account for the variability experienced by patients in terms of their response to the same drug (Kerwin 2001, Ozaki 2004). This study was focussed on the genetic aspect, to see if there is a link between polymorphisms within different receptor genes and response to Clozapine. Therefore response is the main outcome measure.

This study has mainly focussed upon Dopamine and Serotonin (5-HT) receptor subtypes. Trying to establish a link, between polymorphisms and response, has proven to be a difficult task, not only for the reason mention above, but also, because the pharmacology which links genotype to response, is unclear.

6.1 – D4

The general view regarding the Dopamine receptors, is that firstly, the D4 receptor was expected to be an ideal candidate for pharmacogenetic studies into clozapine response, due to the high affinity between this receptor and clozapine (Kohn 1997, Rietschel 1996) but this was not the case. The majority of the studies conducted to investigate this link found no association (Kohn 1997, Rietschel 1996, Shaikh 1993,1995 and Rao 1994). Only the study by Zhao and co-workers stated that the results of their study suggested that inherited variants of D4 may explain some of the interinidividual variability seen in patients taking Clozapine (Zhao 2005). One reason

for this could be confounding factors, for example ethnicity since all the studies used different sample populations, covering a wide geographical area. The study by Rietschel and co-workers seems to be the least homogenous as the other studies have far stricter inclusion criterias. For example, the studies by Kohn and co-workers and Zhao and co-workers stated they recruited Israeli Jews and Han Chinese patients respectively, they then further define their inclusion criteria by stating, they enrolled Israeli Jews, who had to be either Ashkenazi or Non-Ashkenazi (Kohn 1997), and Han Chinese patients but only those from the Hu Nan province (Zhao 2005). Whereas, the study by Rietschel and co-workers only set their inclusion criteria to subjects of German descent.

There are also significant methodological differences between the studies. This is particularly clear in the study by Kohn and co-workers, where the authors explain how subdividing their patients according to ethnicity and response, may have reduced the power of the study. Kohn and co-workers also mentioned differences in the rating scales used as a possible reason for some discrepancy between findings of studies. The study by Rietschel and co-workers, divided patients according to how they responded to treatment this is different to using the rating scales, with secondary designation into responders and non-responders. A reason for dividing according to efficacy was that this would enable smaller effects to be detected (Rietschel 1996). Another critical aspect of the classification of response is the time at which the decision is made on whether the patient is a responder or non-responder and the criteria used in doing so. The study by Zhao and co-workers found that there may be an association between the 48bp exon III polymorphism and clozapine response since, in this polymorphism, the frequencies of the 5 allele and the 5/5 genotype were

significantly higher among non-responders compared to responders (Zhao 2005). Further reasons for these findings are firstly, genetic variations in pharmacokinetics and pharmacodynamics may influence outcome of response (Ozaki 2004). For example, particularly in pharmacokinetics, an individuals ability to metabolise clozapine may affect the levels of the drug in the blood and its binding area .

6.2 – D2

This study has also examined current literature on the other dopamine receptors, D2 and D3. Although their affinities for clozapine were not as high as that of D4 (Van Tol 1991), other reasons implicated them as potential candidates. For example, D2 is responsible for all antipsychotic drug action (D2 antagonism is the mechanism of action for all antipsychotics) (Butcher 2000, Seeman 1992). Only two studies have looked at the relationship between polymorphisms in the D2 receptor and their link to predicting response to clozapine (Arranz 1998, Hwang 2005). Slightly differing views were reported. However, both studies found no association between the –141C Ins/Del polymorphism and clozapine response. The study by Hwang and co-workers which also used two population samples, found an association in one of the sample groups (Hwang 2005). This study (Hwang 2005) analysed twelve polymorphisms in the two sample populations and found associations between some of the polymorphisms and clozapine response, but only in the African-American sample group. Reasons for any discrepancy include, ethnic heterogeneity as different ethnic samples were recruited for investigation. Other factors such as sample size may also have had an impact. No power value was stated for the study by Arranz and co-workers, however the study by Hwang and co-workers had a power of 73%. There

may be a difference in power values as the sample sizes between the studies were very different, the two populations in the study by Arranz and co-workers were recruited in similar numbers while in the study by Hwang and co-workers there is a large difference between the numbers of Caucasians and African-Americans recruited.

6.3 – D3

The Ser9Gly polymorphism in the D3 receptor has been implicated in pharmacogenetic studies of clozapine response, because this polymorphism is said to be linked to dopamine binding (Lannfelt 1992, Lundstrom 1996). Confounding factors, were also important in studies of this receptor. False positives are always a reason for any possible discrepancy, but lack of studies make any identification of false positives / negatives, difficult. Findings of the studies, have again reported conflicting outcomes, with 2 studies finding no association between the Ser9Gly polymorphism and clozapine response (Malhotra 1998, Shaikh 1996) while one study reported opposing views (Scharfetter 1999). The study by Shaikh and co-workers found only weak evidence of non-responders having an increased frequency of the Ser9 allele when compared with responders (Shaikh 1996). The common reason of ethnic heterogeneity used to explain why an association was not found, was equally valid for these studies, as a diverse range of populations were investigated. This reason is only a variable and only may have contributed. However, the significant association found by Scharfetter and co-workers may also have been due to the fact the sample was Asian, rather than Caucasian, as like 'black' subjects (see D2-Hwang 2005), Asians tend to respond differently to antipsychotic drugs, for example, lower doses are required to achieve the same results (Lin & Finder 1983, Rosenblat & Tang

1987, Lin 1989). Contradictory findings have also been reported which state that in both populations (Asian and Caucasians) the optimal doses of the antispychotic drug used were comparable (Sramek 1986, Zhang-Wong 1998). So clearly Asian ethnicity may be a major factor that could explain the outcome of studies. Common factors, such as different rating scales, sample size, and duration of treatment were also mentioned by other studies looking to investigate the same link. Power of the studies, can also play an important role, in deciding whether to confirm or deny findings of previous studies. If the power of a study is low the genes of small effect will not be detected. The power of a study, is linked to sample size; the bigger the sample size the higher the power is likely to be. The standard power is usually set at 80%. This means that the study has enough power to detect the smallest effects, 80% of the time. The power in the study by Scharfetter and co-workers may have been impaired due to it being the smallest in terms of sample size, however no actual value for the power was stated. The study by Malhotra and co-workers stated they had an effect size of 0.01 which would require them to have more than a 1000 subjects to detect an association. So therefore, even the study by Shaikh and co-workers would fall short of the 1000 subjects needed for a statistically significant association. The study by Malhotra and co-workers had a power of 95% and the study by Shaikh and co-workers had a power of 93%. These values which are above the standard 80%, indicate that the studies nearly detected all the small effects all the time, so overlooking something is very unlikely.

Dopamine receptors should have made more of a significant impression on pharmacogenetic studies of response since, originally, interest was aroused in these receptors, by the 'Dopamine theory' (Davis 1991), whose findings state that

dopamine agonists, made symptoms worse, while antagonists, proved effective in treating positive symptoms (Bennett 1998, Davis 1991); this forms the basis of the mechanism of action, for all antipsychotic drugs.

6.4 – 5-HT2A

This study has shown that most clinical studies has focussed on the 5-HT2A receptor, as this receptor, is thought to be associated with hallucinations, produced by the 5-HT2A agonist LSD (Glennon 1984). Hallucinations are a key symptom of schizophrenia. Furthermore, the majority of the serotonin receptors have a high affinity for clozapine (Meltzer 1991, Meltzer 1999, Kapur 1996). This is the reason the other serotonin receptors were investigated. Most of the studies, involved the 5-HT2A receptor, several polymorphisms within this receptor were investigated for their link to clozapine response.

6.4.1 – T102C

For the T102C polymorphism, it was stated by Arranz and co-workers 1995, that the homozygous genotype C/C was more frequent in non-responders. However a further five studies have failed to replicate this finding (see table 19). In these five studies the T/C genotype was more common in non-responders. This genotype was also the most common amongst responders. It has been suggested that the T102C polymorphism, which is a silent mutation and therefore cannot undergo any changes in its sequence, may be in linkage disequilibrium with another polymorphism that is linked to clozapine response (Malhotra 1996). A study by Arranz and co-workers 1998 reported that the G-[1438]A polymorphism was in almost complete linkage disequilbrium with

the T102C polymorphism, therefore, since the T102C polymorphism is silent, the G-[1438]A polymorphism, is more likely to be associated with clozapine response. Therefore it is unlikely that the T102C polymorphism is linked to clozapine response. The failure to confirm findings of the study by Arranz and co-workers 1995 could be attributed to the samples, for example, the Arranz sample consists of Western European Caucasians whereas the sample used in the study by Masellis and co-workers is North American and Nothen and co-workers recruited patients of German descent. Another factor is the rating scales used as both Malhotra and co-workers and Masellis and co-workers used the BPRS to define response, this scale is more focussed on psychopathology, while Arranz and co-workers used the GAS, which is based more on social functioning and is indirectly linked to psychopathology. The study by Nothen and co-workers did not use a rating scale approach and decided to divide patients into groups according to their efficacy to treatment, although the groups did correspond to the GAS.

6.4.2 - G-[1438]A

Looking at the G-[1438]A polymorphism, only two studies focussed on this polymorphism, but reported opposing findings (Arranz 1998, Masellis 1998). Furthermore no genotype data is given in the study by Masellis and co-workers. Ethnic heterogeneity is not a significant factor in this case as the study by Arranz and co-workers recruited Caucasian subjects while the majority of the sample set employed by Masellis and co-workers is also Caucasian. It is difficult to say whether there is a definite association, however further studies could help to clarify this.

6.4.3 – His452Tyr

Slightly more studies looked at the next polymorphism, His452Tyr, but again mixed findings were reported. A common finding was that the Tyr452 allele is associated with poor response, and was significantly higher among non-responders (Arranz 1996, Arranz 1998). Also among both responders and non-responders, the His/His genotype was found by all the studies to be most frequent. Many factors could have caused these discrepancies in findings. The majority of studies have the same factors in common, such as ethnic heterogeneity, possible false positive / negative findings and these can only be resolved by replication studies. More weight can be given to the study by Arranz and co-workers 1998 as it uses 2 independent samples, a means of further confirmation of their findings, a control group was also recruited. Using different rating scales has also been implicated as a possible factor in explaining this discrepancy between positive and negative findings. Surrounding factors such as duration of treatment before patients are classified as responders / non-responders, have also been questioned (Masellis 1998).

6.5 – 5-HT2C

Slightly fewer studies were conducted on the Cys23Ser polymorphism in the 5-HT2C receptor and its link with clozapine response . Of the 4 published studies only one found a significant association (Sodhi 1995). Sodhi and co-workers 1995 suggested that the presence of at least one Ser23 variant would predict good response to clozapine. This would also indicate that since this receptor is located on the X chromosome, females would experience better response since they have two X

chromosomes. However, the other studies could not confirm this. Possible reasons to explain this discrepancy in findings between the four studies, include false positives, sample size, heterogeneity within the sample, or that they simply may have missed something. The study by Masellis and co-workers 1998, was the first to report differences between the Caucasian and African-American samples. Classification of response is also an important confounding factor which can be used to explain the discrepancy in findings. The classification of response amongst the studies was not the same, as was durations of treatment, doses used and different scales used to assess response. For example, 3 studies used established rating scales such as BPRS, CGI and GAS while the remaining study placed patients into groups according to efficacy of treatment (Rietschel 1997). The 3 studies that used rating scales dichotomised their patients into responders and non-responders. Therefore the method of assessing the symptoms can be seen as one variable, while the choice of dichotomisation can be a second variable. An important factor to take into consideration is the time factor, although patients may improve for several months, if a significant response is exhibited in the first week, this generally predicts a more favourable response. This impacts on when patients should be classified as responders / non-responders. Some patients may be classified as non-responders, but may respond after a longer period of time. Therefore, in future studies, there should be some standard duration of treatment after which classification as either responder / non-responder can take place. Far fewer studies, were done on the remaining receptors, therefore, further studies need to be conducted to reach any conclusive outcome.

6.6 – 5-HT3

The study by Gutierrez and co-workers 2002 (Gutierrez 2002) conducted to investigate the association between polymorphisms in the 5-HT3 receptor and clozapine response, found no links. This study found that polymorphisms present within other populations, were not found in the population which was recruited. This suggests that either these polymorphisms are only present in certain populations or that these polymorphisms are extremely rare. Which would suggest that there is a high likelihood that these receptors do not play a major role in response. However further studies are needed to confirm these findings, as this is the only study to have investigated this association.

6.7 – 5-HT5

A study by Birkett and co-workers 2000 to examine polymorphisms within the 5-HT5 receptor and its link to clozapine response found no association. A point to take into consideration is the sample size, which in this study was small, 75. An obvious explanation is false positives, due to multiple testing or population stratification. The two polymorphisms in this receptor were silent substitution mutations, and therefore may be in linkage disequlibrium with a functional variant that is still undetected. As with the 5-HT3 receptor further studies for this receptor are also needed.

6.8 – 5-HT6

Studies performed to investigate the link between the C267T polymorphism in the 5-HT6 receptor and clozapine response, have reported conflicting findings. The study by Yu and co-workers 1999, found that patients with the 267 T/T genotype were more likely to experience a better response. Whereas Masellis and co-workers 2001, did not find any association between the C267T polymorphism and clozapine response. Both studies reported that the C/C genotype was most common amongst both responders and non-responders. This discrepancy, between the findings of the two studies may be attributed to a number of factors, such as false positives from multiple testing. Also, since antispsychotic drugs have a multitarget profile any single gene may only play a minor role. A further reason why this receptor may not be involved in response is that since this polymorphism is a silent mutation it could be in linkage disequilibrium with a functional variant that affects clozapine binding. Furthermore methodological differences could also be blamed for this disagreement in reported findings. For example, Yu and co-workers used ANOVA to calculate differences in BPRS scores while Masellis and co-workers used non-parametric tests. Another factor which may contribute to explaining this discrepancy in findings, is that in the majority of studies there is ethnic heterogeneity between the samples. More attention will now be paid on the serotonin receptors as opposed to the dopamine receptors. This is for two reasons, firstly since atypical agents are becoming more common and secondly because their mechanism of action is linked to serotonin as well as dopamine (Ichikawa 1999).

The studies that have been published to date suggest that there may be polymorphisms which predict response to clozapine. However, although there are definite indications of possible associations it is important to be cautious because of the lack of primary

studies. Association studies of polymorphisms within both the dopamine and serotonin receptors have reported some possible associations with response, however there is a great deal of contradiction within these results.

6.9 – Other receptor systems

The adrenergic, glutamatergic and histaminergic receptors, are also possible candidates for an association, but as with some of the other receptors only one study has been done on polymorphisms in these receptors and response to clozapine, so this is an area for future work (Bolonna 2000, Mancama 2002, Hong 2001). Another approach would be to look at other antipsychotic drugs, namely chlorpromazine, haloperidol, olanzapine and risperidone to see if response to these drugs is linked to polymorphisms within the dopamine and serotonin systems. However, there were far fewer studies looking at these associations. The majority of studies have been on clozapine response. Since it is the archetypal atypical antipsychotic, but more importantly is the only drug that can help treatment resistant patients. If an association between genetic polymorphisms and clozapine response is identified, this link can be adapted to include response to any antipsychotic drug. Variation in response to antipsychotic drugs, cannot solely be attributed to genetic aspects. Psychosocial / Environmental factors are also important in contributing to the eventual observed differences. These factors include smoking through pregnancy and obstetric complications (Mueser 2004) (see page 22).

The contribution of the present study is that it has brought together all the work that has been done on the area of looking at genetic polymorphisms and their link to clozapine response. It provides a comprehensive, concise and systematic review of

relevant published trials. So informed decisions can be made as all the information is present.

Although, all the findings that have been reported are important and crucial in furthering our understanding of pharmacogenetics, none of them can fully explain the heterogeneity in response that is observed with antipsychotic drug treatment. Therefore, future work which can be conducted in this area includes, replication studies this is particularly important for the lesser examined receptors such as 5-HT3, 5-HT5 and 5-HT6, as well as D2. For these receptors, there are only one or two studies and therefore further studies need to be undertaken to confirm or deny the findings of the studies that have already been done. However, replication studies are also needed for the more investigated receptors, as in the current studies, there are many conflicting findings. Furthermore, due to the lack of studies, conducting a meta-analysis was not appropriate.

6.10 – Limitations

Important limitations that may impact the outcome of a trial are discussed in more detail below. Ethnicity of the sample can greatly affect the outcome of a trial, especially if there is heterogeneity between studies. Therefore this area should be investigated further to examine if a link between ethnicity, polymorphisms and response is present. Differences in response amongst the various ethnic groups has been observed since the 1950s. However, this variability has been poorly understood in the past, therefore similar doses of medication were being prescribed for all ethnic groups regardless of their ethnicity. The fact that different populations, react

differently to the same drug, is already known for example Asians need lower doses to achieve the same effect as their Caucasian counterparts, while Negroid patients need higher doses (see p108). This should be explored further so patients from different ethnicities or countries can receive individualised treatment based on their ethnicity, as well as their genotype.

Other factors which may influence response and so should be examined are age, dose and gender. Age may be seen as a predictor (Balant-Gorgia 1993), since children and the elderly especially may be particularly sensitive to drugs. This sensitivity may influence the rate of pharmacokinetic activities such as drug absorption, distribution, metabolism and excretion. For example, in elderly patients the function of organs involved in drug absorption and elimination are commonly reduced. Furthermore, with elderly patients there is a higher likelihood of them suffering from multiple illnesses and therefore would be taking several concurrent medications that are likely to interact with each other. This may go some way in explaining the increased rate and severity of adverse effects, reported in this age group. At the other end of the scale, in newborn babies particularly those who are premature the majority of the enzymes responsible for normal metabolic functions are not yet fully developed. These factors account for pharmacokinetic differences, which may contribute to the variability in drug response.

Dose is another factor, which could explain variability in response (Young 1980). However there is a great deal of variability in the studies. Different doses are effective in different patients, this is a generally accepted fact. Low doses work in some patients, while much higher doses work in others. The question of dose may also be

linked to ethnicity. The dose factor, may also be potential predictor but is a far broader area of research.

Gender does not seem to be a major factor in the prediction of response (Masellis 2000). Differences in pharmacokinetics may be down to factors, such as body composition, hormonal status and weight. General differences between the genders have been reported, such as women need lower doses to achieve the same response as men. But in terms of predicting response, gender does not seem to a significant factor.

These factors are very much linked to the next point, population stratification is a key limitation in pharmacogenetic studies . Researchers should try to reduce any confounding effects by taking into account the effect of gender and ethnicity. Therefore, it is recommended that future studies recruit patients from homogenous isolated populations.

Another important issue, which needs to be resolved before any progress can be made, is the definition of response. Studies investigating the same polymorphism are using different rating scales. All definitions of response are based on semi-qualitative scales. Furthermore there is no clinically measurable marker that provides scale data, this is comparable for example with BP (blood pressure) or blood glucose. With variability in samples for example age and ethnicity it is hard to know what to 'standardise' therefore studies are heterogeneous. So the definition of response, should be set beforehand with the studies using the same scale. A point mentioned earlier about the duration of treatment before a patient can be classified as a responder or non-responder also needs to addressed, as at the moment there is no

standard length of time before this can occur. Any classification of response that is done could impact on the trial design, if this is improved better results may be provided.

Methods used to identify genes for schizophrenia can be roughly separated into 2 groups, parametric and non-parametric methods. Parametric methods are ideal for finding genes of major effect therefore a downfall of this approach is that they cannot detect genes of small effect, a key feature of complex traits such as drug response. Non-parametric methods, also known as model-free analysis, are mainly used for linkage analysis where affected siblings pairs are recruited. An obvious downside of this method is the substantial number of sibling pairs needed. However, in terms of response, studies have stated that using non-parametric statistics is not advised and it would be better to use mean changes in the clinical score over time, in an analysis of variance with genotype being the grouping factor. Using molecular genetic associations as an approach to pharmacogenetics, may allow for the analysis of several candidates genes spanning various biological systems. Each contributing a small amount to the total variance observed in clozapine response.

It is hoped that as well as focussing studies on clozapine response, other studies will be done , that look at other antipsychotic drugs. There is hope that the 'psychopharmacogenetics' field which looks at pharmacogenetics in the psychiatric field, will progress to 'psychopharmacogenomics', which looks at genetic determinants of drug response at the level of the entire human genome. When the high density mapping of the whole genome is complete it will be possible to identify drug response markers by scanning the full genome looking for particular polymorphisms.

By widening the search for polymorphisms that predict drug response, pharmacogenomics will slowly overtake pharmacogenetics which uses the candidate gene approach, pharmacogenomics, will use genome-wide scanning using linkage disequilibrium that can identify genes even if their mechanisms of action are unknown.

Despite looking at both pharmacogenetics and pharmacogenomics the overall message remains the same. It is hoped that pharmacogenetics / pharmacogenomics may in the not too distant future, lead to individualised pharmacotherapy for patients. This individualised treatment will be based on the genetic, demographic and environmental characteristic of each patient. With the overall aim being to reduce the risk of adverse effects and relapse but increase efficacy, so patients get the most benefit from the treatment. This will avoid patients taking unnecessary drugs, that may not work and may consequently induce needless side-effects. The trial and error approach, currently used (Basile 2001), will hopefully be replaced by this new method. Added advantages of this approach, include reduced hospitalisation costs incurred by side-effects brought about by possibly taking the wrong drug or the wrong dose of drug, this would not happen with genotype testing, as the patient would receive the drug, most suited to their genotype (Kerwin 2001). For example, the area of investigation in the present study is looking to see if by having a particular polymorphism does this predict, that the patient will have a better or worse response. Another advantage is reduced drug costs, as with patients getting drugs according to their genotype they will hopefully get the right drug the first time instead of changing medication several times, trying to establish which drug suits them the best. From the findings of published studies, the original rationale and objective has been satisfied. However, no firm conclusions could be reached due to the conflicting results reported

but there are strong indications of several possible associations. Studies so far are not sufficiently discriminating to give definite results. There may be no single genetic link, due to the multitarget profile and complex mechanism of action of antipsychotic drugs, which suggest that more than one gene is involved. So a change in one receptor may not produce on overall measurable change. The answer to interindividual variability may lie in multigene interactions.

CHAPTER 7

Conclusion

The aim of this study was to establish whether there was any link between polymorphisms in receptor subtypes and clozapine response. As mentioned previously, no firm conclusions could be reached but there are several indications of potential associations such as the His452Tyr polymorphism in the 5-HT2A receptor and clozapine response. As well as possible positive associations like the one mentioned above, various associations ruling out any link between polymorphisms and response were also identified. These include the majority of studies looking at polymorphisms within the D4 receptor and clozapine response but also the T102C polymorphism in the 5-HT2A receptor and clozapine response, in both sets of studies the majority showed there was no link to clozapine response.

The reasons for this include insufficient sample size, ethnic heterogeneity and heterogeneity in pharmacological response. A common opinion, among the majority of studies is that more replication studies are needed, as is standardising classification of response.

It was expected that the Dopamine receptors, would have made more of an impact on drug response, based on evidence of their link to the mechanism of action of antipsychotic drugs . The results of studies have found conflicting findings. So no definite associations can be reported.

The situation is similar for the serotonin receptors, although the 5-HT2A receptor has attracted more interest. These receptors, were implicated in pharmacogenetic

studies of clozapine, due to the high affinity clozapine has for these receptors, 5-HT2A also has been linked to the pathophysiology of hallucinations making it even more worthwhile to investigate.

Although in its initial stages, pharmacogenetic studies of interindividual variability in response may lead to significant advancements in the treatment of schizophrenia. Furthermore, an understanding of the relationship between genetic variation and drug response may hopefully lead to individualised pharmacotherapy for patients.

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Shaikh S., Collier D.A. Analysis of clozapine response and polymorphisms of the dopamine D4 receptor gene (DRD4) in schizophrenic patients. Am J Med Genet. 1995; 60: 541–545.

Shaikh S., Collier D.A. Dopamine D4 subtypes and response to clozapine. Lancet. 1993; 341: 116.

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Young M.A. The relationship of demographic, clinical and outcome variables to neuroleptic treatment requirements. Schizophr Bull. 1980; 6: 88-101.

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Zhang-Wong J. An investigation of ethnic and gender differences in the pharmacodynamics of haloperdiol. Psychiatry Research. 1998; 81: 333–9.

Zhao A.L., Zhao J.P. Dopamine D4 receptor gene exon III polymorphism and interindividual variation in response to clozapine. Internal J Neurosci . 2005; 115: 1539– 1547.

Appendix A

Here are tables of the other neurotransmitters that were not included in the main thesis, namely Adrenaline, Glutamate and Histamine. Muscarine was mentioned in the thesis but no relevant studies were found. One study was retrieved for the association between polymorphisms in the Histamine receptors and clozapine response, however this study did not contain any data (see p186).

Table 28: shows studies that have investigated polymorphisms in the Adrenergic receptors and their link to clozapine response

Author	Year	Receptor	Polymorphism	Notes	No of patients	No of controls	DSM	Ethnicity	Type of schizophrenia	Defn of response	Responder - Genotypes			Non-responder genotypes			Result
											Arg / Arg	Arg / Cys	Cys / Cys	Arg / Arg	Arg / Cys	Cys / Cys	
Bolonna	2000	Alpha 1a adrenoceptor	Arg492Cys		289	122	DSM-IIIR or IV	Caucasians of British origin	Treatment-refractory	20 point improvement in GAS score	29	91	67	20	52	24	No association
											C / C	C / G	G / G	C / C	C / G	G / G	
		Alpha 2a adrenoceptor	(-) 1291-C/G		289	122	DSM-IIIR or IV	Caucasians of British origin	Treatment-refractory	20 point improvement in GAS score	89	67	12	49	31	6	No association
											G / G	G / A	A / A	G / G	G / A	A / A	
			(-) 261-G/A		289	122	DSM-IIIR or IV	Caucasians of British origin	Treatment-refractory	20 point improvement in GAS score	147	42	4	81	15	0	No association
Tsai	2001	Alpha 2a adrenoceptor	(-) 1291-C/G	Excluded , as data not in a format suitable for our work													

Table 29: shows a study that has investigated polymorphisms in the Glutamate receptor and its link to clozapine response

										Genotypes - Responders			Genotype - Nonresponders			
Author	Year	Receptor	Polymorphism	Aim of study	No of patients	DSM	Ethnicity	Type of schizophrenia	Defn of response	2664 C/C (n = 25)	2664 C/T (n = 49)	2664 T/T (n = 26)	2664 C/C (n = 25)	2664 C/T (n = 49)	2664 T/T (n = 26)	Result
Hong	2001	Glutamate	C2664 T (polymorphism in the NMDA 2B subunit of the glutamate receptor) .	To examine the relationship of the GRIN 2B C2664T polymorphism and clozapine response , psychiatric symptoms also analysed .	100	DSM-IV	Chinese	Treatment-refractory	1. > 20% reduction in total BPRS score after 8 wks treatment . 2. Percentage of BPRS score reduction [(visit - baseline) x 100 / baseline] .	14	34	12	11	15	14	No link between clozapine response and polymorphisms in Glutamate system .

This is the first study , looking at polymorphisms in the glutamate system . Responders were converted to actual no. , non-responders , were worked out by (total - responders) .

Table 30: shows studies that have investigated polymorphisms in the Histamine receptors and its link to Clozapine response

Author	Year	Receptor	Polymorphism	Aim of study	No of patients	DSM	Ethnicity	Type of schizophrenia	Defn of response	Genotypes - Responders	Genotype - Nonresponders	Result
Mancama	2002	Histamine		To describe the systematic screening	158	DSM-III-R		Treatment-refractory or	Assessed retrospectively ,	NO DATA	NO DATA	A potential association of the
				for novel polymorphisms of putative				intolerant to typicals .	20 point improvement in			H2 receptor polymorphisms , and
		H1	(-) 17-C/T	promoter sequences encoding the H1					GAS scale , after > 3 months			clozapine treatment response
			(-) 974-C/A	and H2 receptors , which we					of treatment with clozapine .			was identified .
			(-) 1023-A/G	subsequently investigated for								
			(-) 1536-G/C	involvement in schizophrenia and								
				clozapine drug response .								
		H2	(-) 294-A/G									
			(-) 592-A/G									
			(-) 1018-G/A									
			(-) 1077-G/A									

Appendix B

Given below are lists of the studies that were identified by the database searches for each receptor subtype. A list of those studies that were excluded is also given for each subtype as is their reason for exclusion.

D2

List of the studies identified by initial search: (n=24)

Arranz M.J., Li T., Munro J. Lack of association between a polymorphism in the promoter region of the dopamine-2 receptor gene and clozapine response. Pharmacogenetics. 1998; 8: 481-484.

Bullock C.M., Li C. Sensitisation of adenylate cyclase induced by a dopamine D2 receptor mutant: inverse agonism by D2 receptor antagonist. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2001; 25: 1387-1402.

Cohen B.M., Ennulat D.J., Centorrino F. Polymorphisms of the dopamine D4 receptor response to antispychotic drugs. Psychopharmacology (Berl). 1999; 141: 6-10.

Hwang R., Shinkai T., Deluca V. Dopamine D2 receptor gene variants and quantitative measures of positive and negative symptom response following clozapine treatment. Eur Neuropsychopharmacol. 2005;16: 248-259

Hwang R., Shinkai T., Deluca V. Association study of 12 polymorphisms spanning the dopamine D(2) receptor gene and clozapine treatment response in two treatment refractory/intolerant populations. Psychopharmacology (Berl). 2005; 181: 179-187.

Kaiser R., Konneker M., Henneken M. Dopamine D4 receptor 48-bp repeat polymorphism: no association with response to antipsychotic treatment, but association with catatonic schizophrenia. Mol Psychiatry. 2000; 5: 418-424.

Kerwin R., Collier D., Shaikh S. Pharmacological Genetic Association Studies and clozapine response. Eur Neuropsychopharmacology. 1996; 6: 25

Kohn Y., Ebstein R.P., Heresco-Levy U. Dopamine D4 receptor gene polymorphisms: relation to ethnicity, no association with schizophrenia and response to clozapine in Israeli subjects. Eur Neuropsychopharmacol. 1997; 7: 39-43.

Malhotra A.K. Candidate gene studies of antipsychotic drug efficacy and drug-induced weight gain. Neurotox Res. 2004; 6: 51-56.

Malhotra A.K., Goldman D., Buchanan R.W. The dopamine D3 receptor (DRD3) Ser9Gly polymorphism and schizophrenia: a haplotype relative risk study and association with clozapine response. Mol Psychiatry. 1998; 3: 72-75

Pauwels P.J., Tardif S., Wurch T. Real-time analysis of dopamine: antagonist interactions at recombinant human D2long receptor upon modulation of its activaion state. Br J Pharmacol. 2001; 134: 88-97.

Rao P.A., Pickar D., Gejman P.V. Allelic variation in the D4 dopamine receptor (DRD4) gene does not predict response to clozapine. Arch Gen Psychiatry. 1994; 51: 912-917

Reynolds G.P. Neurotransmitter receptors, genes and schizophrenia. Eur Neuropsychopharmacolgy. 1996; 6: S4.

Rietschel M., Naber D., Oberlander H. Efficacy and side-effects of clozapine: testing for association with allelic variation in the dopamine D4 receptor gene. Neuropsychopharmacolgy. 1996; 15: 491-496.

Sanyal S., Van Tol H.H. Review the role of dopamine D4 receptors in schizophrenia and antipsychotic action. J Psychiatr Res. 1997; 31: 219-232.

Scharfetter J., Chaudhry H.R., Hornik K. Dopamine D3 receptor gene polymorphism and response to clozapine in schizophrenic Pakistani patients. Eur Neuropsychopharmacol. 1999; 10: 17-20.

Shaikh S., Collier D.A., Sham P.C. Allelic association between a Ser-9-Gly polymorphism in the dopamine D3 receptor gene and schizophrenia. Hum Genet. 1996; 97: 714-719.

Shaikh S., Collier D.A., Sham P.C. Analysis of clozapine response and polymorphisms of the dopamine D4 receptor gene (DRD4) in schizophrenic patients. Am J Med Genet. 1995; 60: 541-545.

Shaikh S., Collier D., Kerwin R.W. Dopamine D4 receptor subtypes and response to clozapine. Lancet. 1993; 341: 116

Sundram S., Joyce P.R., Kennedy M.A. Schizophrenia and bipolar affective disorder: perspectives for the development of therapeutics. Curr Mol Med. 2003; 3: 393-407

Szekeres G., Keri S., Juhasz A. Role of dopamine D3 receptor (DRD3) and dopamine transporter (DAT) polymorphism in cognitive dysfunctions and therapeutic response to atypical antipsychotics in patients with schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2004; 124: 1-5.

Wiffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

Wilson J., Lin H., Fu D. Mechanisms of inverse agonism of antipsychotic drugs at the D(2) dopamine receptor: use of a mutant D(2) dopamine receptor that adopts the activated conformation. J Neurochem. 2001; 77: 493-504.

Wurch T., Boutet-Robinet E.A., Pauwels P. Inverse agonism at dopamine D2 receptors: a receptor recalcitrant to high levels of constitutive activation. International Congress Series. 2003; 1249: 163-183

Papers excluded on basis of title: (n=22)

Bullock C.M., Li C. Sensitisation of adenylate cyclase induced by a dopamine D2 receptor mutant: inverse agonism by D2 receptor antagonist. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2001; 25: 1387-1402.

Cohen B.M., Ennulat D.J., Centorrino F. Polymorphisms of the dopamine D4 receptor response to antispychotic drugs. Psychopharmacology (Berl). 1999; 141: 6-10.

Hwang R., Shinkai T., Deluca V. Dopamine D2 receptor gene variants and quantitative measures of positive and negative symptom response following clozapine treatment. Eur Neuropsychopharmacol. 2005;16: 248-259

Kaiser R., Konneker M., Henneken M. Dopamine D4 receptor 48-bp repeat polymorphism: no association with response to antipsychotic treatment, but association with catatonic schizophrenia. Mol Psychiatry. 2000; 5: 418-424.

Kerwin R., Collier D., Shaikh S. Pharmacological Genetic Association Studies and clozapine response. Eur Neuropsychopharmacology. 1996; 6: 25

Kohn Y., Ebstein R.P., Heresco-Levy U. Dopamine D4 receptor gene polymorphisms: relation to ethnicity, no association with schizophrenia and response to clozapine in Israeli subjects. Eur Neuropsychopharmacol. 1997; 7: 39-43.

Malhotra A.K. Candidate gene studies of antipsychotic drug efficacy and drug-induced weight gain. Neurotox Res. 2004; 6: 51-56.

Malhotra A.K., Goldman D., Buchanan R.W. The dopamine D3 receptor (DRD3) Ser9Gly polymorphism and schizophrenia: a haplotype relative risk study and association with clozapine response. Mol Psychiatry. 1998; 3: 72-75

Pauwels P.J., Tardif S., Wurch T. Real-time analysis of dopamine: antagonist interactions at recombinant human D2long receptor upon modulation of its activaion state. Br J Pharmacol. 2001; 134: 88-97.

Rao P.A., Pickar D., Gejman P.V. Allelic variation in the D4 dopamine receptor (DRD4) gene does not predict response to clozapine. Arch Gen Psychiatry. 1994; 51: 912-917

Reynolds G.P. Neurotransmitter receptors, genes and schizophrenia. Eur Neuropsychopharmacolgy. 1996; 6: S4.

Rietschel M., Naber D., Oberlander H. Efficacy and side-effects of clozapine: testing for association with allelic variation in the dopamine D4 receptor gene. Neuropsychopharmacolgy. 1996; 15: 491-496.

Sanyal S., Van Tol H.H. Review the role of dopamine D4 receptors in schizophrenia and antipsychotic action. J Psychiatr Res. 1997; 31: 219-232.

Scharfetter J., Chaudhry H.R., Hornik K. Dopamine D3 receptor gene polymorphism and response to clozapine in schizophrenic Pakistani patients. Eur Neuropsychopharmacol. 1999; 10: 17-20.

Shaikh S., Collier D.A., Sham P.C. Allelic association between a Ser-9-Gly polymorphism in the dopamine D3 receptor gene and schizophrenia. Hum Genet. 1996; 97: 714-719.

Shaikh S., Collier D.A., Sham P.C. Analysis of clozapine response and polymorphisms of the dopamine D4 receptor gene (DRD4) in schizophrenic patients. Am J Med Genet. 1995; 60: 541-545.

Shaikh S., Collier D., Kerwin R.W. Dopamine D4 receptor subtypes and response to clozapine. Lancet. 1993; 341: 116

Sundram S., Joyce P.R., Kennedy M.A. Schizophrenia and bipolar affective disorder: perspectives for the development of therapeutics. Curr Mol Med. 2003; 3: 393-407

Szekeres G., Keri S., Juhasz A. Role of dopamine D3 receptor (DRD3) and dopamine transporter (DAT) polymorphism in cognitive dysfunctions and therapeutic response to atypical antipsychotics in patients with schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2004; 124: 1-5.

Wiffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

Wilson J., Lin H., Fu D. Mechanisms of inverse agonism of antipsychotic drugs at the D(2) dopamine receptor: use of a mutant D(2) dopamine receptor that adopts the activated conformation. J Neurochem. 2001; 77: 493-504.

Wurch T., Boutet-Robinet E.A., Pauwels P. Inverse agonism at dopamine D2 receptors: a receptor recalcitrant to high levels of constitutive activation. International Congress Series. 2003; 1249: 163-183

Studies included in analysis: (n=2)

Arranz M.J., Li T., Munro J. Lack of association between a polymorphism in the promoter region of the dopamine-2 receptor gene and clozapine response. Pharmacogenetics. 1998; 8: 481-484.

Hwang R., Shinkai T., Deluca V. Association study of 12 polymorphisms spanning the dopamine D(2) receptor gene and clozapine treatment response in two treatment refractory/intolerant populations. Psychopharmacology (Berl). 2005; 181: 179-187.

D3

List of the studies identified by initial search: (n=11)

Kaiser R., Konneker M., Henneken M. Dopamine D4 receptor 48-bp repeat polymorphism: no association with response to antipsychotic treatment, but association with catatonic schizophrenia. Mol Psychiatry. 2000; 5: 418-424.

Kerwin R., Collier D., Shaikh S. Pharmacological Genetic Association Studies and clozapine response. Eur Neuropsychopharmacology. 1996; 6: 25

Malhotra A.K., Goldman D., Buchanan R.W. The dopamine D3 receptor (DRD3) Ser9Gly polymorphism and schizophrenia: a haplotype relative risk study and association with clozapine response. Mol Psychiatry. 1998; 3: 72-75

Pickar D., Goldman D. Predicting clozapine response: systematic evaluation of allelic variation in candidate genes. Schizophrenia Research. 1997; 24: 216

Potkin S.G., Basile V.S., Jin Y. D1 receptor alleles predict PET metabolic correlates of clinical response to clozapine. Mol Psychiatry. 2003; 8: 109-113

Reynolds G.P. Neurotransmitter receptors, genes and schizophrenia. Eur Neuropsychopharmacolgy. 1996; 6: S4.

Sanyal S., Van Tol H.H. Review the role of dopamine D4 receptors in schizophrenia and antipsychotic action. J Psychiatr Res. 1997; 31: 219-232.

Scharfetter J., Chaudhry H.R., Hornik K. Dopamine D3 receptor gene polymorphism and response to clozapine in schizophrenic Pakistani patients. Eur Neuropsychopharmacol. 1999; 10: 17-20.

Shaikh S., Collier D.A., Sham P.C. Allelic association between a Ser-9-Gly polymorphism in the dopamine D3 receptor gene and schizophrenia. Hum Genet. 1996; 97: 714-719.

Szekeres G., Keri S., Juhasz A. Role of dopamine D3 receptor (DRD3) and dopamine transporter (DAT) polymorphism in cognitive dysfunctions and therapeutic response to atypical antipsychotics in patients with schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2004; 124: 1-5.

Wiffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

Papers excluded on basis of title: (n=5)

Kaiser R., Konneker M., Henneken M. Dopamine D4 receptor 48-bp repeat polymorphism: no association with response to antipsychotic treatment, but association with catatonic schizophrenia. Mol Psychiatry. 2000; 5: 418-424.

Potkin S.G., Basile V.S., Jin Y. D1 receptor alleles predict PET metabolic correlates of clinical response to clozapine. Mol Psychiatry. 2003; 8: 109-113

Reynolds G.P. Neurotransmitter receptors, genes and schizophrenia. Eur Neuropsychopharmacolgy. 1996; 6: S4.

Sanyal S., Van Tol H.H. Review the role of dopamine D4 receptors in schizophrenia and antipsychotic action. J Psychiatr Res. 1997; 31: 219-232.

Wiffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

Papers excluded for not fulfilling inclusion criteria: (n=3)

Kerwin R., Collier D., Shaikh S. Pharmacological Genetic Association Studies and clozapine response. Eur Neuropsychopharmacology. 1996; 6: 25

Pickar D., Goldman D. Predicting clozapine response: systematic evaluation of allelic variation in candidate genes. Schizophrenia Research. 1997; 24: 216

Szekeres G., Keri S., Juhasz A. Role of dopamine D3 receptor (DRD3) and dopamine transporter (DAT) polymorphism in cognitive dysfunctions and therapeutic response to atypical antipsychotics in patients with schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2004; 124: 1-5.

Studies included in analysis: (n=3)

Malhotra A.K., Goldman D., Buchanan R.W. The dopamine D3 receptor (DRD3) Ser9Gly polymorphism and schizophrenia: a haplotype relative risk study and association with clozapine response. Mol Psychiatry. 1998; 3: 72-75

Scharfetter J., Chaudhry H.R., Hornik K. Dopamine D3 receptor gene polymorphism and response to clozapine in schizophrenic Pakistani patients. Eur Neuropsychopharmacol. 1999; 10: 17-20.

Shaikh S., Collier D.A., Sham P.C. Allelic association between a Ser-9-Gly polymorphism in the dopamine D3 receptor gene and schizophrenia. Hum Genet. 1996; 97: 714-719.

D4

List of the studies identified by initial search: (n=16)

Cohen B.M., Ennulat D.J., Centorrino F. Polymorphisms of the dopamine D4 receptor response to antispychotic drugs. Psychopharmacology (Berl). 1999; 141: 6-10.

Kaiser R., Konneker M., Henneken M. Dopamine D4 receptor 48-bp repeat polymorphism: no association with response to antipsychotic treatment, but association with catatonic schizophrenia. Mol Psychiatry. 2000; 5: 418-424.

Kennedy J.L., Badri F., Masellis M. Genetic studies of dopamine and serotonin system genes in clinical response to clozapine. Eur Neuropsychopharmacology. 1996; 6: 162.

Kohn Y., Ebstein R.P., Heresco-Levy U. Dopamine D4 receptor gene polymorphisms: relation to ethnicity, no association with schizophrenia and response to clozapine in Israeli subjects. Eur Neuropsychopharmacol. 1997; 7: 39-43.

Nothen M.M., Rietschel M. Molecular genetic studies of variation in dopamine and serotonin receptor genes. Eur Neuropsychopharmacology. 1996; 6: 162

Pickar D., Goldman D. Predicting clozapine response: systematic evaluation of allelic variation in candidate genes. Schizophrenia Research. 1997; 24: 216

Rao P.A., Pickar D., Gejman P.V. Allelic variation in the D4 dopamine receptor (DRD4) gene does not predict response to clozapine. Arch Gen Psychiatry. 1994; 51: 912-917

Reynolds G.P. Neurotransmitter receptors, genes and schizophrenia. Eur Neuropsychopharmacolgy. 1996; 6: S4.

Ricketts M.H. Genetic variants and treatment response in depression and schizophrenia. Biological Psychiatry. 1996; 39: 540

Rietschel M., Naber D., Oberlander H. Efficacy and side-effects of clozapine: testing for association with allelic variation in the dopamine D4 receptor gene. Neuropsychopharmacolgy. 1996; 15: 491-496.

Sanyal S., Van Tol H.H. Review the role of dopamine D4 receptors in schizophrenia and antipsychotic action. J Psychiatr Res. 1997; 31: 219-232.

Segman R., Ebstein R., Katz M. Pharmacogenetic factors in schizophrenia: treatment response and adverse effects. Eur Neuropsychopharmacology. 1996; 6: 162

Shaikh S., Collier D.A., Sham P.C. Analysis of clozapine response and polymorphisms of the dopamine D4 receptor gene (DRD4) in schizophrenic patients. Am J Med Genet. 1995; 60: 541-545.

Shaikh S., Collier D., Kerwin R.W. Dopamine D4 receptor subtypes and response to clozapine. Lancet. 1993; 341: 116

Wiffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

Zhao A.L., Zhao J.P., Zhang Y.H. Dopamine D4 receptor gene exon III polymorphism and interinidividual variation in response to clozapine. Int J Neurosci. 2005; 115: 1539-1547.

Papers excluded on basis of title: (n=1)

Wiffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

Papers excluded for not fulfilling inclusion criteria: (n=8)

Cohen B.M., Ennulat D.J., Centorrino F. Polymorphisms of the dopamine D4 receptor response to antispychotic drugs. Psychopharmacology (Berl). 1999; 141: 6-10.

Kaiser R., Konneker M., Henneken M. Dopamine D4 receptor 48-bp repeat polymorphism: no association with response to antipsychotic treatment, but association with catatonic schizophrenia. Mol Psychiatry. 2000; 5: 418-424.

Kennedy J.L., Badri F., Masellis M. Genetic studies of dopamine and serotonin system genes in clinical response to clozapine. Eur Neuropsychopharmacology. 1996; 6: 162.

Nothen M.M., Rietschel M. Molecular genetic studies of variation in dopamine and serotonin receptor genes. Eur Neuropsychopharmacology. 1996; 6: 162

Reynolds G.P. Neurotransmitter receptors, genes and schizophrenia. Eur Neuropsychopharmacolgy. 1996; 6: S4.

Ricketts M.H. Genetic variants and treatment response in depression and schizophrenia. Biological Psychiatry. 1996; 39: 540

Sanyal S., Van Tol H.H. Review the role of dopamine D4 receptors in schizophrenia and antipsychotic action. J Psychiatr Res. 1997; 31: 219-232.

Segman R., Ebstein R., Katz M. Pharmacogenetic factors in schizophrenia: treatment response and adverse effects. Eur Neuropsychopharmacology. 1996; 6: 162

Papers excluded as data was not suitable for analysis: (n=4)

Pickar D., Goldman D. Predicting clozapine response: systematic evaluation of allelic variation in candidate genes. Schizophrenia Research. 1997; 24: 216

Rao P.A., Pickar D., Gejman P.V. Allelic variation in the D4 dopamine receptor (DRD4) gene does not predict response to clozapine. Arch Gen Psychiatry. 1994; 51: 912-917

Shaikh S., Collier D.A., Sham P.C. Analysis of clozapine response and polymorphisms of the dopamine D4 receptor gene (DRD4) in schizophrenic patients. Am J Med Genet. 1995; 60: 541-545.

Shaikh S., Collier D., Kerwin R.W. Dopamine D4 receptor subtypes and response to clozapine. Lancet. 1993; 341: 116

Papers included in analysis: (n=3)

Kohn Y., Ebstein R.P., Heresco-Levy U. Dopamine D4 receptor gene polymorphisms: relation to ethnicity, no association with schizophrenia and response to clozapine in Israeli subjects. Eur Neuropsychopharmacol. 1997; 7: 39-43.

Rietschel M., Naber D., Oberlander H. Efficacy and side-effects of clozapine: testing for association with allelic variation in the dopamine D4 receptor gene. Neuropsychopharmacolgy. 1996; 15: 491-496.

Zhao A.L., Zhao J.P., Zhang Y.H. Dopamine D4 receptor gene exon III polymorphism and interinidividual variation in response to clozapine. Int J Neurosci. 2005; 115: 1539-1547.

5-HT2A

List of the studies identified by initial search: (n=29)

Arranz M.J., Munro J., Owen M.J. Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. Mol Psychiatry. 1998; 3: 61-66

Arranz M.J., Munro J., Sham P. Meta-analysis of studies on genetic variation in the 5-HT2A receptors and clozapine response. Schizophrenia Research. 1998; 32: 93-99.

Arranz M.J., Munro J., Collier D.A. Further evidence for association between polymorphisms in the 5-HT2A receptor gene and clozapine response. Schizophrenia Research. 1998; 29: 127

Arranz M.J., Munro J., Sham P. Polymorphisms in the 5-HT2A receptor gene and promoter region associated with clozapine response. Schizophrenia Research. 1997; 24: 90

Arranz M.J., Collier D.A., Munro J. Analysis of a structural polymorphism in the 5-HT2A receptor and clinical response to clozapine. Neurosci Lett. 1996; 217: 177-178

Arranz M.J., Collier D.A., Sodhi M. Association between clozapine response and allelic variation in the 5-HT2A receptor gene. Lancet. 1995; 346: 281-282.

Aschauer H.N., Scharfetter J., Fuchs K. Dopamine and serotonin receptor genotypes and therapeutic response to neuroleptics in schizophrenia. Biological Psychiatry. 1997; 42: 137S

Bray N.J., Buckland P.R., Hall H. The serotonin-2A receptor gene locus does not contain common polymorphism affecting mRNA levels in adult brain. Mol Psychiatry. 2004; 9: 109-114.

Burnet P.W., Harrison P.J. Genetic variation of the 5-HT2A receptor and response to clozapine. Lancet. 1995; 346: 909

Chen C.H., Lee Y.R., Wei F.C. Lack of allelic association between 102T/C polymorphism of serotonin receptor type 2A gene and schizophrenia in Chinese. Psychiatr Genet. 1997; 7: 35-38

Davies M.A., Setola V., Strachan R.T. Pharmacological analysis of non-synonymous coding h5-HT2A SNPs reveals alterations in atypical antipsychotic and agonist efficacies. Pharmacogenomics. 2006; 6: 42-51.

Hamdy S.I., Hiratsuka M., Narahara K. Allele and genotype frequencies of polymorphic DCP1, CETP,ADRB2 and HTR2A in the Egyptian population. Eur J Clin Pharmacol. 2002; 58: 29-36.

Harvey L., Reid R.E., Ma C. Human genetic variations in the 5-HT2A receptor: a single nucleotide polymorphism identified with altered response to clozapine. Pharmacogenetics. 2003; 13: 107-18.

Joober R., Benkelfat C., Brisebois K. T102C polymorphism in the 5-HT2A gene and schizophrenia: relation to phenotype and drug response variability. J Psychiatry Neurosci. 1999; 24: 141-146.

Kerwin R., Collier D., Shaikh S. Pharmacological Genetic Association studies and clozapine response. Eur Neuropsychopharmacology. 1996; 6: 25

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Lin C.H., Tsai S.J., Yu Y.W. No evidence for association of serotonin-2A receptor variant (102T/C) with schizophrenia or clozapine response in a Chinese population. Neuroreport. 1999; 10: 57-60.

Malhotra A.K., Goldman D., Ozaki N. Lack of association between polymorphisms in the 5-HT2A receptor gene and the antipsychotic response to clozapine. Am J Psychiatry. 1996; 153: 1092-1094

Masellis M., Basile V.S., Meltzer H.Y. Lack of association between the TC267 serotonin 5-HT6 receptor gene (HTR6) polymorphism and prediction of response to clozapine in schizophrenia. Schizophrenia Res. 2001; 47: 49-58

Masellis M., Basile V.S., Meltzer H.Y. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology. 1998; 19: 123-132.

Masellis M., Paterson A.D., Badri F. Genetic variation of 5-HT2A receptor and response to clozapine. Lancet. 1995; 346: 1108

Mata-Pastor I., Arranz-Calderon M.J., Beperet-Urmeneta M. Influence of serotonergic transmission on response to olanzapine. Acta Esp Psiquiatr. 2002; 30: 265-271.

Nothen M.M., Rietschel M., Cichon S. Molecular Genetic Studies of variation in dopamine and serotonin receptor genes. Eur Neuropsychopharmacology. 1996; 6: 162

Nothen M.M., Rietschel M., Erdmann J. Genetic variation of the 5-HT2A receptor and response to clozapine. Lancet. 1995; 346: 908-909.

Ozaki N. Molecular genetic approach to schizophrenia: direct analysis of 5-HT receptor genes. Nihon Shinkei Seishin Yakurigaku Zasshi. 1996; 16: 175-180.

Pickar D., Goldman D. Predicting clozapine response: systematic evaluation of allelic variation in candidate genes. Schizophrenia Research. 1997; 24: 216

Reist C., Mazzanti C., Vu R. Inter-relationships of intermediate phenotypes for serotonin function, impulsivity, and a 5-HT2A candidate allele: His452Tyr. Mol Psychiatry. 2004; 9: 871-878.

Wilffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

Yu Y.W., Tsai S.J., Yang K.H. Evidence for an association between polymorphism in the serotonin-2A receptor variant (102T/C) and increment of N100 amplitude in schizophrenics treated with clozapine. Neuropsychobiology. 2001; 43: 79-82.

Papers excluded on basis of title: (n=6)

Bray N.J., Buckland P.R., Hall H. The serotonin-2A receptor gene locus does not contain common polymorphism affecting mRNA levels in adult brain. Mol Psychiatry. 2004; 9: 109-114.

Davies M.A., Setola V., Strachan R.T. Pharmacological analysis of non-synonymous coding h5-HT2A SNPs reveals alterations in atypical antipsychotic and agonist efficacies. Pharmacogenomics. 2006; 6: 42-51.

Masellis M., Basile V.S., Meltzer H.Y. Lack of association between the TC267 serotonin 5-HT6 receptor gene (HTR6) polymorphism and prediction of response to clozapine in schizophrenia. Schizophrenia Res. 2001; 47: 49-58

Mata-Pastor I., Arranz-Calderon M.J., Beperet-Urmeneta M. Influence of serotonergic transmission on response to olanzapine. Acta Esp Psiquiatr. 2002; 30: 265-271.

Reist C., Mazzanti C., Vu R. Inter-relationships of intermediate phenotypes for serotonin function, impulsivity, and a 5-HT2A candidate allele: His452Tyr. Mol Psychiatry. 2004; 9: 871-878.

Yu Y.W., Tsai S.J., Yang K.H. Evidence for an association between polymorphism in the serotonin-2A receptor variant (102T/C) and increment of N100 amplitude in schizophrenics treated with clozapine. Neuropsychobiology. 2001; 43: 79-82.

Papers excluded for not fulfilling inclusion criteria : (n=4)

Hamdy S.I., Hiratsuka M., Narahara K. Allele and genotype frequencies of polymorphic DCP1, CETP,ADRB2 and HTR2A in the Egyptian population. Eur J Clin Pharmacol. 2002; 58: 29-36.

Joober R., Benkelfat C., Brisebois K. T102C polymorphism in the 5-HT2A gene and schizophrenia: relation to phenotype and drug response variability. J Psychiatry Neurosci. 1999; 24: 141-146.

Ozaki N. Molecular genetic approach to schizophrenia: direct analysis of 5-HT receptor genes. Nihon Shinkei Seishin Yakurigaku Zasshi. 1996; 16: 175-180.

Wilffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

Papers excluded as data was not suitable for analysis: (n=11)

Arranz M.J., Munro J., Sham P. Meta-analysis of studies on genetic variation in the 5-HT2A receptors and clozapine response. Schizophrenia Research. 1998; 32: 93-99.

Arranz M.J., Munro J., Collier D.A. Further evidence for association between polymorphisms in the 5-HT2A receptor gene and clozapine response. Schizophrenia Research. 1998; 29: 127

Arranz M.J., Munro J., Sham P. Polymorphisms in the 5-HT2A receptor gene and promoter region associated with clozapine response. Schizophrenia Research. 1997; 24: 90

Aschauer H.N., Scharfetter J., Fuchs K. Dopamine and serotonin receptor genotypes and therapeutic response to neuroleptics in schizophrenia. Biological Psychiatry. 1997; 42: 137S

Burnet P.W., Harrison P.J. Genetic variation of the 5-HT2A receptor and response to clozapine. Lancet. 1995; 346: 909

Chen C.H., Lee Y.R., Wei F.C. Lack of allelic association between 102T/C polymorphism of serotonin receptor type 2A gene and schizophrenia in Chinese. Psychiatr Genet. 1997; 7: 35-38

Harvey L., Reid R.E., Ma C. Human genetic variations in the 5-HT2A receptor: a single nucleotide polymorphism identified with altered response to clozapine. Pharmacogenetics. 2003; 13: 107-18.

Kerwin R., Collier D., Shaikh S. Pharmacological Genetic Association studies and clozapine response. Eur Neuropsychopharmacology. 1996; 6: 25

Kerwin R. The 5-HT2A receptor as a site for antispychotics. Eur Psychiatry. 1996; 11: 227S

Nothen M.M., Rietschel M., Cichon S. Molecular Genetic Studies of variation in dopamine and serotonin receptor genes. Eur Neuropsychopharmacology. 1996; 6: 162

Pickar D., Goldman D. Predicting clozapine response: systematic evaluation of allelic variation in candidate genes. Schizophrenia Research. 1997; 24: 216

Papers included in analysis: (n=8)

Arranz M.J., Munro J., Owen M.J. Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. Mol Psychiatry. 1998; 3: 61-66

Arranz M.J., Collier D.A., Munro J. Analysis of a structural polymorphism in the 5-HT2A receptor and clinical response to clozapine. Neurosci Lett. 1996; 217: 177-178

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Lin C.H., Tsai S.J., Yu Y.W. No evidence for association of serotonin-2A receptor variant (102T/C) with schizophrenia or clozapine response in a Chinese population. Neuroreport. 1999; 10: 57-60.

Malhotra A.K., Goldman D., Ozaki N. Lack of association between polymorphisms in the 5-HT2A receptor gene and the antipsychotic response to clozapine. Am J Psychiatry. 1996; 153: 1092-1094

Masellis M., Basile V.S., Meltzer H.Y. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology. 1998; 19: 123-132.

Masellis M., Paterson A.D., Badri F. Genetic variation of 5-HT2A receptor and response to clozapine. Lancet. 1995; 346: 1108

Nothen M.M., Rietschel M., Erdmann J. Genetic variation of the 5-HT2A receptor and response to clozapine. Lancet. 1995; 346: 908-909.

5-HT2C

List of the studies identified by initial search: (n=15)

Ellingrod V.L., Perry P.J., Ringold J.C. Weight gain associated with the –759C/T polymorphism of the 5-HT2C receptor and olanzapine. Am J Med Genet B Neuropsychiatr Genet. 2005; 134: 76-78

Jenck F., Bos M., Wichmann J. The role of 5-HT2C receptors in affective disorders. Expert Opin Investig Drugs. 1998; 7: 1587-1599

Kerwin R., Collier D., Shaikh S. Pharmacological Genetic Association studies and clozapine response. Eur Neuropsychopharmacology. 1996; 6: 25

Kerwin R. The 5-HT2A receptor as a site for antispychotics. Eur Psychiatry. 1996; 11: 227S

Malhotra A.K. Candidate gene studies of antipsychotic drug efficacy and drug-induced weight gain. Neurotox Res. 2004; 6: 51-56.

Malhotra A.K., Goldman D., Ozaki N. Clozapine response and the 5-HT2C Cys23Ser polymorphism. Neuroreport. 1996; 7: 2100-2102

Masellis M., Basile V.S., Meltzer H.Y. Lack of association between the TC267 serotonin 5-HT6 receptor gene (HTR6) polymorphism and prediction of response to clozapine in schizophrenia. Schizophrenia Res. 2001; 47: 49-58

Masellis M., Basile V.S., Meltzer H.Y. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology. 1998; 19: 123-132.

Mata-Pastor I., Arranz-Calderon M.J., Beperet-Urmeneta M. Influence of serotonergic transmission on response to olanzapine. Acta Esp Psiquiatr. 2002; 30: 265-271.

Murad I., Kremer I., Dobrusin M. A family-based study of the Cys23Ser 5-HT2C sertonin receptor polymorphism in schizophrenia. Am J Med Genet. 2001; 105: 236-238

Ozaki N. Molecular genetic approach to schizophrenia: direct analysis of 5-HT receptor genes. Nihon Shinkei Seishin Yakurigaku Zasshi. 1996; 16: 175-180.

Rietschel M., Naber D., Fimmers R. Efficacy and side-effects of clozapine not associated with variation in the 5-HT2C receptor. Neuroreport. 1997; 8: 1999-2003

Sodhi M.S., Kirov G., Aitchison K.J. Allelic variation of the 5-HT2C receptor in psychosis. Schizophrenia Research. 1997; 24: 90-91

Sodhi M.S., Arranz M.J., Curtis D. Association between clozapine response and allelic variation in the 5-HT2C receptor gene. Neuroreport. 1995; 7: 169-172.

Wilffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

Papers excluded on basis of title: (n=5)

Ellingrod V.L., Perry P.J., Ringold J.C. Weight gain associated with the –759C/T polymorphism of the 5-HT2C receptor and olanzapine. Am J Med Genet B Neuropsychiatr Genet. 2005; 134: 76-78

Jenck F., Bos M., Wichmann J. The role of 5-HT2C receptors in affective disorders. Expert Opin Investig Drugs. 1998; 7: 1587-1599

Malhotra A.K. Candidate gene studies of antipsychotic drug efficacy and drug-induced weight gain. Neurotox Res. 2004; 6: 51-56.

Masellis M., Basile V.S., Meltzer H.Y. Lack of association between the TC267 serotonin 5-HT6 receptor gene (HTR6) polymorphism and prediction of response to clozapine in schizophrenia. Schizophrenia Res. 2001; 47: 49-58

Mata-Pastor I., Arranz-Calderon M.J., Beperet-Urmeneta M. Influence of serotonergic transmission on response to olanzapine. Acta Esp Psiquiatr. 2002; 30: 265-271.

Papers excluded for not fulfilling inclusion criteria: (n=6)

Kerwin R., Collier D., Shaikh S. Pharmacological Genetic Association studies and clozapine response. Eur Neuropsychopharmacology. 1996; 6: 25

Kerwin R. The 5-HT2A receptor as a site for antispychotics. Eur Psychiatry. 1996; 11: 227S

Murad I., Kremer I., Dobrusin M. A family-based study of the Cys23Ser 5-HT2C sertonin receptor polymorphism in schizophrenia. Am J Med Genet. 2001; 105: 236-238

Ozaki N. Molecular genetic approach to schizophrenia: direct analysis of 5-HT receptor genes. Nihon Shinkei Seishin Yakurigaku Zasshi. 1996; 16: 175-180.

Sodhi M.S., Kirov G., Aitchison K.J. Allelic variation of the 5-HT2C receptor in psychosis. Schizophrenia Research. 1997; 24: 90-91

Wilffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

Papers included in analysis: (n=4)

Malhotra A.K., Goldman D., Ozaki N. Clozapine response and the 5-HT2C Cys23Ser polymorphism. Neuroreport. 1996; 7: 2100-2102

Masellis M., Basile V.S., Meltzer H.Y. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology. 1998; 19: 123-132.

Rietschel M., Naber D., Fimmers R. Efficacy and side-effects of clozapine not associated with variation in the 5-HT2C receptor. Neuroreport. 1997; 8: 1999-2003

Sodhi M.S., Arranz M.J., Curtis D. Association between clozapine response and allelic variation in the 5-HT2C receptor gene. Neuroreport. 1995; 7: 169-172.

5-HT3

List of the studies identified by initial search: (n=7)

Arranz M.J., Munro J., Owen M.J. Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. Mol Psychiatry. 1998; 3: 61-66

Aschauer H.N., Scharfetter J., Fuchs K. Dopamine and serotonin receptor genotypes and therapeutic response to neuroleptics in schizophrenia. Biological Psychiatry. 1997; 42: 137S

Gutierrez B., Arranz M.J., Huezo-Diaz P. Novel mutations in 5-HT3A and 5-HT3B receptor genes not associated with clozapine response. Schizophrenia Research. 2002; 58: 93-97.

Masellis M., Basile V.S., Meltzer H.Y. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology. 1998; 19: 123-132.

Murad I., Kremer I., Dobrusin M. A family-based study of the Cys23Ser 5-HT2C sertonin receptor polymorphism in schizophrenia. Am J Med Genet. 2001; 105: 236-238

Sundram S., Joyce P.R., Kennedy M.A. Schizophrenia and bipolar affective disorder: perspectives for the development of therapeutics. Curr Mol Med. 2003; 3: 393-407

Tsai S.J., Hong C.J., Yu Y.W. Association study of a functional serotonin transporter gene polymorphism with schziophrenia, psychopathology and clozapine response. Schizophrenia Research. 2000; 44: 177-181.

Papers excluded on basis of title: (n=6)

Arranz M.J., Munro J., Owen M.J. Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. Mol Psychiatry. 1998; 3: 61-66

Aschauer H.N., Scharfetter J., Fuchs K. Dopamine and serotonin receptor genotypes and therapeutic response to neuroleptics in schizophrenia. Biological Psychiatry. 1997; 42: 137S

Masellis M., Basile V.S., Meltzer H.Y. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology. 1998; 19: 123-132.

Murad I., Kremer I., Dobrusin M. A family-based study of the Cys23Ser 5-HT2C sertonin receptor polymorphism in schizophrenia. Am J Med Genet. 2001; 105: 236-238

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Papers included in analysis: (n=1)

Gutierrez B., Arranz M.J., Huezo-Diaz P. Novel mutations in 5-HT3A and 5-HT3B receptor genes not associated with clozapine response. Schizophrenia Research. 2002; 58: 93-97.

5-HT5

List of the studies identified by initial search: (n=38)

Arranz M.J., Bolonna A.A., Munro J. The serotonin transporter and clozapine response. Mol Psychiatry. 2000; 5: 124-125

Arranz M.J., Munro J., Sham P. Meta-analysis of studies on genetic variation in the 5-HT2A receptors and clozapine response. Schizophrenia Research. 1998; 32: 93-99.

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Hamdy S.I., Hiratsuka M., Narahara K. Allele and genotype frequencies of polymorphic DCP1, CETP,ADRB2 and HTR2A in the Egyptian population. Eur J Clin Pharmacol. 2002; 58: 29-36.

Harvey L., Reid R.E., Ma C. Human genetic variations in the 5-HT2A receptor: a single nucleotide polymorphism identified with altered response to clozapine. Pharmacogenetics. 2003; 13: 107-18.

Jenck F., Bos M., Wichmann J. The role of 5-HT2C receptors in affective disorders. Expert Opin Investig Drugs. 1998; 7: 1587-1599

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Malhotra A.K., Goldman D., Ozaki N. Clozapine response and the 5-HT2C Cys23Ser polymorphism. Neuroreport. 1996; 7: 2100-2102

Malhotra A.K., Goldman D., Ozaki N. Lack of association between polymorphisms in the 5-HT2A receptor gene and the antipsychotic response to clozapine. Am J Psychiatry. 1996; 153: 1092-1094

Mancama D., Arranz M.J., Kerwin R.W. Genetic predictors of therapeutic response to clozapine: current status of research. CNS Drugs. 2002; 16: 317-324.

Masellis M., Basile V.S., Meltzer H.Y. Lack of association between the TC267 serotonin 5-HT6 receptor gene (HTR6) polymorphism and prediction of response to clozapine in schizophrenia. Schizophrenia Res. 2001; 47: 49-58

Masellis M., Basile V.S., Meltzer H.Y. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology. 1998; 19: 123-132.

Masellis M., Paterson A.D., Badri F. Genetic variation of 5-HT2A receptor and response to clozapine. Lancet. 1995; 346: 1108

Mata-Pastor I., Arranz-Calderon M.J., Beperet-Urmeneta M. Influence of serotonergic transmission on response to olanzapine. Acta Esp Psiquiatr. 2002; 30: 265-271.

Murad I., Kremer I., Dobrusin M. A family-based study of the Cys23Ser 5-HT2C sertonin receptor polymorphism in schizophrenia. Am J Med Genet. 2001; 105: 236-238

Nothen M.M., Rietschel M., Cichon S. Molecular Genetic Studies of variation in dopamine and serotonin receptor genes. Eur Neuropsychopharmacology. 1996; 6: 162

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Ozaki N. Molecular genetic approach to schizophrenia: direct analysis of 5-HT receptor genes. Nihon Shinkei Seishin Yakurigaku Zasshi. 1996; 16: 175-180.

Pickar D., Goldman D. Predicting clozapine response: systematic evaluation of allelic variation in candidate genes. Schizophrenia Research. 1997; 24: 216

Reist C., Mazzanti C., Vu R. Inter-relationships of intermediate phenotypes for serotonin function, impulsivity, and a 5-HT2A candidate allele: His452Tyr. Mol Psychiatry. 2004; 9: 871-878.

Rietschel M., Naber D., Fimmers R. Efficacy and side-effects of clozapine not associated with variation in the 5-HT2C receptor. Neuroreport. 1997; 8: 1999-2003

Sodhi M.S., Arranz M.J., Curtis D. Association between clozapine response and allelic variation in the 5-HT2C receptor gene. Neuroreport. 1995; 7: 169-172.

Sundram S., Joyce P.R., Kennedy M.A. Schizophrenia and bipolar affective disorder: perspectives for the development of therapeutics. Curr Mol Med. 2003; 3: 393-407

Tsai S.J., Hong C.J., Yu Y.W. Association study of a functional serotonin transporter gene polymorphism with schziophrenia, psychopathology and clozapine response. Schizophrenia Research. 2000; 44: 177-181.

Veenstra-VanderWeele J., Anderson G.M. Pharmacogenetics and the serotonin system: initial studies and future directions. Eur J Pharmacology. 2000; 410: 165-181

Papers excluded on basis of title: (n=37)

Arranz M.J., Bolonna A.A., Munro J. The serotonin transporter and clozapine response. Mol Psychiatry. 2000; 5: 124-125

Arranz M.J., Munro J., Sham P. Meta-analysis of studies on genetic variation in the 5-HT2A receptors and clozapine response. Schizophrenia Research. 1998; 32: 93-99.

Arranz M.J., Munro J., Owen M.J. Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. Mol Psychiatry. 1998; 3: 61-66

Arranz M.J., Munro J., Sham P. Polymorphisms in the 5-HT2A receptor gene and promoter region associated with clozapine response. Schizophrenia Research. 1997; 24: 90

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5-HT6

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Masellis M., Basile V.S., Meltzer H.Y. Lack of association between the TC267 serotonin 5-HT6 receptor gene (HTR6) polymorphism and prediction of response to clozapine in schizophrenia. Schizophrenia Res. 2001; 47: 49-58

Masellis M., Basile V.S., Meltzer H.Y. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology. 1998; 19: 123-132.

Reynolds G.P. Neurotransmitter receptors, genes and schizophrenia. Eur Neuropsychopharmacology. 1996; 6: S4

Wilffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

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Papers excluded on basis of title: (n=6)

Arranz M.J., Munro J., Owen M.J. Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. Mol Psychiatry. 1998; 3: 61-66

Davies M.A., Setola V., Strachan R.T. Pharmacological analysis of non-synonymous coding h5-HT2A SNPs reveals alterations in atypical antipsychotic and agonist efficacies. Pharmacogenomics. 2006; 6: 42-51.

Ellingrod V.L., Perry P.J., Ringold J.C. Weight gain associated with the –759C/T polymorphism of the 5-HT2C receptor and olanzapine. Am J Med Genet B Neuropsychiatr Genet. 2005; 134: 76-78

Masellis M., Basile V.S., Meltzer H.Y. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology. 1998; 19: 123-132.

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Wilffert B., Zaal R., Brouwers J.R. Pharmacogenetics as a tool in the therapy of schizophrenia. Pharm World Sci. 2005; 27: 20-30.

Papers included in analysis: (n=2)

Masellis M., Basile V.S., Meltzer H.Y. Lack of association between the TC267 serotonin 5-HT6 receptor gene (HTR6) polymorphism and prediction of response to clozapine in schizophrenia. Schizophrenia Res. 2001; 47: 49-58

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Adrenaline

List of the studies identified by initial search: (n=7)

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Hsu J.W., Wang Y.C., Lin C.C. No evidence for association of alpha 1a adrenoceptor gene polymorphism and clozapine-induced urinary incontinence. Neuropsychobiology. 2000; 42: 62-65

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Wurch T., Boutet-Robinet E.A., Pauwels P. Inverse agonism at dopamine D2 receptors: a receptor recalcitrant to high levels of constitutive activation. International Congress Series. 2003; 1249: 163-183

Papers excluded on basis of title: (n=3)

Basile V.S., Masellis M., McIntyre R.S. Genetic dissection of atypical antipsychotic-induced weight gain: novel preliminary data on the pharmacogenetic puzzle. J Clin Psychiatry. 2001; 62: 45-66

Hsu J.W., Wang Y.C., Lin C.C. No evidence for association of alpha 1a adrenoceptor gene polymorphism and clozapine-induced urinary incontinence. Neuropsychobiology. 2000; 42: 62-65

Wurch T., Boutet-Robinet E.A., Pauwels P. Inverse agonism at dopamine D2 receptors: a receptor recalcitrant to high levels of constitutive activation. International Congress Series. 2003; 1249: 163-183

Papers excluded as data was not suitable for analysis: (n=3)

Hamdy S.I., Hiratsuka M., Narahara K. Allele and genotype frequencies of polymorphic DCP1, CETP,ADRB2 and HTR2A in the Egyptian population. Eur J Clin Pharmacol. 2002; 58: 29-36.

Reynolds G.P. Neurotransmitter receptors, genes and schizophrenia. Eur Neuropsychopharmacology. 1996; 6: S4

Tsai S.J., Wang Y.C., Yu Y.W.Y. Association analysis of polymorphism in the promoter region of the alpha2a-adrenoceptor gene with schizophrenia and clozapine response. Schizophrenia Research. 2001; 49: 53-58.

Papers included in analysis: (n=1)

Bolonna A.A., Arranz M.J., Munro J. No influence of adrenergic receptor polymorphisms on schizophrenia and antipsychotic response. Neurosci Letters. 2000; 280: 65-68

Glutamate

List of the studies identified by initial search: (n=3)

Hong C.J., Yu Y.W., Lin C.H. Association analysis for NMDA receptor subunit 2B (GRIN2B) genetic variants and psychopathology and clozapine response in schizophrenia. Psychiatr Genet. 2001; 11: 219-222.

Pickar D., Goldman D. Predicting clozapine response: systematic evaluation of allelic variation in candidate genes. Schizophrenia Research. 1997; 24: 216

Reynolds G.P. Neurotransmitter receptors, genes and schizophrenia. Eur Neuropsychopharmacology. 1996; 6: S4

Papers excluded on basis of title: (n=2)

Pickar D., Goldman D. Predicting clozapine response: systematic evaluation of allelic variation in candidate genes. Schizophrenia Research. 1997; 24: 216

Reynolds G.P. Neurotransmitter receptors, genes and schizophrenia. Eur Neuropsychopharmacology. 1996; 6: S4

Papers included in analysis: (n=1)

Hong C.J., Yu Y.W., Lin C.H. Association analysis for NMDA receptor subunit 2B (GRIN2B) genetic variants and psychopathology and clozapine response in schizophrenia. Psychiatr Genet. 2001; 11: 219-222.

Histamine

List of the studies identified by initial search: (n=3)

Basile V.S., Masellis M., McIntyre R.S. Genetic dissection of atypical antipsychotic-induced weight gain: novel preliminary data on the pharmacogenetic puzzle. J Clin Psychiatry. 2001; 62: 45-66

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Mancama D., Arranz M.J., Munro J. Novel polymorphisms in the histamine 1 and 2 receptor genes, schizophrenia and clozapine drug response. Schizophrenia Research. 2000; 41: 242

Papers excluded on basis of title: (n=1)

Basile V.S., Masellis M., McIntyre R.S. Genetic dissection of atypical antipsychotic-induced weight gain: novel preliminary data on the pharmacogenetic puzzle. J Clin Psychiatry. 2001; 62: 45-66

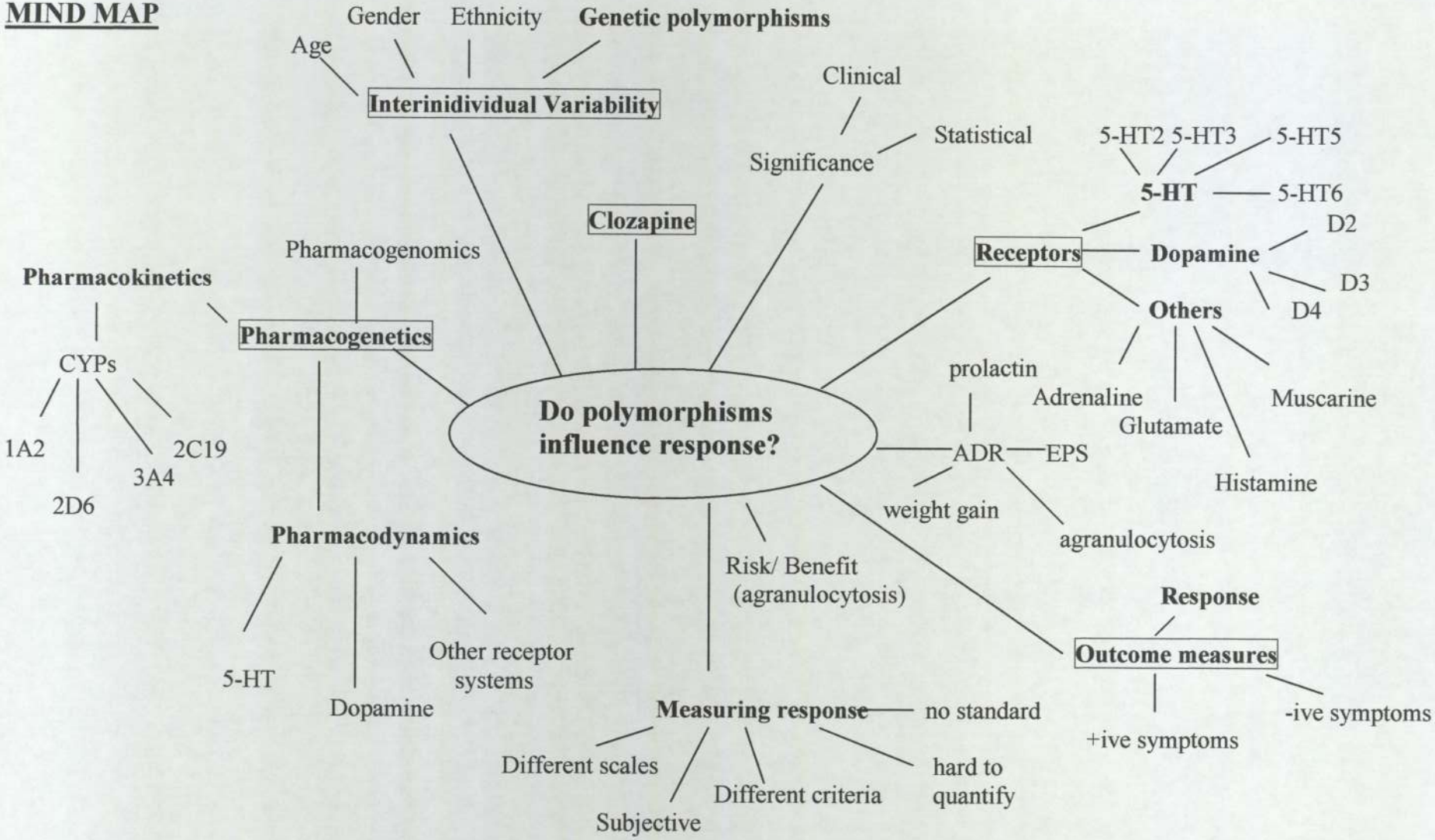
Papers excluded as data was not suitable for analysis: (n=2)

Mancama D., Arranz M.J., Munro J. Investigation of promoter variants of the histamine 1 and 2 receptors in schizophrenia and clozapine response. Neurosci Letters. 2002; 333: 207-211

Mancama D., Arranz M.J., Munro J. Novel polymorphisms in the histamine 1 and 2 receptor genes, schizophrenia and clozapine drug response. Schizophrenia Research. 2000; 41: 242

No papers involving Histamine receptors were included in the analysis

MIND MAP


Gender
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Significance
5-HT2
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5-HT5
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Clozapine
D2
Receptors
Dopamine
D3
D4
Others
Pharmacogenomics
Pharmacokinetics
Pharmacogenetics
CYPs
1A2
2D6
3A4
2C19
Do polymorphisms influence response?
prolactin
Adrenaline
Glutamate
Muscarine
Histamine
ADR
EPS
weight gain
agranulocytosis
Pharmacodynamics
5-HT
Dopamine
Other receptor systems
Risk/ Benefit (agranulocytosis)
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Measuring response
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Subjective
Different criteria
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