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CHAPTER 1

Introduction
The first antipsychotic drug, chlorpromazine (marketed as Largactil in Europe -Figure 1- and as Thorazine in the United States), was synthesised in 1950 as an anaesthetic drug (Bennet, 1998). Its benefit in the treatment of psychosis was discovered in 1952, in the Parisian mental hospital Saint Anne (Delay et al., 1952a,b; Bennet, 1998; Kapur and Mamo, 2003).

At the time of the introduction of chlorpromazine, Jean Thuillier was a psychiatrist at Saint Anne and a pharmacologist: a rare combination in those days. In the book Les dix ans qui ont changé la folie (translated title: Ten years that changed the face of mental illness; Thuillier, 1980) he describes his experiences before and after the introduction of chlorpromazine. Before the discovery of chlorpromazine, psychiatry was heavily focused on the psychoanalytical theories put forth by Freud and there was hardly any place for biological psychiatry. Knowledge on neurotransmitters was very limited. The focus of most psychiatrists was more on understanding mental illness than on treating it. Patients with psychosis were put away in mental asylums and treatment options were limited to several types of shock therapies, including induced coma (e.g. insulin-induced), induced convulsions (e.g. electroconvulsive therapy without anaesthesia), and induced fever (e.g. through infection with malaria).

The introduction of chlorpromazine as a treatment for psychosis has been described as ‘the French revolution of 1952’ (Thuillier, 1980). It led to a remarkable change in the prognosis of patients with psychosis and psychiatric wards were no longer filled with cries of rage. In fact, the effect of chlorpromazine could be measured by recording the sound levels outside a psychiatric ward (Thuillier, 1980). It was also the start of the era of psychopharmacology.

Soon after the discovery of chlorpromazine in Europe, the drug reserpine was developed in the United States (Lehman and Ban, 1997). Reserpine is a plant-derived anti-hypertensive, acting by depletion of monoamines, originating in India. It was introduced into Western medicine in 1949 and psychiatry in 1954 (Kline, 1954; Lehmann and Ban, 1997; Bennet, 1998). The revolutionary changes that were seen after treatment with chlorpromazine...
and reserpine, let to the introduction of many more antipsychotic drugs with a similar mechanism of action, which are now referred to as typical antipsychotics (e.g. haloperidol, flupentixol, droperidol).

In 1963, Carlsson and Lidqvist discovered that dopamine acts as a neurotransmitter (Carlsson and Lidqvist, 1963), for which Carlsson received the Nobel Prize of Medicine in 2000. This led to the believe that dopamine antagonism was essential to the mechanism of action of the typical antipsychotics (Carlsson and Lidqvist, 1963; Bennet, 1998; Benes, 2001; Seeman, 2002). This dopamine hypothesis of psychosis was only formed in 1967 by van Rossum and refined in the early 1970s, more than fifteen years after the discovery of chlorpromazine. The similarity between the symptoms elicited by a pharmacological challenge with amphetamine (which increases the release of dopamine into the synaptic cleft) and the symptoms of psychosis further supported the dopamine hypothesis (Lehmann and Ban, 1997; Featherstone et al., 2007). There are four distinct dopaminergic systems (Bennet, 1998; Lieberman, 2004; see also Figure 2): the mesocortical system (from the ventral tegmentum in the mesencephalon to the frontal lobes and cingulate cortex), the mesolimbic system (from the ventral tegmentum to the hippocampus and amygdala), the nigrostriatal system (from the substantia nigra to the striatum) and the tuberoinfundibular system (from the hypothalamus to the posterior pituitary). Although all drugs also affected the serotonergic system, the blockade of dopamine receptors within the nigrostriatal system was considered the primary target of (typical) antipsychotic drugs (Seeman, 2002).

The first clinical trials with clozapine, which has a wide range of receptor effects including a relatively low affinity for dopamine D₂ receptors and high affinity for serotonin 5-HT₂ receptors, were carried out in 1966 (Bennet, 1998). It was withdrawn from the market in 1975, because of the severe side-effects of agranulocytosis (Idänpää–Heikkilä et al., 1975, 1977). However, after a pivotal comparative study between chlorpromazine and clozapine, which showed superior efficacy of clozapine on both positive and negative symptoms, clozapine was again approved for treatment of refractory schizophrenia (Kane et al., 1988).
Following the introduction of clozapine, several other drugs were developed with different, ‘atypical’, working mechanisms (e.g. olanzapine, risperidone, quatiapine). The definition of ‘atypical’ is very varied and can refer to the occurrence of extra-pyramidal side effects, the relative affinity for dopamine \( \text{D}_2 \) versus serotonin \( 5\text{-HT}_2 \) receptors, or the fast or slow dissociation rate at the dopamine \( \text{D}_2 \) receptor (Meltzer, 1999; Kapur and Remington, 2001; Seeman, 2002; Kapur and Mamo, 2003). Initially, these drugs were thought to be more effective and have fewer side-effects. However, three large, multi-center trials (Clinical Antipsychotic Trials of Intervention Effectiveness-\text{CATIE}; Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study-\text{CUTLASS}; European First-Episode Schizophrenia Trial-\text{EUFEST}) showed that all antipsychotic drugs are similar in effectiveness (Lieberman et al., 2005, Jones et al., 2006; Kahn et al., 2008). Clozapine is the only drug that has demonstrated superior efficacy (Chakos et al., 2001; Lieberman et al., 2005; Carpenter and Davis, 2012).

**Current perspectives**

Even though dopamine antagonists have been able to reduce symptoms of psychosis (in particular the positive symptoms), the long-term prognosis of schizophrenia remains poor (Carpenter and Koenig, 2008). All currently available antipsychotics have comparable dopamine occupancy at clinically relevant doses (Farde et al., 1988; de Visser et al., 2001; Seeman, 2002; Agid et al., 2007). It is hypothesized that dopamine dysregulation might be the final common pathway of different pathophysiological pathways of schizophrenia, with other pathophysiological mechanisms as the primary disturbance (Howes and Kapur, 2009). Many drugs targeting other pathways are currently under development, although none has been successful yet (Miyamoto et al., 2012). These include drugs targeting glutamatergic and cannabinoid systems (Ferretjans et al., 2012; Javitt et al., 2012).
**Preclinical models for psychosis and schizophrenia**

Currently used preclinical models for psychosis and antipsychotic drug action are not able to model the highly complex phenomenon of psychosis and schizophrenia (Carpenter and Koenig, 2008; Nestler and Hyman, 2010). Many models measure the ability to block or reverse a ‘hyperdopaminergic’ state, which results in pharmacologic isomorphism (novel drugs that pass these models will likely have a similar mechanism of action as the drugs that are currently on the market; models that have different mechanisms of action will likely fail at these models; Carpenter and Koenig, 2008; Nestler and Hyman, 2010). Although many new preclinical models, including mechanistic models, have been developed (reviewed by Pratt et al., 2012), there is no clear standardisation in their use and both positive and negative results are easily ignored because of limited predictive power (Nestler and Hyman, 2010, Jones et al., 2011).

**Clinical challenge models**

As an alternative for preclinical models, clinical studies with pharmacological challenges can be used. A pharmacological challenge influences a specific regulating system by means of a pharmacological agent. The resulting change in effect provides information about the mediating process (van Gerven, 2005). A pharmacological challenge can also be used to assess the effect of a drug that interacts with a certain regulating system. For example, administration of glucagon will lead to hyperglycaemia and can be used as a model in diabetes research (van Dongen et al., in preparation). The HPA axis can be stimulated when 5-hydroxytryptophan or desmopressin are administered; changes in the concentrations of cortisol and ACTH describe the sensitivity of the HPA axis (Smarius et al., 2008; Jacobs et al., 2011a,b).
Pharmacological challenges for psychosis and antipsychotic drug action

Several pharmacological agents can be used to illicit psychomimetic symptoms in healthy volunteers and patients (reviewed in detail by Gouzoulis-Mayfrank et al., 1998). Systematic scientific research into the properties of hallucinogenic compounds started around 1900 with mescaline, an agonist of both dopaminergic and serotonergic receptors. Administration of mescaline primarily leads to disturbances of perception - predominantly visual hallucinations - and was considered an excellent model for psychosis at the time. When Albert Hofmann discovered the psychomimetic effects of lysergic acid diethylamide (LSD, a serotonergic agonist) in 1943, a new phase of research into drug-induced psychomimetic effects as a model for psychosis started. LSD was not only used to study psychosis-like states in patients or healthy volunteers, but also to let researchers and psychiatrists experience the effects of psychosis. It is interesting to note, that the response in a pharmacological challenge with LSD played a role in assessing the efficacy of both chlorpromazine (Thuillier, 1980) and reserpine (Ban et al., 2010). The development of phencyclidine (PCP) in 1957, brought along a glutamatergic agent that could be used as a model for psychosis. PCP was never registered for use in humans, but the pharmacologically related N-methyl-D-aspartate (NMDA) antagonist ketamine is used for this purpose. The abuse of psychedelic drugs in the general population (i.e. the hippie movement) led to major restrictions in the use of these drugs and scientific interest in psychedelics faded in the end of the 1960s. In the last two decades, a renewed interest in the drug-induced psychomimetic effects as a model for psychosis has arisen. The pharmacological mechanisms underlying these effects are of particular interest, as they may elude the underlying pathophysiological mechanisms of psychosis and schizophrenia.
Challenges in drug development for schizophrenia

In general, the market for drug development is not very positive. The cost of developing a single drug had increased to more than 800 million dollars per approved drug in 2003 (DiMasi et al., 2003). Many drugs fail during clinical development, with only 7.9% of all drugs and only 3.8% of drugs with a target in the central nervous system reaching the market (DiMasi et al., 2010). This has in the recent years led to the stop of development of psychiatric drugs in several major pharmaceutical companies (van Gerven and Cohen, 2011; Nutt and Goodwin, 2011). A thorough understanding of the pathophysiology, pharmacology of potential agents and adequate models to test drug efficacy early in development are essential to develop new drugs (especially drugs with a new mechanism of action) in the field of psychopharmacology (Cohen, 2010; van Gerven and Cohen, 2011).

Scope of this thesis

This thesis describes the improvement of two pharmacological challenge models (based on a cannabinoid and glutamatergic mechanism of action) that can be used to model aspects of psychosis. It includes a search to improve the optimal use of outcome measures used to measure effects and an exploration of the influence of individual differences on the measured effect.

Chapter 1 provides an overview of the history of antipsychotic drugs and a general introduction to the use of pharmacologic challenges in drug development. It focuses on challenge models used to model aspects of psychosis and antipsychotic drug action. In Chapter 2 the effect of a known antipsychotic drug (olanzapine) on the tetrahydrocannabinol (THC) challenge model of psychosis is investigated. It shows that administration of olanzapine inhibits the psychomimetic effects of THC in healthy volunteers.
The subjective effects of THC, as measured using visual analogue scales (VAS), are looked at more closely in Chapter 3. These subjective effects can be grouped into three distinct clusters: changes in perception, feelings of relaxation and dysphoric reactions.

Chapter 4 explores the relation between differences in the subjective response to THC and personality traits.

In Chapter 5 the ketamine challenge as a model of psychosis is investigated. A particular emphasis is placed on the finding of an optimal target concentration and outcome measure.

Chapter 6 investigates a proposed VAS for psychomimetic effects and compares this new VAS to other commonly used outcome measures for subjective effects.

Chapter 7 takes a closer look at resting state functional magnetic resonance imaging (RS-FMRI) responses to different pharmacological challenges. The functional connectivity of resting state networks is related to the subjective effects of different drugs.

In Chapter 8, the findings within this thesis are related to the information that was already known.
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FIGURE 1  Original packaging of Largactil (reproduced with permission: Boerhaave Museum, Leiden).
FIGURE 2  Overview of the different dopamine projections in the brain (adapted from: TRC).